Behavioral and brain mechanisms of grapheme-color synesthesia and their relationships with perceptual binding and visual imagery

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Abstract

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Synesthesia is an unusual blending of the senses that occurs in about four percent or more of the human population. Much effort has been devoted to establishing criteria to define what synesthesia is ever since the phenomenon reemerged as a fascination within the scientific community in the late 1970s. To date, the most common criteria for synesthesia are that synesthetic experiences be automatic, consistent, rely on an external stimulus that triggers the phenomenological experience, and that this experience is fully conscious to the mind. This framework allows for some differentiation of synesthetes compared to non-synesthetes within the human population, and yet it also creates a self-selecting bias in the synesthetic population; if the scientific community defines criteria for synesthesia, and then only studies people whom fit those criteria, the resulting data will likely validate the definitions if only because they have been defined that way. What is left unknown are ways that synesthetes, as a community of otherwise normal human beings, vary in subtle ways, both in their psychophysical behavior and in their neurobiological form and function in relation to other human beings who do not experience any form of conscious, unusual sensory blendings yet defined as synesthesia.

The studies described in this thesis explore whether perception in the population of individuals currently defined as synesthetes is in fact uniquely different from perception in the rest of the human population. These unique differences in perception are also used here to better inform our understanding of the functions of the human brain. Chapter 2 introduces the concept of perceptual binding and its relation to synesthesia. Some synesthetes experience colors that are associated with letters and numbers, and these so-called grapheme-color synesthetes may rely on similar brain mechanisms to bind their synesthetic colors to space as the ones they (and most humans) use to bind color to space normally. Chapter 3 addresses the question of binding with regard to an unusual phenomenon specific to grapheme-color synesthetes: that it is possible for some of these synesthetes to experience two colors that are spatially co-localized without blending. The results of this behavioral study will be shown to correlate with the vividness of visual imagery, a measure that extends beyond synesthetic phenomenology. Finally, Chapter 4
demonstrates how synesthetes differ from well-matched non-synesthetes in relation to behavior and the anatomy of the brain. Specifically, synesthetes have more vivid visual imagery as a population, more arborized white matter, and show a positive correlation between vivid imagery and increased axonal branching that is absent in non-synesthete controls. Together, these studies suggest that the brains of synesthetes rely on attention-specific mechanisms used by most humans to bind color to space. However, synesthesia as a whole may not simply be one end of a continuum of brain differences. Rather, synesthetes may be unique both in their phenomenological experiences of the world, and in some ways, the organization of the brain that creates them.
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“...Oatmeal n, noodle-limp l, and the ivory-backed hand mirror of o take care of the whites...Passing on to the blue group, there is steely x, thundercloud z, and huckleberry k...In the green group, there are alder-leaf f, the unripe apple of p, and the pistachio t. Dull green, combined somehow with violet, is the best I can do for w...The word for rainbow, a primary, but decidedly muddy, rainbow, is in my private language the hardly pronounceable: kzspygy.”

— Vladimir Nabokov
Dedication

To Zeda.
1. Introduction

Synesthesia is a distinction within the domain of human perception and therefore operates similarly to visual perception as an automatic process leading to a consistent outcome that arises into the awareness of the observer; the synesthete. Synesthetic experiences, most often called concurrents, are also distinguished by researchers as added features of perception. This distinction seems obvious at first, since for all forms of scientifically defined synesthesia, the synesthetic concurrent is not experienced by the vast majority of the human population, and logically, this concurrent must then be an addition, distortion, or illusion of an already complete perceived experience. This may in fact be the case. However, it is also possible that to a synesthete, the unusual concurrent experience is a necessary part of the full experience much in the same way that letters are a complete percept of the combined experience of shape and meaning of the letter form for literate readers but seen simply as shapes by an illiterate observer.

The synesthetic participants whose data are described in this manuscript often experienced multiple forms of synesthesia. They all had in common a particular variation of synesthesia called grapheme-color synesthesia in which a synesthetic color concurrent is triggered when experiencing the shape-concept of a grapheme (e.g., a letter or number). Grapheme-induced colors are often thought of as additional percepts not inherent to the grapheme itself and this is true in the experience of the non-synesthete. However, it is likely a mistake to think this way if we consider that it is challenging if even possible for an average reader to look at this text and not experience the “additional” language concepts triggered automatically within the mind. If you can read this, there can be no argument that these shapes are words. To a synesthete with colors triggered by letter shapes, there is no question that words are colored, even though the synesthete can make the distinction that the print color may be different than their idiosyncratic synesthetic experience. Thus, synesthesia cannot be assumed to be a modification or addition to a complete perceptual experience. It is in fact, a distinction made within the complete perceptual experience of a synesthete, who most often does not consider (or even notice) their concurrent experiences are unusual until they are contrasted to the cultural norm of “not that”.

This thesis details several studies that examine synesthesia in comparison to normal human perceptual distinctions in an attempt to further understand the nature of “synesthesia”. The goal of these studies is three-fold: (1) to outline the cognitive mechanisms forming and underlying synesthetic experience and ground these mechanisms in relation to normal human visual integration, or perceptual binding, (2) to use behavioral testing to better understand the paradoxical relationship between simultaneously experienced synesthetic color and print color, and (3) to use a general behavioral metric (visual imagery) together with psychophysical and neuroanatomical (diffusion weighted imaging, DWI) measures to explore how the synesthetic brain may or may not generalize with respect to the cognitively normal human population.

The perceptual binding discussed in Chapter 2 requires attention, and the role attention plays in binding synesthetic color has become a lasting debate in the synesthesia literature (Robertson 2003). A handful of studies initially gave support for the idea that synesthetic color (specifically grapheme-color synesthesia) could create pre-attentive pop-out effects and prime color without conscious awareness (Smilek, Dixon, Cudahy, & Merikle, 2001; Wagar, Dixon,
Smilek, Cudahy, 2002). To my knowledge, these studies have not been replicated; in fact, a number of behavioral studies support the idea that attention is needed to experience synesthetic concurrents (Mattingley, Rich, Yelland, & Bradshaw, 2001; Rich & Mattingley, 2003; Laeng, Svartdal, & Oelmann, 2004; Sagiv, Heer, & Robertson, 2005; Mattingley, Payne, & Rich, 2006; Rich & Mattingley, 2010). More recently, Brang et al (2010) used magnetoencephalography (MEG) to show that color-selective regions of inferior temporal cortex become active within 10 milliseconds of activation of grapheme-specific regions when grapheme-color synesthetes view achromatic letters. Likewise, Jäncke, Rogenmoser, Meyer & Elmer (2012) used electroencephalography to show that the binding process underlying colored-hearing synesthesia begins with a pre-attentive process. Both studies give support for the automaticity of synesthetic experience, and yet it remains unclear whether the conscious experience of synesthesia requires an attention-dependent binding mechanism. Attention-dependent perceptual binding is thought to rely on spatial integration via the parietal cortex, and parietal activation is ubiquitous in brain-based studies of synesthesia. In the two-stage model of synesthetic representation (Hubbard 2007), the synesthetic experience results from direct cross-activation between neighboring brain regions. For grapheme-color synesthesia, this is commonly thought to be between color-selective area V4 and neighboring grapheme-selective inferotemporal cortex. Synesthetic color is thought to be bound to space via attention-dependent projections between infero-temporal cortex and the parietal lobe. As we will see, there is some uncertainty to the exact infero-temporal mechanisms that are responsible for creating the perception of grapheme-induced color (e.g., see Hupé, Bordier, & Dojat, 2012; van Leeuwen, Petersson, & Hagoort, 2010), while there is substantial and growing evidence for a number of roles the parietal cortex plays in synesthesia.

Understanding perceptual binding may help unravel an anomalous quality of synesthetic perception that is unique to grapheme-color synesthetes. Print and synesthetic color can appear to exist in the same location of space simultaneously without blending into a new, single color. Synesthetic color conflicts with print color when the two hues are incongruent (Odgaard, Flowers, & Bradman, 1999; Mills, Boteler, & Oliver, 1999; Dixon, Smilek, & Merikle, 2004; Ward, Li, Salih, & Sagiv, 2007), suggesting a difference in the representation of the two forms of color. However, it has also been proposed that synesthetic color relies on the same color-selective region (V4) that is most commonly thought to be involved as a hub in selective representation of print color. It is possible that print and synesthetic colors use the same cortical regions at the same time but if this is so, it is not clear how synesthetic color and print color can exist simultaneously as separate percepts. This dichotomy of synesthetic and print colors may be similar but not identical with overlapping, but distinct mechanisms that parallel the relationship between visual perception and visual mental imagery (Ganis, Thompson, & Kosslyn, 2004; Mechelli, Price, Friston, & Ishai, 2004). This relationship will be explored in the studies described within this thesis.

In order to better understand the relationship between imagery and synesthesia, and to better define synesthesia, it is also informative to look at the basic differences in brain structure, if any, between synesthetes and non-synesthetic populations. The neural representation of synesthesia is an ongoing debate. One side argues that synesthesia is the result of early-developing anatomical differences in the cortex (Rouw & Scholte, 2007; Maurer & Mondloch, 2005; Wagner & Dobbins, 2009), resulting from a protracted period of cortical pruning (Simner, Harrold, Creed, Monro, & Foulkes 2009) between neighboring cortical regions, whereas others
argue that synesthesia results from physiological changes in connectivity without the need for changes in the hard-wiring of the brain (Grossenbacher & Lovelace, 2001; Cohen Kadosh, Henik, Catena, Walsh, & Fuentes, 2009; Smilek, Dixon, Cudahy, & Merikle, 2001). Studies supporting the former view suggest that synesthetic differences in neuroanatomy exist at a local level between specific cortical regions involved in the synesthetic representation (i.e., in grapheme-color synesthetes, the color-selective area V4 and the grapheme-selective area adjacent to it). However, a number of studies dating back several decades show that synesthetic phenomena may lie on a continuum that extends into the non-synesthetic population (e.g., Marks, 1974; Rich, Bradshaw, & Mattingley, 2005; Simner, Gärtner, & Taylor, 2011). This continuum also holds true for factors that are not specific to synesthesia, including mental imagery (Barnett and Newell, 2008). Furthermore, genealogical studies have shown that synesthesia seems to run in families (Barnett, et al., 2008; Ward and Simner, 2005; Smilek, Dixon, & Merikle, 2005; Tomson, et al., 2011) and genomic studies have identified multiple chromosomal sites associated with synesthesia (Asher, et al., 2009; Tomson, et al., 2011). It is unlikely that genes encode a phenotype as specific as experiencing grapheme-triggered colors and in fact, synesthetic phenotypes can be highly varied even within families. To the degree that genes influence synesthesia, they probably do so systemically throughout the brain and to varying degrees of intensity. This could result in some portion of the population developing explicit synesthesia and others developing patterns of brain anatomy and physiology that would be synesthetic or synesthesia-like if it were more vivid, or if it were within the bounds of the current defined niches of synesthetic experience. The definition of synesthesia is not entirely clear, and it is possible that a synesthesia-like brain also lies on continua that generalize to more ubiquitous differences in experience common to synesthetes and non-synesthetes; specifically for the purposes here visual mental imagery (Barnett and Newell, 2008). Equally possible, synesthetes may have a categorically different pattern of cortical organization that results in the phenomenological phenotype called synesthesia, but also leads to broader and most often unrecognized differences in perception and cognition beyond synesthesia.

Chapter 2 describes how synesthesia is an excellent model for understanding perceptual binding in the human brain. Current evidence suggests that if synesthetic color is bound, it is through the same attention-dependent integration of feature maps that occurs in other forms of binding. Synesthetic color arises after the point that separate wavelengths blend in normal color vision, which creates a perceptual paradox where synesthetic and print color can appear bound to a single location without blending. If a letter is printed in a color that is different from the synesthetic color it induces, the two hues will activate different hue-selective maps allowing for dual representation of color, but if synesthetic and print colors are the same/similar they will co-activate the same hue-selective map and should create an amplified color signal. Studies suggest that the parietal cortex plays a key role in this binding of synesthetic and/or print color to shape. An earlier version of this chapter was published here: Alvarez, B. D., & Robertson, L. C. (2013). Synesthesia and binding. Oxford Handbook of Synesthesia, 317. http://ukcatalogue.oup.com/category/academic.do

Chapter 3 addresses a unique juxtaposition within synesthetic experience. Synesthetic color induced by graphemes is well understood to be an automatic perceptual phenomenon paralleling print color in some ways but also differing in others. We investigated this by asking how synesthetes are affected by synesthetic and print colors that are the same. We tested two
groups of grapheme-color synesthetes using a basic color priming method in which a grapheme prime was presented, followed by a color patch (probe), the color of which was to be named as quickly and accurately as possible. Primes induced either no color, print color only, synesthetic color only, or both forms of color (e.g., a letter “A” printed in red that also triggers synesthetic red). As expected, responses to name the probe color were faster if it was congruent with the prime color than if it was incongruent. The new finding (Expt 1) was that a prime that induced the same print and synesthetic color led to substantially larger priming effects than either one individually, an effect that could not be attributed to semantic priming (Expt 2). In addition, the synesthesia effects correlated with a standard measure of visual imagery. These findings are discussed in the context of the hypothesis that print and synesthetic color converge on similar color mechanisms.

Finally, Chapter 4 shows for the first time a correlation between the neuroanatomy of the synesthetic brain and a metric that measures a facet of behavior that extends beyond the synesthetic experience. Grapheme-color synesthetes who experience colors triggered by viewing or thinking of specific letters or numbers showed lower white matter integrity, as measured with diffusion tensor imaging, compared with carefully matched non-synesthetic controls. Further analysis suggested that these differences were likely due to the presence of more crossing pathways in the brains of synesthetes. Additionally, these differences in white matter integrity correlated negatively with a measure of the vividness of visual imagery in synesthetes but not in non-synesthetes. That is, synesthetes who reported the most vivid visual imagery had the lowest white matter integrity. We conclude that synesthetes as a population vary along a continuum in their neuroanatomy and behavior while showing categorical differences in neuroanatomy and behavior compared to non-synesthetes.
2. Synesthesia and Perceptual Binding

2.1. Introduction to Synesthesia and Perceptual Binding

Many synesthetic experiences, like colors triggered by letters, numbers, sequences, auras, flavors, spoken words, and touch, are perceived by some synesthetes as occupying specific locations in the external world. Of these many manifestations of synesthetic experience, colored graphemes (e.g., letters and numbers) have been studied most extensively, and the combined knowledge collected from grapheme-color synesthetes will form the basis for this chapter. Our aim is to understand when and how synesthetic experiences can be bound by attention to a specific location in space, similar to the way that typical features, including colors, are bound on a daily basis.

One fascinating paradox that remains unanswered in the study of grapheme-color synesthesia is how it is possible for a synesthete who perceives synesthetically colored letters to experience print and synaesthetic color simultaneously, appearing in the same place without the two colors blending together. As an example, imagine looking at this text printed in black ink, but also seeing “orange” in the same place at the same time. A grapheme-color synesthete that projects color onto text might describe seeing a synesthetic orange color appearing in the same place as the black printed letters, but the colors would remain distinct. Likewise, synesthetes that see colors in their mind’s eye still report the dual experience of print and synesthetic colors that do not interact.Synesthetes describe the synesthetic color in various ways: as a transparency, as ‘filling in’ the letter, or as being in the mind’s eye. However, no length of description can capture the full experience for one who does not experience synesthesia. The black color of the text in this example is the normal form of color that is triggered by different wavelengths reflected from printed pigments and received by the retina. We will refer to this color as “print color”. The other form of color is synesthetic color, which in this example arises when shape (of a grapheme) triggers hue selective networks to produce the phenomenological experience of color. We will refer to synesthetic color (and other synesthetic experiences) as “concurrents”, in accord with the tradition within the field. For the same reason, the stimulus (e.g., a grapheme) that triggers synesthetic color will be called the “inducer”.

Are synesthetic colors bound in perception, and if so, are they bound through the same mechanisms as print colors? The answers to these questions are still unknown and are complex because of both individual differences between synesthetes and the level of binding in question. This chapter will give an overview of what is known about this issue and summarize current models for synesthetic binding. It will build upon the synesthetic binding model originally proposed by Robertson (2003) to explain the mechanism of perceptual binding of synesthetic color in grapheme-color synesthesia, especially those cases in which synesthetic and print colors appear to be in the same place simultaneously. We will first summarize how perceptual binding is thought to occur normally in typical brains and then discuss how the same mechanism may account for binding of synesthetic color and graphemes in at least some grapheme-color synesthetes. We will also review existing theories that include a role for attention in synesthetic experience and will briefly suggest how Robertson’s binding theory may account for other forms of synesthesia. Although it is not fully understood whether synesthetic color is bound like print color, current evidence suggest that if synesthetic color is bound, it is bound through the same
attention-dependent integration of feature maps that occurs in other forms of binding, making synesthesia an excellent model for understanding perceptual binding in the healthy human brain.

2.2. What a Synesthetic Binding Model Needs to Account for

Any account of synesthetic binding must acknowledge many years of research showing that synesthetic experiences are automatic, consistent, and can be perceptual-like in nature (not just memories, metaphors, or make believe). A model of synesthetic binding must also take into consideration evidence that synesthetic color and print color are not represented in exactly the same way. For example, synesthetic color does not “pop out” in visual search like printed color (Sagiv, Heer, and Robertson 2006; Palmeri et al. 2002), nor does it show effects as robust or consistent between subjects as printed color (Hubbard et al. 2005) or rely on the same neural mechanisms (van Leeuwen, Petersson, and Hagoort 2010). Synesthetic color normally requires attention to be allocated to the inducer for perceptual binding, spatial localization, and conscious perception (for a review of attention see Mattingley 2009). A role for attention in synesthetic experience has been supported with only rare exception, possibly due to individual differences in a handful of synesthetes (Smilek, Dixon, and Merikle 2005; Wagar et al. 2002). Lastly, a binding model of synesthesia must account for the synesthetic paradox, where synesthetic (grapheme) inducers and printed (color) concurrents can appear co-localized simultaneously. Ideally, this model should also account for individual differences in subjective experience amongst grapheme-color synesthetes and perceptual binding in other forms of synesthesia, if and when it exists. To date, no single theory can meet all of these criteria perfectly, which leaves open the opportunity for exploration into a very important aspect of synesthesia research, namely the perceptual binding of synesthetic concurrents.

2.3. What is Perceptual Binding?

After visual information leaves the retina, it is segmented into many different types of features, including hue, luminance, size, shape, motion, etc., (Livingstone and Hubel 1988; DeYoe and Van Essen 1988). The brain must then bind these many segmented features correctly into different objects. For example, imagine you just woke up for an early breakfast and you want to have a sip of orange juice before adding creamer to your coffee. You reach for the orange cylindrical glass of juice while avoiding the blue creamer carton. As you look out upon the table, your brain segments orange from blue, cylinder from rectangle, tall from short, and many other featural dimensions of the objects before you. Quickly, the brain then “binds” these individual features into their correct objects and in the correct locations to give you an accurate view of the layout before you. If there had been a problem with the binding, you might have unexpectedly taken a sip of cream instead.

Decoding the mechanisms underlying this “binding problem” (Robertson, 2003) presents a challenge for researchers, and finding an adequate model for the study of binding in humans has been a priority. Decades ago, behavioral studies revealed that features in a display could be incorrectly bound in perception, and these were termed “illusory conjunctions” (A. Treisman & Schmidt, 1982). In an illusory conjunction, features (e.g., color and shape) are perceived to be conjoined in a way that is not consistent with their real world properties. For example, in a real-world display of colored printed letters, an orange “O” and a blue “B” might appear to the observer incorrectly in the opposite colors of orange “B” and blue “O” (under special
circumstances). For cognitively healthy subjects, these circumstances are not easily achieved and typically require both colored letters to be presented simultaneously in close proximity for exposure durations of two seconds or less (Prinzmetal, Henderson, & Ivry, 1995). In rare cases of bilateral brain damage to the parietal lobes, illusory conjunctions are much more common, as will be discussed below. Intrusion errors, replacing one color with another that is not present in the visual environment (e.g., seeing a green “B”), are far more rare than illusory conjunctions, suggesting that the problem is a misbinding of existing features rather than a generalized error of reporting arbitrarily incorrect features. Binding errors seldom occur in feature search tasks with only one dimension of difference (e.g., searching for a blue “B” amongst orange “B”’s (only the color is different) or a blue “B” amongst blue “O”’s (only the shape is different)). Instead, it is when attention is limited by the complexity and diversity of a scene that binding becomes challenging (Treisman, 1999). This research supports the idea that the binding problem is one of conjoining the right features into the correct object representations when multiple features of the same domain (e.g., orange vs. blue color and cylinder vs. rectangular shape in the breakfast example) are competing for attention.

The question of binding has been central to an influential theory of attention, namely Feature Integration Theory (FIT, (A. M. Treisman & Gelade, 1980)). According to FIT, spatial attention is required to bind features (e.g., color, shape, etc.) of a multi-itemed display into object representations. FIT has received strong support through studies of deficits in attention suffered by brain damaged patients. When attentional mechanisms are severely impaired by a stroke or other brain damage, illusory conjunctions can become quite common even under free viewing conditions.

One of the most striking cases of a binding problem was studied in patient R.M., a 58 year old man who suffered nearly symmetrical bilateral parieto-occipital lesions, resulting in Balint’s syndrome (Robertson et al. 1997; Friedman-Hill, Robertson, and Treisman 1995; Robertson 1994). R.M. could perceive individual objects but could not localize them to particular spatial locations. In other words, he could not bind spatial information correctly with object features that were present in a scene. Furthermore, when R.M. was presented with an array of objects he would describe seeing only one and could not shift his attention to search for others. In fact, his spatial abilities were so poor that he could not correctly discriminate the horizontal position of a target (whether it was on the left or right of a screen), even when it was presented alone with no distracters. As a result, and consistent with FIT, he was often unable to perceptually bind features such as color and shape. For instance, when shown two letters X and O colored in red and blue, respectively, he frequently reported illusory conjunctions (i.e., reversed colors) even with up to ten seconds of viewing time. R.M. also exhibited similar illusory conjunctions of color and size, and motion and shape (Bernstein and Robertson 1998). Despite R.M.’s problems with binding features accurately in space, he could identify (but not localize) targets in a feature search display (e.g., a red dot among several blue dots) when the target only differed from distracters in one feature. R.M.’s unique case supports the theoretical view that features undergo a certain degree of processing prior to awareness and without spatial attention (Treisman and Gelade 1980). However, attention is needed to correctly bind features into the correct representation and in the correct location in space. R.M.’s data also make a strong case for the role of the parietal cortex in spatial attention and feature binding.
Another more common attentional problem, called visual spatial neglect, interferes with binding only on one side of space (Cohen and Rafal 1991) and most often occurs following a unilateral lesion of the cortex that interferes with fronto-parietal or cortical-subcortical communication (see Bartolomeo et al. 2007; Bartolomeo, De Schotten, & Doricchi, 2007). Visual neglect is different from the hemianopsia caused by lesions in primary visual cortex, in which a patient is blind in one visual field but is still aware that the blind side of space exists and can accommodate accordingly. A patient with neglect cannot attend to the neglected part of the visual field and appears to have no awareness of its existence.

Studies of patients with neglect have contributed to understanding some of the subtleties of the binding problem and its relationship to attention. Stimuli presented to the neglected visual field of a patient may not reach awareness but information is still processed and integrated to a certain degree. For example, van Vleet and Robertson (2009) showed that neglect patients’ performance was affected equally in a visual feature priming task (Figure 1) where features were presented to the neglected versus normal visual fields. Performance between neglected and normally perceived sides was also equal between conditions when the stimulus presentation time was made easily visible (75% corrected hit rate) versus hardly visible (25% corrected hit rate). When the same task involved a target embedded in a conjunction search display (where attention and correct binding are necessary), patients with neglect performed well in the conjunction condition (Figure 2) when detection was thresholded at 75% (easy condition), but performed
very poorly when the detection threshold was adjusted to 25% detection (hard condition). This difference was not due to differences in difficulty between search displays, as difficulty was equated using an adaptive staircase procedure for each condition. Rather, these results suggest that patients with neglect can represent features equally well whether the features are perceived explicitly or only represented implicitly, but they cannot implicitly represent conjunctions within their neglected field when detection is hard.

Overall, research has taught us that the visual system can represent features implicitly, even when they are presented briefly, below detection thresholds, or among multiple objects. However, to correctly bind different features in the correct spatial locations in a briefly presented display, attention must be utilized. When attention is redirected or lacking, illusory conjunctions occur.

A drawback to interpreting the findings from neglect patients is that they often suffer severe and extensive brain damage that affects motivation, basic perceptual abilities, and other factors beyond attentional control. To better understand the normal binding process what is needed is a healthy group of subjects that bind features in a way that is consistent with normal binding but also distinguishable from normal perception in control populations.

![Figure 2. The priming effect per condition in (feature or conjunction prime/high TPT or low TPT) Experiment 1.](image)

RT to relevant probe presented at central fixation when preceded by a conjunction or feature prime minus when it was preceded by a neutral conjunction or feature display. Results show that there was no significant effect of attention on magnitude of feature priming whereas in the conjunction prime condition, only primes presented at the high TPT duration produced a significant priming effect compared with the low TPT condition. Figure and text from van Vleet and Robertson, 2009. TPT is threshold presentation time.
2.4. Background on Binding in Synesthesia

One reason synesthesia, and grapheme-color in particular, is such an interesting model to help understand the binding problem is that these synesthetes experience an unusual binding of color to form that is more easily induced and stable than illusory conjunctions. Unlike patients with neglect or Balint’s syndrome, synesthetes are cognitively and neurologically normal. Synesthetic color can coexist with print color but remains distinct from it in most cases, so synesthetes experience normal binding of both print color and synesthetic color separately. Thus, studying the underlying networks involved when isolating synesthetic color specifically may be a way to reveal the underlying mechanisms of binding more generally. Esterman, Verstynen, Ivry, & Robertson (2006) proposed the term “hyperbinding” to suggest that synesthetes have additional binding of features not found in non-synesthetes. Here, we expand upon this concept and clarify the binding model for grapheme-color synesthetes, suggesting that when synesthetic color is bound it may be through the same mechanisms as normal feature binding, with the feature of synesthetic color simply arising through an atypical route (e.g., hue induced by shape; see Robertson 2003).

Before explaining synesthetic binding in more detail, it is important to mention two caveats. The first caveat is that not all grapheme-color synesthetes may bind color to form in the same way, and in fact some (or most) may not bind color at all, or may not bind it to an external spatial location in the same way print color appears to be bound. The difference here has been proposed by some to be between projector and associator synesthetes; the former seem to experience synesthetic color externally on the page, and the later experience their concurrent colors only in their “mind’s eye”. The second caveat is that our binding model may not apply to all forms of synesthesia but may offer an explanation for phenomenological experiences of at least some forms of synesthesia besides grapheme-color, in which the concurrent experience appears to be attention-dependent or bound to a spatial location. We will focus on binding in grapheme-color synesthesia since this type of synesthesia has the most available research, and speculate about other forms of synesthesia afterwards.

2.5. Synesthetic Binding Part I: Representation of Features

The case where synesthetic and print colors appear in the same place at the same time without blending implies that these two forms of color maintain separate feature representations. Importantly, however, the two color signals may combine when synesthetic and print colors are the same (Alvarez and Robertson 2013), implying that they converge at some point in visual processing. How can a model of synesthetic binding account for both competition and convergence of print and synesthetic hues, depending on their similarity? At least one answer involves the unique way that synesthetic color is induced. Here we will begin with a summary of early visual processing and then summarize higher order attention-based systems to fully represent the binding of synesthetic color.

Grapheme-induced color cannot form without representation of graphemes, or at least their components (Brang et al. 2010). It has also been suggested that synesthetic color may not arise until after the meaning of the grapheme is registered by higher cortical areas that feed back to earlier visual areas (Smilek, Dixon, Cudahy, & Merikle, 2001; Smilek et al., 2001). However, the normal process of color formation begins much earlier, with trichromatic cone receptors in the retina leading to an opponent system in the lateral geniculate nucleus of the thalamus (LGN)
(De Valois, Abromov, and Jacobs 1966), and transitioning into double opponent systems in area V1 that maintain color constancy (Conway 2001). Hue-selective cortical columns within early visual areas have been identified and named in areas V1 (“blobs”, Xiao et al. 2007), V2 (“thin stripes”, Xiao, Wang, and Felleman 2003), and V4 (Conway & Tsao, 2009; Tanigawa, Lu, & Roe, 2010). It is not known exactly how these hue-selective columns interact to produce perceived hue, although blobs in V1 have been shown to connect anatomically to thin stripes in V2 (Livingstone & Hubel, 1984) and thin stripes project to large patches in V4 (Felleman & Van Essen, 1991). It is likely that color blending occurs at some stage before V4 and that multiple hue-selective columns in this region can be active simultaneously without blending to represent the experience of a multicolored world.

2.6. **Brain-Based Models of Synesthetic Color**

There are several different theories of how synesthetic color is induced and what cortical areas are involved that are relevant to understanding synesthetic binding. Color and letter networks may be connected via direct projections between hue-selective and grapheme-selective cortical maps (Rouw and Scholte 2007; Hubbard 2007; Brang et al. 2010), and the presence of these direct anatomical and functional pathways may vary between synesthetes (van Leeuwen, den Ouden, and Hagoort, 2011). Synesthetic color is likely influenced functionally via cortical disinhibition or unmasking from a higher-order nexus (Grossenbacher & Lovelace, 2001; Smilek et al., 2001) or via reentrant feedback from more anterior areas of the temporal lobes involving letter meaning (Smilek et al., 2001). Finally, synesthetic color may be perceptually bound via direct (Felleman & Van Essen, 1991) or indirect pathways between occipito-parietal regions such as area V4 and the intraparietal sulcus (IPS) (Esterman et al., 2006; Robertson, 2003).

Brain-based studies of grapheme-color synesthesia offer much support for the involvement of ventral color-selective visual areas in representing synesthetic color. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) studies consistently show increased activation in color-selective area V4 when synesthetes are presented with achromatic printed graphemes or spoken words (Paulesu et al. 1995; Nunn et al. 2002; Hubbard et al. 2005; Steven, Hansen, and Blakemore 2006; van Leeuwen, Petersson, and Hagoort 2010; Sperling et al. 2006; Brang et al. 2010), compared to a non-grapheme baseline. Some fMRI studies that do not report V4 activation during synesthetic viewing presented graphemes in baseline conditions, which may have negated the effects (Aleman, Rutten, Sitskoorn, Dautzenberg, & Ramsey, 2001; Weiss, Zilles, & Fink, 2005). EEG and MEG studies have shown that synesthetic concurrent-related increases in activity can occur quickly (e.g., by 114 msec) after stimulus onset within the ventral stream (Beeli, Esslen, & Jäncke, 2008; Brang, Hubbard, Coulson, Huang, & Ramachandran, 2010a), and neuroanatomical studies (diffusion tensor imaging (DTI), voxel-based morphometry (VBM)) have provided some evidence that ventral stream areas, including area V4, have differences in white matter coherence, cortical thickness, and/or surface area in synesthetes (Rouw & Scholte, 2007a, 2010a; Weiss & Fink, 2009a).
Brang et al. (2010) proposed a cascaded cross-tuning model of synesthetic color processing to explain how synesthetic color arises (Figure 3). MEG data were collected from four grapheme-color synesthetes, all of whom experienced color projected onto the page (projector synesthetes). MEG allows for millisecond temporal resolution and millimeter spatial resolution, making it an excellent tool to analyze the functional activation of synesthetic activity in real time. First, the color-selective region V4 of the ventral occipital cortex and grapheme-selective region (posterior temporal grapheme area, (PTGA), just anterior to V4, were localized. Next, achromatic graphemes that induced synesthetic color consequents were presented to
synesthetes while MEG data were recorded. Early activity within the PTGA region of interest (ROI) differed significantly from baseline for synesthetes (105 – 109 ms) and for a group of matched non-synesthete controls (115 -119 ms) with the onset, and the magnitude of early responses did not vary between the groups. However, synesthetes also showed significant activity within area V4 (111 – 114 ms onset) while controls did not at any point in time. Thus, both groups processed graphemes similarly, whereas graphemes also triggered color activity early and automatically only in synesthetes. Brang et al. suggested that direct projections from PTGA to V4 account for the rapid parallel activation of color as graphemes are being processed. According to their cascaded cross-tuning model (Figure 3), synesthetic color first emerges when the components of a grapheme are processed and trigger a broad range of hue maps via direct projections to area V4. As grapheme components are assembled into a completed letter shape, increased interaction between PTGA and V4 leads to convergence on a single grapheme shape and a single hue map, creating a specific and consistent shape-induced synesthetic color. This idea has support from a recent finding that a subsection of V4 does contain hue-selective maps in macaques (Tanigawa et al., 2010) and from developmental theories suggesting that synesthesia arises from a lack of cortical pruning during infant development (Maurer & Mondloch, 2005).

The study by Brang and colleagues has some limitations that can be addressed in the future. They used a relatively small sample of synesthetes, all of whom were classified by self-report as projectors, based on their phenomenology. Inferring activity patterns across all grapheme-color synesthetes based on data from a subset of projectors alone is not trivial. Researchers differ in their opinions regarding whether grapheme-color synesthetes should be classified categorically (Dixon, Smilek, & Merikle, 2004; Rouw & Scholte, 2007a, 2010a) or on one or more continua (Hubbard et al. 2005; Ward et al. 2007; Ward 2011), based on the phenomenological experience of synesthetic color and other factors. Thus, different synesthetes may show the same patterns of cascaded cross-tuning found by Brang et al (2010), but to varying degrees, or show completely different patterns of activity altogether. It will be fascinating to see the patterns of activity that emerge from similar brain imaging studies of other types of grapheme-color synesthetes and other varieties of synesthesia more generally.

In sum, the perception of print color begins with processes that respond to different wavelengths of light at the retina, whereas synesthetic color emerges from something other than wavelength opponent processing and occurs during and after the inducer (e.g., grapheme) has been processed. Visual area V4 in the ventral stream of the cortex may serve as the (or one) locus at which synesthetic and print colors converge and share hue-selective maps that determine perceived color.

2.7. Synesthetic Binding Part II: Bind of Synesthetic Color to Space

As discussed earlier, results from cognitive and neurophysiological studies have shown that attention is required to conjoin features in complex scenes. However, simple features can be encoded as object representations pre-attentively, as shown by van Vleet and Robertson (2009) and by studies of patient R.M. EEG and MEG studies show that synesthetic mechanisms begin very early in cortical processing of letter shapes, as described in the previous section. The majority of studies suggest that synesthesia requires attention to be spatially bound or perceived, although in a handful of rare cases synesthesia has been suggested to operate pre-attentively
(Smilek, Dixon, and Merikle 2005; Wagar et al. 2002). How is it possible to account for these different reports?

The study by Brang et al., (2010) showed activation of color-selective regions in synesthetes’ brains in response to achromatic graphemes, but a further measure of behavior will be needed in future studies to determine whether this activation requires attention in the emergence of the synesthetically bound percept. It may be that the onset of V4 activity, coupled with grapheme activation in PTGA, explains the early emergence of a synesthetic color representation, but this does not mean that it is bound to the grapheme at this stage or fully brought into awareness until it has interacted with other brain regions associated with attention1.

Activation of parietal cortex is ubiquitous with synesthetic experience in the neurophysiology literature, where parietal activity has been shown using every form of brain imaging tool that has been used to study it2. Of special note among these studies are those using TMS, as they offer direct evidence that disruption of activity of parietal cortex can suppress synesthetic concurrents. The direct involvement of the parietal cortex in synesthesia fits well with related ideas of attention-dependent perceptual binding (A. M. Treisman & Gelade, 1980, 1980). Consistently, behavioral data collected from synesthetes suggest critical roles for awareness and attention for the induction of colors from grapheme shapes (Mattingley et al. 2001; Rich and Mattingley 2003; Laeng, Svartdal, and Oelmann 2004; Mattingley, Payne, and Rich 2006; Sagiv, Heer, and Robertson 2006; Rich and Mattingley 2010; Smilek et al. 2001).

Synesthetic color likely requires attention to be spatially bound and may be bound through the same mechanism as print color. But if this is true, how do we address the paradox of synesthetic and print color appearing in the same place at the same time without blending? Synesthetic and print colors may rely on similar mechanisms for binding, but these mechanisms are not identical, and although the differences may be subtle, they are important when addressing the paradox.

van Leeuwen et al. (2010) examined the amount of overlap in brain activity between synesthetic and print color using an fMRI method that shows repetition suppression. Repetition suppression occurs when the brain adapts to repeated exposures of a stimulus, resulting in decreased activity over trials in regions that represent the repeated stimulus. van Leeuwen and colleagues hypothesized that if synesthetic and print color mechanisms overlapped exactly, then repeating a stimulus that induced synesthetic color would create repetition suppression effects in regions that represent the printed color of a subsequent target. However, there was no evidence

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1The pulvinar nucleus of the thalamus is directly involved in sustained attention and also projects to nearly every area of the cortex. The thalamus and other subcortical regions may play an important role in synesthetic representation and even development.
2(PET/fMRI: (Eraldo Paulesu et al., 1995), Right parietal lobe; (Aleman, Rutten, Sitskoorn, Dautzenberg, & Ramsey, 2001) inferior parietal lobe (IPL); Nunn et al. 2002, Left angular gyrus; Weiss et al. 2005, Left intraparietal sulcus (IPS); Steven et al. 2006, bilateral IPL, superior parietal lobe (SPL); Rouw and Scholte, 2010, Left IPS; van Leeuwen et al. 2011, Left IPL; Neufeld, et al. 2012, left inferior parietal cortex (IPC); EEG: Beeli et al. 2008 using LORETA for 7mm voxel resolution, Left precuneus, Right IPS; Jancke and Langer 2011 left parietal lobe; TMS: Esterman et al. 2006, Right angular gyrus (AG); Muggleton et al. 2007, Right AG; Rothen et al. 2010 bilateral parieto-occipital junction; DTI/VBM: Rouw and Scholte 2007, Left posterior parietal cortex (PPC); Weiss and Fink 2008, Left IPS; Rouw and Scholte 2010, Left SPL; although see Jancke et al. 2009 for a contrary finding).
of repetition suppression effects induced by synesthetic color in ROIs that represented the printed color. The lack of a repetition suppression effect suggests that synesthetic and print colors do not share the exact same neural substrates, although van Leeuwen and colleagues were careful to stay agnostic to the degree that the two color systems may partially overlap.

One possible interpretation of these results is that synesthetic and print colors exist as entirely separate feature maps. This idea cannot be ruled out, but it seems unlikely, since van Leeuwen and colleagues (and many other groups prior) report significant overlap (but not repetition suppression) in activity between synesthetic and print colors, particularly in color-selective region V4. It is more likely that synesthetic and print color overlap partially but not to the extent that they would produce equal repetition suppression effects in functional imaging measures (a method that has a low signal to noise ratio).

There are behavioral data that suggest at least partial overlap between print and synesthetic color. For instance, Alvarez and Robertson (2013) conducted a behavioral study similar in design to that used by van Leeuwen and colleagues to study repetition suppression effects, but which measured how a preceding stimulus (the prime) changed response time. Thirteen synesthetes were presented with four types of primes; those that triggered print color only (e.g., red “Ω”), synesthetic color only\(^3\) (e.g., a black “A”), both print and synesthetic colors simultaneously (e.g., a red “A”), or primes that triggered no colors (e.g., black “Ω”, to serve as a baseline). Primes were immediately followed by centrally presented circles (target probes), which were congruent or incongruent in color to the prime (e.g., red “A” followed by either a red or green probe). Participants named the color of the probes out loud as quickly and accurately as they could. Synesthetes were faster to name congruent compared to incongruent probes, replicating previous reports of synesthetic priming effects (Mattingley, Rich, Yelland, & Bradshaw, 2001; Spruyt, Koch, Vandromme, Hermans, & Eelen, 2009). Most importantly, the size of the priming effect (difference between congruent and incongruent reaction times) was significantly larger for the prime that induced both synesthetic and print colors (e.g., a red “A”) than the priming effect induced by either synesthetic or print color alone (e.g., black “A”, or red “Ω”). These findings suggest that synesthetic and print colors converge during cortical processing, for example by utilizing the same feature map of hue. When synesthetic and print hues are very similar or equal they sum to create an amplified neural signal for that hue, leading to an increased priming effect. One alternative to this account would be that either print or synesthetic colors prime the color name and that a different name slows response time. In fact, pairwise comparisons revealed that synesthetic priming was highly significant while print color priming did not reach significant levels. Thus, in this case synesthetic color would act as a strong naming prime, while print color would not, resulting in similar priming effects across synesthetic-only and print plus synesthetic color conditions.

To summarize, in almost every case, synesthetic color arises after the point at which separate wavelengths blend in normal color vision, meaning that if synesthetic and print color do converge, they cannot blend, even in the extreme case where they share a single spatial location. If a letter is printed in a color different from the synesthetic color it induces, the two hues will activate different hue-selective maps, thereby allowing for dual representation of color, but if

\(^3\) Black in this case is considered a neutral color because none of the chosen primes induced black synesthetically and no probe was ever colored in black. Thus, printed black primes acted as a baseline condition for all subjects.
synesthetic and print colors are the same/similar they will co-activate the same hue-selective map and create an amplified color signal. Studies suggest that the parietal cortex plays a key role in this binding of synesthetic and/or print color to shape.

2.8. Applying the Synesthetic Binding Model to Other Types of Synesthesia

This chapter has focused on research on grapheme-color synesthesia as a means of understanding a model of perceptual binding of synesthetic concurrents. Many other varieties of synesthetic experience have been reported to be externalized as well, including projected colors triggered by music (Cytowic and Eagleman 2009), locations of sequences such as weekdays, months, or numbers (Galton 1880; Sagiv et al. 2006b; Eagleman 2009), colored auras that are projected onto a face or body (Cytowic and Eagleman 2009), synesthetic flavors that are experienced as existing on the tongue (Beeli, Esslen, and Jancke 2005), words that are visualized as floating in space or spilling out of a speaker’s mouth (Linn et al. 2008), and touch that is experienced mirrored from another person’s body and physically felt on the body of the synesthete as is the case with mirror touch synesthesia (Blakemore et al. 2005; Banissy this handbook). Variations of all of these synesthetic forms involve concurrents that are projected into an external spatial location for the synesthete. There are multiple reference frames of space (body centered, head centered, eye centered, near space, far space, allocentric, etc.,) and these different synesthetic experiences seem to rely on different reference frames, most (but not all) of which are within the peripersonal space on or within arm’s reach of the body.

In almost all of these forms of synesthesia, the synesthetic concurrents are likely to be triggered through atypical pathways of feature representation. But for any of these synesthetic concurrents to be bound, the mechanisms of binding are probably similar to the attention-dependent ones that bind non-synesthetic features. Understanding these mechanisms and the subtlety of their differences has great potential to inform research on perceptual binding in general and to address a host of other questions in cognitive psychology and neuroscience such as the representation and integration of low level and high level features, the role of cortical-subcortical interactions in sensory experience, the importance of feedback and context on sensory perception, and the role of individual differences in development in perception.
3. The Interaction of Synesthetic and Print Color and its Relation to Visual Imagery

3.1. Introduction to the Interaction of Synesthetic and Print Color

For a small percentage of the population, two colors may be triggered by one physical stimulus and reported as appearing simultaneously, without mixing or canceling. This unique experience is hard to imagine for typical observers, but is described vividly by grapheme–color synesthetes. These synesthetes experience automatic, conscious, and consistent colors triggered by a grapheme (e.g., a letter or number), independent of the color in which the grapheme is printed. Understanding the interaction of grapheme–induced synesthetic color and wavelength-induced color may help to explain the mechanisms underlying color vision more generally. Grapheme-induced colors in synesthetes are thought to arise through mechanisms similar to those in normal visual perception (Kim, Blake, & Palmeri, 2006) and to be perceptually bound to shape by the same brain mechanisms that process typical features of vision (Robertson, 2003; Sagiv, Heer, & Robertson, 2006; Ward, Li, Salih, & Sagiv, 2007). However, in typical observers two hues cannot be experienced simultaneously in the same spatial location. This seems to call into question both the anecdotal self-reports of some grapheme–color synesthetes who say that different synesthetic and printed hues appear in the exact same location simultaneously and the hypotheses that synesthesia can function through normal mechanisms of perception and binding. On the contrary, in this study we suggest a model based strongly on previous research that will help to explain how such a self-report by synesthetes is not only possible but not unexpected, given what is known about the representation of synesthetic color.

Maljkovic and Nakayama (1994) first showed that a color presented on one trial can influence response times (RT) on subsequent trials in a non-synesthetic group of participants, speeding the response to a specific color when it had appeared previously, and slowing the response when it had not. Perceptual color-priming effects were first extended to the study of synesthetic color by Mattingley, Rich, Yelland, and Bradshaw (2001). This group showed that synesthetic color, induced by a black-printed grapheme, created a positive priming effect: Synesthetes were faster to name the print color of a color patch probe when the probe was congruent to the synesthetic color induced by an achromatic grapheme prime. Mattingley et al. (2001) named this effect a “congruency effect,” and we will use this terminology for the remainder of this article. This finding suggests that the synesthetic and print color pathways overlap enough that one form of color representation can trigger the other. Similar studies have validated such an interaction between synesthetic and print color both behaviorally (Alvarez & Robertson 2013; Kim & Blake, 2005; Kim et al., 2006) and neurophysiologically (Brang, Hubbard, Coulson, Huang, & Ramachandran, 2010; Hubbard, Arman, Ramachandran, & Boynton, 2005).

However, several studies have also shown that synesthetic and print colors do not operate in the same way. Synesthetic color requires attention and awareness of the grapheme in order to be induced (Laeng, Svartdal, & Oelmann, 2004; Mattingley, Payne, & Rich, 2006; Mattingley et al., 2001; Rich & Mattingley, 2003, 2010; Sagiv et al., 2006), unlike the preattentive “pop-out” effects attainable with print color (Maljkovic & Nakayama 1994; Treisman 1982). Likewise, many research groups have created synesthetic Stroop-like effects by presenting graphemes that are printed in hues incongruent to their synesthetic colors (e.g., the letter “A” printed in blue,
while inducing synesthetic red; Dixon, Smilek, & Merikle, 2004; Mills, Boteler, & Oliver, 1999; Odgaard, Flowers, & Bradman, 1999; Ward et al., 2007).

The synesthetic Stroop effect relies on the fact that synesthetic and print colors do not blend. This synesthetic Stroop effect, combined with the dual-color self-reports of synesthetes and the results of recent brain-imaging studies (Hupe, Bordier, & Dojat, 2012; van Leeuwen, Petersson, & Hagoort, 2010), suggests that synesthetic and print colors are neurophysiologically independent and operate through different, and possibly rival, networks. Synesthetic color has been hypothesized to result from either direct connections between hue-selective (V4) and shape-selective cortical maps (Brang et al., 2010; Hubbard, 2007), via reentrant feedback between higher semantic and lower visual cortical regions (Smilek, Dixon, Cudahy, & Merikle, 2001), or from feed forward and feedback interactions of early visual and higher-order cortical binding mechanisms through color-processing pathways (Hubbard, 2007; Robertson, 2003). In the present experiments, we used a behavioral measure to determine how print and synesthetic color might interact in perception and discuss the results in relation to neurobiological evidence of print and synesthetic color processing.

We adopted a color-priming method similar to that of Mattingley et al. (2001). However, we created four conditions: A prime appeared that triggered synesthetic color (s), print color (p), the combination (c) of synesthetic and print colors, or no color (b, baseline) on randomly interleaved trials. In the case of primes triggering the combination of synesthetic and print colors, we were careful to make sure that the primes were printed in the same synesthetic color that they induced, triggering the perception of the same hue through print and synesthetic mechanisms. The prime was followed immediately by a print colored probe that was congruent or incongruent to the color of the prime (see Figure 4). In the first experiment, the prime appeared for 750 ms and was followed immediately by a colored probe. In the second experiment, all conditions were the same, except that the prime appeared for only 200 ms. The shortened prime duration was created in order to address the possibility that our congruency effects were the results of semantic priming (e.g., thinking “red” in conditions in which the print, synesthetic, or both colors were primed) rather than perceptual priming. The shorter prime duration also allowed us to examine the interaction of print and synesthetic color priming at shorter and longer processing times.

![Figure 4. Color priming experimental design. Participants were primed and asked to name the color of a subsequent probe aloud into a headset. Primes induced no color (baseline, b), print color only (p), synesthetic color only (s), or the combination (c) of print and synesthetic color. Probes were congruent (CC) or incongruent (IC) to prime color. In Expt. 1, 13 synesthetes and 13 controls were presented with a 750 msec Prime. In Expt. 2, the Prime duration was reduced to 200 msec and presented to nine synesthetes.](image)
We will propose two likely models based on the available research and test them with our behavioral-priming paradigm. In one model, synesthetic and print colors operate through discrete neurophysiological pathways that do not converge before hue has been processed. In this model, a letter that induces the same hue through synesthetic and print pathways (e.g., a print-colored red “A” that also triggers the experience of synesthetic red) will only create as much of a priming effect as either a print colored or a synesthetically colored letter on its own; since the two color pathways remain separate, the effects of the combination condition cannot exceed either individual effect. In the second model, synesthetic and print colors begin via separate pathways for shape and wavelength, respectively, and then converge on overlapping cortical regions that process hue, such as hue-selective visual area V4 (Brang et al., 2010; Hubbard et al., 2005). This model predicts that when a letter is printed in the same color that it triggers synesthetically, the two color signals will converge, and the resulting priming effect will be larger than either effect triggered from only synesthetic color or print color primes alone. Neurophysiological and psychological studies have confirmed the presence of hue-selective regions in several early visual areas (Conway, 2001; Xiao, Casti, Xiao, & Kaplan, 2007; Xiao, Wang, & Felleman, 2003), including area V4 (Conway & Tsao, 2009; Tanigawa, Lu, & Roe, 2010), and studies have validated the role of the inferotemporal regions of the cortex (Rouw & Scholte, 2007), and specifically area V4 (Brang et al., 2010; Hubbard et al., 2005), in synesthetic color experience for grapheme–color synesthetes.

As a final point, grapheme–color synesthesia can be experienced simply by imagining a grapheme without the presence of a physical stimulus (Elias, Saucier, Hardie, & Sarty, 2003; Jansari, Spiller, & Redfern, 2006; Spiller & Jansari, 2008). The relationship of synesthetic experience to visual imagery was proposed by Ramachandran and Hubbard (2001) and has since been validated in synesthetes (Barnett & Newell, 2008; Price, 2009). Barnett and Newell (2008) used a qualitative self-report survey called the Vividness of Visual Imagery Questionnaire (Marks, 1973) to show that a population of synesthetes had more vivid imagery than did non-synesthetic controls. We were curious whether this difference in visual imagery was simply a passive phenomenon, or whether it might correlate with a behavioral metric of visual perception. For this reason, we used the same measure of the vividness of visual imagery (the VVIQ) to test for a correlation between synesthetic congruency effects and visual imagery in our experiment. We hypothesized that more vivid imagery would correlate with larger congruency effects for synesthetes, perhaps due to a general increase in hue sensitivity (Ward et al., 2007) in perceptual networks that overlap with those responsible for generating internal visual representations (Mechelli, Price, Friston, & Ishai, 2004).

3.2. Methods

3.2.1. Participants

All participants had normal or corrected-to-normal vision, no reported history of neurological or psychiatric disorder, and gave signed informed consent before entering the study (as approved by the UCB Committee for Protection of Human Subjects). All participants participated for cash compensation.
Thirteen grapheme–color synesthetes between the ages of 19 and 40 ($M = 27.7, SD = 7.23$; four male, nine female) participated in Experiment 1, and nine synesthetes between the ages of 19 and 32 ($M = 24.0, SD = 5.5$; one male, eight female) participated in Experiment 2. Five synesthetes participated in both experiments. In these experiments, a prime was followed immediately by a colored patch probe on each trial. Each participant was given instructions to name the color of the probe as rapidly as possible. A total of 13 non-synesthete controls matched for age and sex ($M = 27.2, SD = 5.32$, 9 female) also participated in Experiment 1. The synesthetes and controls in Experiment 1 were yoked: Each control participant named the same specific probe colors as the synesthete that he or she was matched to.

The data from two additional synesthetic participants were excluded from Experiment 1, one because of a post-participation report of being in a coma for several days during the weeks just prior to participation, and the other because of too many errors during the task (26% of all trials were removed for this participant, which was far beyond the 10% maximum criterion).

### 3.2.2. Materials and procedure

Synesthesia was assessed and color matches were gathered using the online Synesthesia Battery (Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007). Upon arriving at the lab, each synesthete used the testing computer to re-match colors for three letters chosen as primes that induced the most consistent color representations for that synesthete. We used only colors that could be named using easily spoken basic color terms (red, yellow, blue, or green).

The synesthetes and yoked controls performed a color-naming task (Figure 4) in which a prime was followed by a print colored probe. Primes consisted of one of four randomized stimulus types: achromatic non-inducing symbols (baseline, b), print-colored symbols (print, p), achromatic letters that induced synesthetic color (synesthesia, s), or letters that induced synesthetic color and were colored in their congruent synesthetic color (combo, c). Probes appeared in either the congruent or the incongruent color, relative to the prime. Note that, in the case of the baseline condition, the congruent–incongruent distinction was irrelevant, since the baseline primes did not induce any form of color. On each trial, one of three possible achromatic grapheme primes (e.g., “A” in Figure 4) appeared in the center of the display for either 750 ms (Figure 4) or 200 ms (Experiment 2). A colored probe then replaced the prime, appearing in the same foveal location and remaining until response. The participants sat 57 cm from the monitor and named the color of the target patch as quickly and accurately as possible. Voice onset times of the verbal response were recorded using a head-mounted microphone, and the data were filtered for outliers and hardware errors after the experiment was complete.

Stimuli were presented with a Dell Dimension DM051 2.80 GHz Intel Pentium processor on a Viewsonic G225f CRT computer monitor, with a refresh rate of 120 Hz (8.3 ms per frame). Graphics were presented using a NVIDIA Quadro fx 1300 graphics driver and response time to name the target patch color was recorded with millisecond accuracy using a Plantronics DSP 400 digitally enhanced headset.

A frame remained on the screen for the duration of each block and acted as a fixation guide during the intertrial interval. This frame was made of thin white lines outlining the four
corners of a box (4.3 deg wide) with 2 deg of separation between each of the four corner sections (see Figure 4). Letter primes were presented in Arial font and subtended an average visual angle of 1.65 × 2.25 deg. Non-inducing grapheme shapes (e.g., ⭐, ™, ☴) were created using Wingdings fonts, the Greek alphabet, or Pesenti symbols (Pesenti, Thioux, Seron, & Volder, 2000) and subtended the same average visual angle as letters. The probes were circular colored patches (2.04 deg). A complete trial began with a prime (750 ms in Exp. 1, 200 ms in Exp. 2), followed immediately by a probe that remained on the screen until voice onset. The response was followed by an intertrial interval (750 ms in both experiments), during which only the reference frame remained on the monitor.

In Experiment 1, a total of 240 trials were run, divided into four blocks of 60 trials, and in Experiment 2, the number was reduced to 192 trials, divided into four blocks of 48 trials. We reduced the number of trials to shorten the overall presentation. All blocks in both experiments contained equal numbers of all possible combinations of the conditions (4 primes × 2 color congruency). The order of trials was pseudorandomized so that the primes appeared randomly, but no more than two trials of the same color probe could appear consecutively. Incongruent colors were also pseudorandomly matched to primes, so that a patch congruent to the color of one prime was assigned as the incongruent color to another prime. This assured that equal numbers of congruent and incongruent trials were presented. This counterbalanced, pseudorandomized design controlled for semantic priming effects that could occur if one color was named several times in a row, as well as for variance in luminance between the colored probes. Luminance was not equated, because it was essential that the probe colors chosen matched the synesthetic colors.

To begin the experiment, participants completed four practice trials presented at the beginning of the first block that contained a letter prime not used in the test trials. These practice trials allowed participants to practice naming colors into the head-mounted microphone.

3.2.3. **Data analysis**

To assess whether participants responded correctly to the probe color patches, the researcher sat next to the participant and checked whether the spoken response matched the target color that appeared. If the participant did not clearly produce the correct color name on the first try, the response was discarded. Response times three standard deviations or more above the mean were excluded, as were those occurring earlier than 150 ms after the offset of the prime. Less than 1% of the responses fell within this early period, and those that did were due to accidental noises made by the participant (e.g., mouth smacking or coughing). Mechanical and response errors resulted in the removal of 4.11% of the data in Experiment 1 (synesthetes 4.01%, controls 4.39%) and 4.63% of the data in Experiment 2 (synesthetes only).

In Experiment 1, a mixed design (with Group as a between-subjects factor) was first used to compare the priming effects of synesthetes to yoked controls after outliers and errors were removed. Next, the data were analyzed separately for synesthetes and controls in Experiment 1, and for synesthetes in Experiment 2, using a 2 × 4 (Color Congruency×Prime Type) within-subjects analysis of variance (ANOVA). Afterward, a congruency effect metric was calculated for each participant by subtracting congruent color (CC) means from incongruent color (IC)
means separately for each type of prime (baseline [no color: b], print color only [p], synesthetic color only [s], and combination of print and synesthetic color [c]) to compare the size of the congruency effect (CC – IC) across prime types (b, p, s, and c). A one-way ANOVA was run on these four difference means, and a Šidák–Bonferroni post-hoc analysis was used to correct for pair-wise comparisons on conditions for which there were no a priori hypotheses (as discussed in more detail below).

Data from a slightly modified (i.e., the instructions were shortened, but the questions remained identical) version of the Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973) were also collected from all synesthetes in both experiments and from the yoked controls, and separate averages were made for the eyes-open and eyes-closed ratings on that scale for each participant (16 identical questions each). A paired-samples t test indicated that scores were not significantly different for synesthetes in the eyes-open condition ($M = 2.31, SD = 0.86$) and the eyes-closed condition ($M = 2.19, SD = 0.85$) for Experiment 1, $t(12) = 1.27, p = .23$, or for synesthetes in Experiment 2 (eyes open, $M = 2.15, SD = 0.82$; eyes closed, $M = 2.15, SD = 0.86$), $t(8) = 0.00, p = 1$. Scores were also not significantly different for controls in the eyes-open condition ($M = 2.34, SD = 0.98$) and the eyes-closed condition in Experiment 1 ($M = 2.55, SD = 1.04$), $t(12) = –0.76, p = .46$. Thus, an average VVIQ score was created by combining the eyes-open and eyes-closed conditions, and this average score was used.

3.3. Results

3.3.1. Experiment 1: Synesthetes and yoked controls, 750-ms prime duration

At the group level, we sought to test whether the synesthetes and yoked controls showed overall differences in their patterns of congruency effects for the different priming conditions. The congruency effect was measured by subtracting congruent from incongruent RTs for each of the four priming conditions (prime type: b, p, s, and c), resulting in a difference mean for each condition. Table 1 shows the mean RTs for synesthetes and controls, and also the difference means (congruency effect) for each condition and each group.

Group differences were analyzed with a mixed design ANOVA. Group was a between-subjects factor, whereas Color Congruency (congruent [CC] and incongruent [IC] probe colors, relative to the prime color), Prime Type (b, p, s, or c primes), and Congruency Effect (the difference means between congruent and incongruent RTs for the b, p, s, and c conditions for each participant) were used as within-subjects factors. The critical component of this analysis was the Group × Congruency Effect interaction, which – if significant – would support the hypothesis that different experiences of the primes (i.e., the presence or absence of synesthetic color) would create different patterns of priming effects for synesthetes than for non-synesthetes. As expected, this interaction was significant $F(3, 22) = 3.35, p = .037, \eta^2 = .31$. The main effect of congruency effect was also significant when collapsed across groups, $F(3, 22) = 9.15, p = .0004, \eta^2 = .56$. 


Table 1. Experiment 1, 750 msec prime duration. Mean response times for synesthetes and yoked controls across four different prime types. For synesthetes, p = print color only, s = synesthetic color only, c = combination of synesthetic and print color. For controls, b and s represent achromatic conditions, and p and c represent color conditions. Asterisks mark a difference score (the Congruency Effect) that is significant between the incongruent (IC) and congruent (CC) color conditions. Note that for controls, color congruency only applies to the p and c conditions, where primes contained print color. Minor inaccuracies in difference scores are the result of rounding to one decimal place in this table. See Fig 2 for a visualization of congruency effects.

| Prime Type | Group | Synesthetes | | | | | | Yoked Controls | | | | | |
|------------|-------|------------|---|---|---|---|---|---|---|---|---|---|
|            |       | b          | P | s | c | b | P | s | c | b | P | s | c |
| IC (msec)  |       | 495.6      | 508.6 | 509.3 | 515.7 | 474.0 | 476.6 | 471.5 | 478.0 | | | | |
| CC (msec)  |       | 496.5      | 491.4 | 475.2 | 457.7 | 479.4 | 459.0 | 472.9 | 455.3 | | | | |
| Congruency Effect (msec) |       | -0.9 | 17.2 | 34.1* | 58.1* | -5.4 | 17.5* | -1.4 | 24.7* | | | | |
| p-value    |       | .900 | .176 | .020 | .008 | .326 | .045 | .883 | .002 | | | | |

3.3.2. Synesthetic group only

Data from synesthetes alone were analyzed using a 2 × 4 ANOVA with the within-subjects factors Color Congruency (prime congruent or incongruent relative to probe) and Prime Type (b, p, s, or c). We found a trend toward a main effect of prime type, \( F(3, 36) = 2.57, p = .07, \eta^2 = .18 \), and a significant main effect of color congruency, \( F(1, 12) = 5.61, p = .035, \eta^2 = .32 \). Mauchly’s test indicated that the assumption of sphericity had been violated for the Color Congruency × Prime Type interaction \( \chi^2(5) = 14.2, p = .015 \), and degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity (\( \epsilon = .55 \)). The original effect of color congruency and prime type was verified by a significant interaction between the two factors, \( F(1.6, 19.6) = 12.66, p = .0005, \eta^2 = .51 \), that was due to a decrease in RTs from the print to synesthetic to combination prime types in the CC condition, \( F(3, 36) = 9.26, p = .0001, \eta^2 = .436 \).

A one-way ANOVA also confirmed a significant difference among the four incongruent RT values, \( F(3, 36) = 4.29, p = .011, \eta^2 = .263 \) (see Table 1). However, this effect was due to significant differences between each color-based prime type (p, s, and c) and the baseline condition (b). The size of the congruency effect for incongruent trials only was not significantly different across color-based prime types. These differences for congruent and incongruent trials show that the congruency effects in this study were due to positive priming resulting in faster RTs over prime types, rather than to increased interference.

We hypothesized that all priming conditions that involved color (print, synesthetic, and combination) would produce congruency effects for synesthetes, measured by subtracting the
congruent from the incongruent RTs within each condition (see Figure 5). Paired-samples \( t \) tests confirmed these a priori hypotheses of significant congruency effects for the combination prime condition, \( t(12) = 3.26, p = .007 \), and the synesthetic color condition, \( t(12) = 2.72, p = .019 \), and an insignificant difference for the print color condition, \( t(12) = 1.48, p = .166 \). RTs from the baseline condition were also compared, even though these primes did not induce any form of color. This result was important, because a prior study had reported that synesthetes can learn novel grapheme–color associations in one testing day (Mroczko, Metzinger, Singer, & Nikolić, 2009), and it was possible that participants learned these color pairings to symbols from their print-colored counterparts. However, RTs from the baseline condition showed no significant congruency effects, \( t(12) = .113, p = .912 \), confirming that these novel color pairings were not associated.

Further analyses of the difference scores showed that the size of the congruency effect was larger for the colored-prime conditions (p, s, c) than for baseline, \( F(3, 10) = 5.11, p = .021, \eta^2 = .605 \). Paired-samples \( t \)-tests confirmed that the size of the congruency effect was significantly smaller for the baseline condition than for the combination color condition, \( t(12) = 3.97, p = .002 \), and the synesthetic color condition, \( t(12) = 3.37, p = .006 \), and showed a trend relative to the print color condition, \( t(12) = 2.10, p = .057 \), that was clearly in the hypothesized direction.

We did not predict a priori whether print color, synesthetic color, or the combination of the two colors would create the greatest congruency effects. Thus, post hoc analyses were conducted on these three comparisons. A Šidák–Bonferroni post-hoc correction (the cutoff for three comparisons was \( p < .0170 \)) indicated that the combination (c) congruency effect was significantly greater than with synesthetic (s) color priming, \( t(12) = 3.04, p = .010 \), and greater than with print (p) color priming, \( t(12) = 4.09, p = .001 \). Synesthetic color congruency effects were also found to be greater than print color congruency effects, \( t(12) = 2.97, p = .012 \).
3.3.3.  **Yoked control group only**

Data from the non-synesthetes were also analyzed using a $2 \times 4$ ANOVA with the within-subjects factors Color Congruency (prime congruent or incongruent relative to probe) and Prime Type (colored letters, colored symbols, black letters, or black symbols). Note that controls viewed the exact same prime stimuli as the synesthetes but did not experience synesthetic color for the letter shapes. Thus, the print colored-letter primes and print colored-symbol primes were expected to produce congruency effects, and black letter and symbol primes were not expected to produce congruency effects. We found no main effect of prime type, $F(3, 36) = 1.28, p = .295, \eta^2 = .096$, and a trend toward a significant main effect of color, $F(1, 12) = 4.41, p = .058, \eta^2 = .269$. However, the interaction of prime type with color was highly significant, $F(1, 12) = 4.78, p = .007, \eta^2 = .285$.

Paired-samples $t$ tests confirmed the a priori hypotheses that primes with print color would create congruency effects in non-synesthetes and that achromatic primes would not. Controls showed significant congruency effects when primed with print-colored letters, $t(12) = 3.88, p = .002$ (the “combination” condition for synesthetes) and print-colored symbols, $t(12) = 2.23, p = .046$ (the “print-color-only” condition for synesthetes). Controls did not show significant congruency effects when primed with achromatic letters, $t(12) = 0.160, p = .875$ (the “synesthetic-color-only” condition for synesthetes) or achromatic symbols, $t(12) = 1.01, p = .331$ (the “baseline” condition for synesthetes). In summary, controls showed color priming when primed with print-colored primes, and did not show color priming when primed with achromatic primes (no synesthesia). These results were as expected.

3.3.4.  **Experiment 2: Synesthetes, 200-ms prime duration**

We collected data in Experiment 2 to check whether semantic priming of the response color (e.g., priming of “red”) would influence our results. This type of semantic priming has traditionally been thought to occur about 250 ms after stimulus onset (Neely, 1977), and if present in this study, it would be expected to decrease the RTs for congruent conditions and increase the RTs for incongruent conditions in a similar way to that in Experiment 1. Thus, in Experiment 2, we shortened the prime duration to 200 ms in order to reduce the chance of semantic priming while preserving synesthetic color priming; synesthetic color priming has been demonstrated at this prime duration previously (Spruyt, Koch, Vandromme, Hermans, & Eelen, 2009).

We used the same within-subjects statistical comparisons in Experiment 2 as had been used to analyze the synesthetic group in the first experiment. A $2 \times 4$ ANOVA with the within-subjects factors Color Congruency and Prime Type was run first. The main effect of prime type was not significant, $F(3, 24) = 0.543, p = .657, \eta^2 = .06$, but the main effect of color congruency was significant, $F(1, 8) = 44.1, p = .0002, \eta^2 = .85$, and a Congruency $\times$ Prime Type interaction did emerge, $F(3, 24) = 12.93, p = .00003, \eta^2 = .62$. All three comparisons passed Mauchly’s test of sphericity, so a normal distribution was assumed.
We again hypothesized that all priming conditions (p, s, and c) with colored primes would show significant color congruency effects, as measured by comparing RTs to congruent versus incongruent probe colors, relative to the color induced in each prime condition. As expected, the print, \( t(8) = 6.23, p = .0003 \), synesthetic, \( t(8) = 3.17, p = .013 \), and combo, \( t(8) = 5.51, p = .0006 \), conditions produced significant congruency effects, whereas the baseline condition did not, \( t(12) = 0.787, p = .454 \).

A one-way ANOVA revealed significant differences between the individual congruency effects, \( F(3, 6) = 6.30, p = .028, \eta^2 = .759 \), so we compared the individual difference means of the congruency effect sizes for each colored-prime condition (p, s, or c) to baseline (b) and to each other, using paired-samples \( t \) tests as in Experiment 1. We again predicted that all congruency effect sizes would be larger than in the baseline condition, and indeed found significant differences in each case: print > baseline, \( t(8) = 4.21, p = .003 \), synesthetic > baseline, \( t(8) = 2.45, p = .039 \), and combo > baseline, \( t(12) = 4.43, p = .002 \) (see Table 2). This would be expected whether perceptual or semantic priming produced the effects. However, if only semantic priming were involved, then print color, synesthetic color, and the combination of the two should not differ from each other.

Table 2. Experiment 2, synesthetic priming at a 200 msec prime duration. Mean response times for the 13 synesthetes who participated in Experiment 1 and the 9 synesthetes who participated in Experiment 2. b = baseline condition with achromatic primes, p = print color only, s = synesthetic color only, c = combination of synesthetic and print color for Experiment 1 (750 ms) and Experiment 2 (200 ms). Asterisks mark a difference score (the Congruency Effect) that is significant between the incongruent (IC) and congruent (CC) color conditions. Minor inaccuracies in scores are the result of rounding to one decimal place in this table.

<table>
<thead>
<tr>
<th>Prime Type</th>
<th>Expt 1 (750 msec)</th>
<th>Expt 2 (200 msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>p</td>
</tr>
<tr>
<td>IC (msec)</td>
<td>495.6</td>
<td>508.6</td>
</tr>
<tr>
<td>CC (msec)</td>
<td>496.5</td>
<td>491.4</td>
</tr>
<tr>
<td>Prime Effect (msec)</td>
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<td>17.2</td>
</tr>
<tr>
<td>p-value</td>
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<td>.176</td>
</tr>
</tbody>
</table>

The results indicated that the combination (c) congruency effect was significantly greater than the synesthetic (s) effect, \( t(8) = 3.91, p = .005 \), and greater than the print (p) color congruency effect, \( t(8) = 2.73, p = .026 \). We found no significant difference between the synesthetic and print color congruency effects with a 200-ms prime duration, \( t(8) = 0.925, p = .382 \).

Five of the synesthetes in Experiment 1 participated in Experiment 2, and it could be argued that the different patterns of results between the two experiments were the result of increased variability introduced by the four new synesthetic participants. For this reason, in Table 3 we present the mean RTs for the five participants who were in both Experiments 1 and 2,
as well as for the full set of nine participants who took part in Experiment 2. As can be seen, this subgroup showed a pattern of RTs that mirrored the respective means of the larger group.

Table 3. Five synesthetes participating in both experiments compared to all Experiment 2 participants. Mean response times for all nine synesthetes in Experiment 2 (left) and the five synesthetes who participated in both Experiments (right), across four different prime types. b = achromatic baseline, p = print color only, s = synesthetic color only, c = combination of synesthetic and print color. Asterisks mark a difference score (the Congruency Effect) that is significant between the incongruent (IC) and congruent (CC) color conditions. Minor inaccuracies in difference scores are the result of rounding to one decimal place in this table.

<table>
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<th>Synesthetes (n=5)</th>
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<tbody>
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</tr>
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<td>p</td>
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<td>S</td>
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<td>C</td>
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<td>36.0*</td>
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<td>82.0*</td>
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<table>
<thead>
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3.3.5. Correlations with self-reported vividness of visual imagery

Scores from the VVIQ were regressed with the size of the congruency effects for each group in each experiment. We hypothesized that more vivid imagery would correlate with a stronger synesthetic representation and thus lead to larger priming effects in conditions in which synesthetic color acted as a color prime. The congruency effects for each of the four priming conditions (b, p, s, and c) were correlated with the average VVIQ scores for synesthetes and for controls (Figure 6). We were careful not to assume a Gaussian distribution for the correlational comparisons, since RTs are often skewed and our survey was categorical. For this reason, we analyzed the data using the nonparametric Spearman’s rho correlation, which also corrects for outliers.

In Experiment 1, synesthetes showed a positive correlation between the vividness of visual imagery and congruency effect magnitude for the condition in which primes induced only synesthetic color (s), Spearman’s $r(13) = –.657$, $p = .015$, and for the combination condition (c), in which primes induced synesthetic and print color, Spearman’s $r(13) = –.765$, $p = .002$. 

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Correlations between the VVIQ and the print and baseline congruency conditions were not significant [Spearman’s $r(13) = –.311$, $p = .301$, and $–.322$, $p = .284$, respectively], nor was the correlation between VVIQ and the grand mean of the RTs for all conditions, Spearman’s $r(13) = –.003$, $p = .993$. For the non-synesthetic controls, we observed no significant correlations between congruency effect magnitude and the vividness of visual imagery (all $p > .354$). However, the controls did show a significant correlation between VVIQ and the grand mean of the RTs of all conditions, Spearman’s $r(13) = –.560$, $p = .046$. Note that a negative $r$ value represents a positive correlation, because lower values on the VVIQ represent more vivid imagery. Thus, for the significant correlations found for synesthetes, the congruency effect size increased as imagery became more vivid (smaller VVIQ scores). For controls, the significant correlation was positive, meaning that smaller (faster) RTs were associated with smaller values (more vivid imagery) on the VVIQ.

In Experiment 2, synesthetes showed a positive correlation between the vividness of visual imagery and congruency effect magnitude only for the synesthesia condition (s), Spearman’s $r(9) = .667$, $p < .05$. It is worth pointing out again that a negative $r$ value indicates a positive correlation (congruency effects increase as imagery becomes more vivid), since the VVIQ rates vivid imagery as lower values. The correlations between the vividness of visual imagery and all other congruency effect conditions (b, p, and c) did not reach significant levels (all $ps > .765$).

**3.4. Discussion**
This study used a perceptual priming task to explore how print and synesthetic color might be related in grapheme–color synesthesia. We presented synesthetes with primes of two different durations (750 and 200 ms) and found that synthetic color priming was robust and comparable in size at both durations (34.1 ms in Exp. 1 and 36 ms in Exp. 2). Conversely, the print color effect was much larger (62.7 ms) at the 200-ms prime duration than at the 750-ms duration (17.2 ms). The 200-ms prime duration was also used as a means to rule out semantic priming as creating the effects. Additionally, congruency effects for synesthetes increased in size significantly from print color priming, to synesthetic color priming, to the prime that induced the combination of both colors simultaneously, at 750 ms. This change in priming mostly reflected improved performance when the colors of the prime and probe were congruent.

The results of Experiment 1 support the conclusion that synesthetic color and print color initially rely on different (form-based vs. wavelength-based) pathways but converge at some point to form a stronger color signal than either color type alone. The presence of color congruency at a shorter duration in Experiment 2 confirms that these results were not due to semantic priming and also shows that synesthetic color does, in fact, prime at 200 ms (Spruyt et al., 2009).

Whereas previous studies had validated the independence of synesthetic and print color (Dixon et al., 2004; Mills et al., 1999; Odgaard et al., 1999; van Leeuwen et al., 2010; Ward et al., 2007), we have demonstrated an exception in which synesthetic and print color can combine into a single amplified signal when the hues of both colors match. The present results are consistent with a model of processing whereby synesthetic and print colors are represented through distinct but overlapping pathways that converge on a map of perceived hue (see Figure 7 for a schematic). When a prime triggers the same print and synesthetic colors, both forms of color converge on the same hue-selective map (e.g., possibly a red-selective cortical hyper column), which results in a larger color signal (e.g., more “red” signal) and a larger perceptual color congruency effect (faster RTs when naming a red probe). When a prime triggers different print and synesthetic colors (e.g., print green and synesthetically induced red), the two hues are still processed in the same general color region, but rely on independent hue-selective maps (e.g., print-induced green and synesthetically induced red cortical hyper columns). Such a model can account for how a prime can lead to faster priming RTs when its print and synesthetic color match, relative to a prime that triggers only one form of color. The same model can also explain how synesthetic color can be perceptually bound to the same location of an incongruent print color without blending, since different hue-selective channels do not likely interact directly within early visual color-selective cortical areas, and thus cannot blend.
Although synesthetic and print colors clearly arise through independent sources – shape-induced color versus wavelength-induced color – the present results suggest that they may converge on the same perceptual, hue-selective cortical region. There is evidence for hue-selective cortical columns in the blobs of V1 (Xiao et al., 2007), the thin stripes of V2 (Conway, 2001; Xiao et al., 2003), and within globs in V4 (Conway & Tsao, 2009; Tanigawa et al., 2010). These hue-selective cortical columns are thought not to connect directly within a cortical region, allowing different hues to be processed independently within a column without blending with other columns. Accordingly, in Figure 7, synesthetic and print colors both converge on the same hue-selective region and do not blend when they are different hues (e.g., letter “A” printed in green that induces synesthetic red). However, synesthetic and print color would converge on a single hue-selective cortical column when they both represent the same hue (e.g., letter “A” printed in red that also induces the same synesthetic red). Thus, when synesthetic and print colors are the same, congruency effects will increase because the perceptual signal (e.g., the color red) is amplified within a hue-selective channel. This combination of synesthetic and print color will create larger congruency effects than are possible when the same hue-selective channel is stimulated by either print or synesthetic color alone. The color-priming data in Experiment 1 match this hypothesis: Priming from a combination of synesthetic and print color exceeds the effects from either form of color individually.

The schematic in Figure 7 also offers an explanation as to how it is possible for a synesthete to experience two colors in the same spatial location without blending. When
synesthetic and print colors are different, they are represented by different hue-selective cortical columns simultaneously, but can still be bound to a single location through mechanisms thought to play an important role in synesthetic and non-synesthetic binding (Robertson, 2003). For synesthetes, color arises through both wavelength and shape-based pathways, which may share the same spatial coordinates but do not converge at any stage early enough to blend into one single hue. It is, of course, possible that a distinct synesthetic hue system exists that coactivates with normal hue-selective channels to produce the redundancy gain reported here. However, this would seem a less parsimonious account, as it would require a completely separate hue-processing system.

Data from Experiment 2 confirm that our initial results (Exp. 1) cannot be accounted for by semantic priming effects alone (the letter or print color priming the response code “red”). Synesthetes still show congruency effects for all three prime conditions (p, s, and c) at 200 ms. At this prime duration, print color congruency effects are not significantly different in size to combo congruency effects and it is possible to interpret this to mean that print and synesthetic color pathways have not fully converged after a prime duration of 200 ms.

A unique finding of the present study is that synesthetic congruency effects correlate significantly with the self-reported vividness of visual imagery on the standardized vividness of visual imagery questionnaire (VVIQ scores). Synesthetes with more vivid visual imagery produced larger congruency effects in Experiment 1 for both conditions in which synesthesia was involved (s and c). In Experiment 2, the vividness of visual imagery correlated significantly only with the synesthetic (s) priming effect RTs. As can be seen in Tables 1 and 2, the congruency effect sizes remained constant for the synesthetic and combo conditions, whereas the print color congruency effect size decreased significantly in the 200-ms experiment, relative to the priming at 750 ms.

Print color priming has been shown to occur pre-attentively at very short durations (i.e., a 14.3-ms prime; Breitmeyer, Ro, & Singhal, 2004) whereas synesthetic color priming is attention-dependent (Mattingley, 2009) and requires the processing of a grapheme shape first (Brang et al., 2010). Thus, it is possible that print color contributed more than synesthetic color in the combo condition at 200 ms, leading to a lack of correlation between this condition (c) and imagery. Our findings show that, at 750 ms, print color effects had faded whereas synesthetic color effects remained, contributing more to the combo condition and likely leading to a positive correlation between combo and imagery.

Although researchers have previously suggested that visual imagery may be associated with synesthesia (Barnett & Newell, 2008; Ramachandran & Hubbard, 2001; Spiller & Jansari, 2008), the present results are the first to demonstrate a clear behavioral link. We cannot claim that synesthetic color is a form of mental imagery, or even that it acts through the same mechanisms of visual imagery, but the present results demonstrate a strong connection between visual imagery in general and the strength of the synesthetic color experience.
4. Global Differences in the White Matter Integrity of Grapheme-Color Synesthetes Correlates with the Vividness of Visual Imagery

4.1. Introduction

John Locke described the blending of senses that characterizes synesthesia in “An Essay Concerning Human Understanding” several centuries ago (Locke 1689). In the time since, synesthesia has come to encompass a growing number of experientially-defined phenomena in which one cognitive domain (e.g., sounds, graphemes, language, emotions, etc.,) triggers another domain automatically, consistently, and consciously. Grapheme-color synesthesia is one of the most closely studied and most common varieties, characterized by consistent and automatic experiences of color triggered when viewing or imagining graphemes (e.g., letters, numbers, etc.). Behavioral and brain-based research have led to a number of new understandings about synesthesia, although synesthesia is by definition a subjective experience and more work is needed to link discoveries about brain mechanisms of synesthetes to their own elusive subjective experiences. In this study we examined how the white matter microstructure of grapheme-color synesthetes differs from that of non-synesthetes: both categorically between the groups and in relation to a behavioral metric (visual imagery) not exclusive to synesthetic experience.

Brain-based models of grapheme-color synesthesia have commonly focused on the involvement of local cortical regions and networks such as visual area V4 in the origin of synesthetic color experience (Brang, et al 2010; Hubbard, Arman, Boynton & Ramachandran 2005). While local regions of visual cortex likely do play a role in synesthetic neurophysiology some studies have failed to confirm the role of V4 in grapheme-color synesthesia (Rouw & Scholte 2007; Rich et al 2006; Hupé, Bordier & Dojat 2012). Other neuroimaging studies (Rouw & Scholte 2007; Weiss & Fink 2009; Nunn et al 2002; Esterman, Verstynen, Ivry & Robertson 2006; Van Leeuwen, Petersson, & Hagoort, 2010; Sinke et al., 2012) have suggested a critical role of parietal and frontal regions in the integration and binding of the components of synesthetic percepts, and recent studies suggest the involvement of highly distributed cortical areas in the synesthetic representation (Hupé et al 2012; Dovern et al 2012; Hänggi, Wotruba & Jäncke 2011) particularly involving fronto-parietal networks. Prefrontal and parietal cortices have been linked with a multitude of behaviors, and are best described as association cortex, receiving inputs from all regions of the brain (Hagmann et al 2008). Seen in this context, is not surprising that synesthetes would demonstrate differences in these networks, because synesthetic perception combines information from multiple cognitive and perceptual domains.

The white matter connections between different brain regions can be analyzed with diffusion tensor imaging (DTI). Water diffuses preferentially along axons rather than perpendicular to them, particularly for myelinated axons in a coherent fiber tract (Beaulieu 2002; Assaf & Pasternak 2008). Diffusion-weighted MRI is sensitive to the direction of water movement and, after fitting this movement to a tensor model, several measures are commonly extracted. Fractional anisotropy (FA), a scaled ratio of the propensity of water to diffuse along axon bundles (parallel diffusivity, $\lambda_1$) versus across them (perpendicular diffusivity, $\lambda_2$), is a proxy measure of white matter microstructure (Basser 1995; Basser & Pierpaoli 1996). Mean diffusivity (MD) is the average of diffusion in all three orthogonal directions. We hypothesized

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that synesthetes would demonstrate globally distributed differences in these measures of water diffusion due to differences in their underlying white matter microstructure.

If grapheme-color synesthesia reflects widespread differences in distributed neural network architecture, it would be expected that synesthetes would show other differences in perceptual processing beyond their specific synesthetic experiences. Indeed, grapheme-color synesthetes show widely distributed increases in stimulus-evoked neural activity when tested via electroencephalography (EEG, Barnett et al. 2008; Volberg, Karmann, Birkner, & Greenlee, 2013; Jäncke & Langer, 2011) and fMRI (Hänggi et al. 2011; Hupé et al. 2012; Dovern et al., 2012), along with increased cross-modal interactions (vision and audition) in response to stimuli that do not induce synesthetic color (Brang, Williams, & Ramachandran 2012, but see Neufeld, Sinke, Zedler, Emrich, & Szycik, 2012 for a contrary finding). Relative to matched controls, grapheme-color synesthetes also show increased excitability in the primary visual cortex (Terhune et al. 2011), more accurate color discrimination (Yaro & Ward 2007), better memory (Yaro & Ward 2007; Smilek, Dixon, Cudahy & Merikle 2002), stronger visual imagery (Barnett & Newell 2008) and heightened creativity (Ward, Thompson-Lake, Ely & Kaminski 2008; Mulvenna, Hubbard, Ramachandran & Pollick 2003). With the possible exception of color discrimination, these factors do not rely specifically on color-selective area V4 or any other single neural locus implied specifically in synesthetic experience.

If specific and unimodal forms of synesthesia such as grapheme-color reflect a broadly distributed pattern of neural activity and anatomy, one might expect to find a correlative behavioral metric that is equally broad, while also being unique in some way to synesthesia. Rouw and Scholte (2007) offer a piece of critical evidence, showing that grapheme-color synesthetic experience can be matched with differences in white matter microstructure. In this study we pursued this finding further, asking whether proxy measures of white matter microstructure obtained using diffusion tensor imaging would correlate with the vividness of visual imagery (VVI, Marks 1973) which is typically enhanced in synesthetic subjects (Barnett and Newell 2008).

Visual imagery is the ability to “see in the mind’s eye” when there are no external stimuli present. Connections between synesthesia and imagery were proposed early on (Ramachandran & Hubbard 2001) and have been substantiated in synesthetes (Barnett & Newell 2008; Price 2009). Most synesthetes have vivid visual imagery. For example, grapheme-color synesthesia can be triggered simply by imagining a grapheme when a physical stimulus is not present (Elias, Saucier, Hardie & Sarty 2003; Jansari, Spiller & Redfern 2006; Spiller & Jansari 2006).

Here, we address the degree to which differences in white matter microstructure in grapheme-color synesthetes are categorically different to non-synesthete controls, and whether the differences correlate with a behavioral measure that is not unique to synesthesia per se. We first seek to replicate previous studies showing that synesthetes have more vivid visual imagery than closely-matched, non-synesthete controls. We then test whether synesthetes show differences in white matter microstructure compared with yoked controls as has been shown in the past (Rouw & Scholte 2007). Finally, we investigate the relationship between VVI and white matter microstructure in both the synesthetic and control populations to see how a cognitively
distributed behavior such as mental imagery (Mechelli, Price, Friston & Ishai 2004) correlates with global differences in neuroanatomy.

4.2. Methods

4.2.1. Participants

Twenty grapheme-color synesthetes and twenty non-synesthete controls participated in this study. All participants had normal or corrected to normal vision, no reported history of neurological or psychiatric disorder, and gave signed informed consent before entering the study as approved by the institutional review board of Veterans Affairs. Synesthesia was verified with the Online Synesthesia Battery (Eagleman et al 2007) and an in-person interview with an expert in synesthesia (BA). Only those who showed consistent and conscious experience of grapheme-color synesthesia and scored less than 1 on the Synesthesia Battery (M = 0.64, SD = 0.14, range of scores = 0.58 to 0.9) were considered eligible as synesthetic subjects, although several grapheme-color synesthetes also reported other forms of synesthesia. Non-synesthete controls also participated in the interview to assure that they experienced none of the various forms of synesthesia. Participants were paid $12 per hour for participation.

Synesthetes and controls were meticulously matched for sex, age, handedness, and years of education, all of which can influence neuroanatomy. All participants were between the ages of 19 and 35 (M = 25.8, SD = 4.1, 34 female) and between 14 and 24 years of education (M = 18.1, SD = 2.3). Each control was yoked to a synesthete of the same sex, handedness, age, and years of education.

4.2.2. Visual Imagery Assessment

All subjects completed the Vividness of Visual Imagery Questionnaire (Marks 1973). This questionnaire consists of 4 sets of 4 questions (16 in total), asking the participant to imagine specific scenarios relating to a topic, first with their eyes open and then with their eyes closed. The subjective report of the vividness of visual imagery is rated by the participant on a 5 point Likert scale where a score of 1 indicates the imagined image is “perfectly clear and as vivid as normal vision” and a score of 5 indicates “no image at all, you only ‘know’ that you are thinking of an object”. These scores were scaled to range between 0 and 1, with 1 representing the “best” visual imagery and 0 representing very poor visual imagery to allow the correlation analyses presented in the results section to be more easily understood. The test is undertaken twice: once with eyes open and again when eyes are closed. Since there was no significant difference between the scores for eyes open or eyes closed, the rest of our analyses focused on the average of each participant’s scores.

4.2.3. Diffusion Tensor Imaging Data Acquisition and Preprocessing

Brain imaging data were collected at the Veterans Affairs Clinic in Martinez, California on a 1.5 T Eclipse Phillips MR scanner using a 4-channel head coil with a maximum gradient strength of 40mT/m. Each participant underwent four sets of cardiac-gated DTI scans using echo-planar imaging (EPI; TR depends on the participant’s heart rate; TE = 115.6 ms; 3 mm3 isotropic voxels). Two non-diffusion-weighted image and 6 diffusion-weighted directions were
acquired per set, with a b-value of 1000 s/mm2. A T1-weighted image was also acquired in each participant for image registration (TR = 15ms; TE = 4.47 ms; voxel size 1.3 x 0.94 x 0.94 mm3). Analyses were performed using tools from FDT (for Functional MRI of the Brain (FMRIB) Diffusion Toolbox, part of FSL 4.1 (Smith et al 2004; Woolrich et al 2009). Brain volumes were skull stripped using the Brain Extraction Tool (Smith 2002) and a 12 parameter affine registration to the non-diffusion weighted volume was applied to correct for head motion and eddy current distortions introduced by the gradient coils. A diffusion tensor model was fitted to the data in a voxelwise fashion to generate whole-brain maps of the three orthogonal eigenvectors and eigenvalues, mean diffusivity (MD), and fractional anisotropy (FA). We refer to the largest eigenvalue ($\lambda_1$) as parallel diffusivity and the average of the two remaining eigenvalues as perpendicular diffusivity ($\lambda_{23^-}$).

A white matter mask was created from each participant’s high resolution T1-weighted scan, after brain extraction, using FAST (FMRIB’s Automated Segmentation Tool, Zhang, Brady & Smith) which segments the brain into grey matter, white matter, and cerebral spinal fluid. This mask was transformed into the participant’s DTI space by applying the inverse of the affine registration of the non-diffusion weighted volume to the high resolution image. Both the registration and calculations of the inverse transform used FLIRT (FMRIB’s Linear Image Registration Tool, Jenkinson, Bannister, Brady & Smith). This mask is an independent definition of white matter voxels in the FA map created from the DTI acquisition.

Finally, each of the participants’ FA maps were aligned into standard space using FNIRT (FMRIB’S Nonlinear Image Registration Tool, Andersson, Jenkinson & Smith). By applying the same transform, mean diffusivity, parallel and perpendicular diffusivity, and the white matter mask were also transformed into standard space.

4.2.4. DTI Analyses: Tract-based Spatial Statistics

We performed voxel-wise statistical analysis using TBSS (Tract-Based Spatial Statistics, Smith et al 2006). After FA maps were aligned to standard space, the mean FA image was generated and thinned to produce a mean FA skeleton that represented the centers of all tracts common to the group. Each subject's aligned FA, $\lambda_1$, $\lambda_{23}$, and MD data were then projected onto this skeleton by finding the nearest maximum FA value for the individual. This projection step aims to remove the effect of cross-subject spatial variability that remains after the non-linear registration. Voxel-wise cross-subject permutation-based nonparametric statistics were performed using randomize (Nichols & Holmes 2002) with 5000 permutations and threshold-free cluster enhancement to correct for multiple comparisons at $P < .05$ (Smith & Nichols 2009).

We conducted three specific statistical tests on each of the measures of white matter microstructure (FA, $\lambda_1$, $\lambda_{23}$ and MD) in turn. The first, a student’s T-test on the difference of means between synesthetes and controls. Secondly, a Pearson’s correlation between white matter microstructure and average VVI for the whole group, and for each group separately. Finally, we looked for regions in which the correlation between VVI and white matter microstructure was significantly different for synesthetes and controls, controlling for differences in mean white matter measures.
We also used a recently developed tensor metric to identify regions of crossing fibers (Douaud et al 2011): the mode of anisotropy (Ennis & Kindlmann 2006). Regions with a positive mode have linear anisotropy, and are likely to be part of a highly directional tract. In contrast, regions with a low or negative mode can be described as having planar anisotropy, and are more likely to contain crossing fibers. We extracted mode values from voxels that were significantly different between synesthetes and non-synesthete controls. Specifically, we extracted mode values from the voxel whose value was projected onto the TBSS skeleton using the non-linear warping described above. Histograms with a bin width of 0.02 were created using fslstats, an FSL tool (Smith 2002). We used a Mann-Whitney U-test to compare the distributions of mode values within these results for synesthetes and non-synesthete controls.

4.3. Results

4.3.1. Behavioral differences in visual imagery

All participants completed the Vividness of Visual Imagery Questionnaire (Marks 1973) by rating a series of questions about their own imagery. All scores were scaled between 0 and 1, where a score of 1 represents imagery as vivid as perception, and a score of 0 represents little to no mental imagery. As shown in Figure 8, we replicated previous findings that grapheme-color synesthetes have more vivid visual imagery than non-synesthetes (Student’s T(38) = 2.53, P < 0.05, two-tailed).

![Figure 8. Vividness of Visual Imagery Scores.](image)

Figure 8. Vividness of Visual Imagery Scores. Differences in vividness of visual imagery score between synesthetes and non-synesthetic matched controls. Synesthetes had significantly higher VVI scores than controls. The box is delimited by the 1st and 3rd quartiles of the data and split horizontally at the median point. Whiskers illustrate the highest and lowest data points that are within 1.5 times the interquartile range. The distribution of the data is shown in green via a kernel density estimate of the probability density function per data point.
4.3.2. Group differences in white matter microstructure

We investigated voxel-based measures of white matter microstructure throughout the brain for all participants using diffusion tensor imaging. We conducted student’s t tests to look for differences in mean value for four measures of white matter microstructure (FA, λ1, λ23 and MD). We found significant differences in FA and λ23 throughout the brain (Figure 9), with synesthetes having lower FA and higher λ23 than non-synesthete controls. No group differences were found in λ1 or MD, and no regions showed higher FA or lower λ23 for synesthetes when compared to non-synesthete controls. Table 4 lists the percentage of each white matter region of interest within the Johns Hopkins University (JHU) White Matter Label Atlas (Mori, Wakana, Van Zijl & Nagae-Poetscher 2005) that showed significant differences between synesthetes and controls.

To better characterize the anatomy of the white matter regions that were different between synesthetes and controls we investigated the mode of anisotropy, a recently developed tensor index (Ennis & Kindlmann 2006) that can be used to identify regions of crossing fibers. We extracted the mode from every voxel on the white matter skeleton that showed significant differences between synesthetes and controls for every subject and plotted their distributions (Figure 10). This method of investigating mode anisotropy has been successfully implemented in non-synesthetic human participants (Mackey, Whitaker, & Bunge 2012), and we apply it here for the first time to a synesthetic population. Synesthetes had a significantly lower median mode (Mann-Whitney U = 2.01 x 1011, df = 129816, P < .001, two tailed) when compared to non-synesthete controls.
Figure 10. Distribution of mode values. Distributions of mode values within voxels showing differences in white matter microstructure between controls and synesthetes. Synesthetes have a significantly lower median mode which is indicative of less coherent white matter tracts in these regions.

Table 4. Significant differences in white matter between synesthetes and controls. Regions of the JHU White Matter Label Atlas that show significant differences between synesthetes and non-synesthete control participants. The number of voxels in the white matter skeleton that fall in each label is listed along with the percentage of these voxels that show significant differences in FA, λ23, and both measures.
4.3.3. Correlations between visual imagery and white matter

We next conducted a Pearson’s correlation between VVI scores and DTI measures of white matter microstructure in order to investigate the individual differences in brain and behavior. As shown in Figure 11, we found a strong negative correlation between VVI and FA throughout the brain for all participants. This was accompanied by a strong positive correlation with \( \lambda_{23} \). The percentage of each white matter region of interest from the JHU atlas (Mori, Wakana, Van Zijl & Nagae-Poetscher 2005) that showed significant correlations between FA, \( \lambda_{23} \), or both, and VVI is tabulated in Table 5.

![Whole brain results](image)

*Figure 11. Whole brain results.* Whole brain results of TBSS analysis showing significant correlations between VVI and FA (negative, red) or \( \lambda_{23} \) (positive, orange) in all participants. Regions in which both results were significant are shown in purple. All analyses were performed on the white matter skeleton; results are filled for easier visualization.

Given the group differences in both brain (Figure 9) and behavior (Figure 8), we chose to investigate correlations in the two groups separately. We saw strong correlations between VVI and white matter structure in synesthetes (negative correlation with FA, positive correlation with \( \lambda_{23} \), Figure 12 and Table 5), concentrated in white matter projecting to association cortex. In contrast, we found no significant results in non-synesthete controls. In order to visualize the correlation, we extracted average FA from every voxel which showed a significant correlation with either FA or \( \lambda_{23} \) when synesthetes were examined alone (Figure 12), and for both synesthetes and controls. Figure 12B illustrates the negative correlation between FA and VVI for synesthetes used to define the ROI. Average FA from the same voxels in control participants showed no correlation (r\(^2\) = 0.004, P = 0.79, Figure 12B). Since it is difficult to interpret the lack of significant results in the control group, we tested the difference in correlations for synesthetes and non-synesthete controls. We found several regions for which the positive correlation between VVI and \( \lambda_{23} \) was stronger in synesthetes than controls: bilateral posterior corona radiata, left superior corona radiata, and the body of the corpus callosum (Figure 12). There were no regions that showed a significantly larger correlation in synesthetes than controls for FA.
Figure 12. Whole brain results and imagery scores. A) Whole brain results of TBSS analysis showing significant correlations between VVI and FA (negative, red) or $\lambda_{23}$ (positive, orange) in synesthetes alone. Regions in which both results were significant are shown in purple. Bright green tracts in the left and right corona radiata are those voxels for which the correlation in synesthetes is significantly larger than the correlation in non-synesthete controls. All analyses were performed on the white matter skeleton; results were filled for easier visualization. B) The correlation of average FA in all voxels of the white matter skeleton that show a significant relationship between FA and/or $\lambda_{23}$ for synesthetes is plotted for visualization purposes only. Shaded regions represent the upper and lower 95% confidence intervals of the regression line. Synesthetes (blue) and non-synesthete controls (yellow) are plotted separately.
4.4. Discussion

This study is the first to provide evidence that grapheme-color synesthetes show a correlation between globally distributed differences in white matter microstructure and the vividness of visual imagery. Synesthetes show significantly lower FA throughout white matter and statistically higher scores on the test of the vividness of visual imagery. These lower global FA and higher average VVI scores are corroborated by a significant negative correlation unique to synesthetes between FA and VVI: synesthetes with the lowest FA have the most vivid visual imagery.

Reports of neuroanatomical differences in grapheme-color synesthetes are increasingly common (Rouw & Scholte 2007; Hupé et al 2012; Dovern et al 2012; Hänggi, Wotruba &

Our study is the first to investigate the mode of anisotropy in synesthetes which describes the type of anisotropy: linear or planar. Water diffusion through crossing fibers will typically result in planar anisotropy, which is represented by more negative mode values. In contrast, diffusion in a single direction (e.g., along a non-decussated fiber bundle) will result in linear anisotropy, represented by more positive mode values. We show that the regions with lower FA and higher \( \lambda_{23} \) also have lower mode values in synesthetes compared to controls. Douaud and colleagues (2011) have shown higher FA and mode values in older adults with mild cognitive impairment (MCI) compared to age-matched controls in the centrum semiovale which contains crossing fiber tracts. They suggest that as one tract deteriorates, the mode and FA increase because white matter coherence in the remaining tract is more clearly revealed. This leads us to interpret the differences between synesthetes and non-synesthete controls as due to less coherent white matter structure throughout the brain rather than reduced myelination. The axons in the synesthetes’ brains are going in different directions, and connecting more disparate regions of cortex.

The results presented in the current study further validate findings showing widely distributed differences in white matter microstructure throughout the brain. It is of particular note that the regions in which we see the strongest correlation between white matter microstructure and VVI (Figure 12) are tracts near association cortex, the axons from which, by definition, project to and from many different cortical targets. Parietal cortex in particular is ubiquitous to both synesthetic neuroanatomical findings and associative processing in general due to its role as a hub of cortical and subcortical interconnectivity in the human brain (Hagmann et al 2008). It is possible that grapheme-color synesthesia represents differences in parietal function (Specht & Laeng 2011). Given the widespread connectivity of the parietal lobe, which is thought to play a role in binding synesthetic color in synesthetes (Esterman et al 2006; Robertson 2003), and the fact that grapheme-color synesthetes show some advantage beyond their synesthetic modalities alone, we looked beyond synesthetic experience to examine relationships between behavioral and neuroanatomical differences in this population. Grapheme-color synesthetes in the present study have more vivid visual imagery than matched controls, replicating a similar result reported by Barnett and Newell (2008). As seen in Figure 12, synesthetes show significant correlations with FA and \( \lambda_{23} \) and visual imagery through fronto-parietal networks, but not within early visual regions. As visual imagery becomes more vivid for synesthetes, white matter microstructure in fronto-parietal networks decreases, becoming less like the non-synesthete control group. Individual differences that are not present in white matter near early visual cortex become apparent in tracts connecting association cortices.

It is important to note that our interpretations of the relationships between our participants’ neuroanatomy and their vividness of visual imagery or synesthetic experience are based on estimates from the diffusion tensor imaging: an inexact, proxy measure of brain structure. We have interpreted differences in FA, \( \lambda_{23} \) and mode of anisotropy as differences in the connections
between regions but this cannot be proven using diffusion weighted MRI of living humans. There are multiple biological factors that affect water diffusion, including but not limited to: fiber diameter, fiber density, membrane permeability, and myelination (Beaulieu, 2002). At this level of resolution it is not possible to differentiate between these possibilities, although alternative imaging techniques such as magnetization transfer contrast (Wolff & Balaban, 1989), and myelin water quantification (MacKay et al, 1994), have been proposed to further elucidate white matter structure. We hope that future studies of synesthesia, a perceptual phenomenon that cannot be investigated in animal models, build on the work presented here in order to clarify our inferences of the relationships between diffusion tensor measures, synesthetic experience and VVI.

Further studies are also needed to investigate the role of strategy differences for grapheme-color synesthetes on the relationship between white matter microstructure and VVI. It is possible that the negative correlation between FA and VVI observed here may be generated by the utilization of a different strategy for grapheme-color synesthetes. Synesthetes with vivid imagery/lower FA may rely on increasingly visual-based imagery, whereas synesthetes that follow a pattern more similar to controls may show a more typical memory-based imagery. Additionally, synesthetes in this study have more vivid imagery and it is possible that this group difference in imagery accounts for the differences in white matter microstructure. Another study, which recruited and compared a control group who matched the synesthetes in their vividness of visual imagery, would elucidate the unique contribution of high VVI on the correlation we have observed only in the synesthetes in this study.
5. General Conclusions

The purpose of the research discussed within this proposal is to advance our understanding of the brain-based and behavioral mechanisms of synesthesia, with a particular emphasis on the mechanisms of perceptual binding and the relationship to another internally generated experience: in this case, the vividness of visual imagery.

Chapter 2 discussed perceptual binding and how it may relate to the binding of synesthetic percepts. Previous models of synesthetic binding were discussed with special consideration to the model originally proposed by Robertson (2003) introducing perceptual binding of synesthetic color for grapheme-color synesthetes as a potential explanation. Chapter 2 of this dissertation set the groundwork for discussion of unusual cases in which synesthetic and print colors appear to be in the same place simultaneously, as was later investigated experimentally in Chapter 3. It is thought that if synesthetic color is in fact bound to shape like print color, it may occur through the same attention-dependent integration of feature maps that occurs in other forms of binding, making synesthesia an excellent model for understanding binding in the healthy human brain.

The findings of Chapter 3 may explain the paradoxical phenomenon in which a grapheme–color synesthete reports experiencing two colors bound to the same spatial location simultaneously without blending. Our hypothesis is that the same cortical region selective to hue is able to support print-based and synesthetic color representations simultaneously, allowing for both color percepts to emerge when they are incongruent. When the synesthetic and print colors trigger the same color experience (e.g., letter “A” printed in red, which triggers the same red synesthetically), this results in an amplified color signal and faster response times to a probe that matches such a doubly congruent prime. Future studies are clearly needed to assess the cortical networks involved in the competition and combination of synesthetic and print color. The present results further suggest that the synesthetic pathways are strongly linked to visual imagery. Additional studies may also address whether specific elements of the VVIQ (e.g., color imagery) are especially strong predictors of synesthetic effects and whether VVIQ correlates with the perceived vividness of synesthetic colors in grapheme–color and other types of synesthesia.

In Chapter 4, we demonstrated that grapheme-color synesthetes show significant decreases in white matter microstructure throughout much of the brain along with more vivid self-reported visual imagery, compared to a control group of non-synesthetes. Reported decreases in fractional anisotropy (FA) are likely due to a higher degree of crossing fibers in synesthetes. Synesthetes with the lowest white matter microstructure (FA) had the most vivid visual imagery.

The relationship between visual imagery and synesthesia may be the most novel finding of the studies discussed in this thesis, and perhaps the timeliest contribution to the literature. Synesthetic experience has been validated as an automatic and consistent perceptual phenomenon. However, as it has been discussed, synesthetic experiences are also not entirely like perception, nor are they really a form of explicitly formed mental imagery. As shown here for the first time, vividness of visual imagery correlates with behavioral measures that are specific to synesthesia (synesthetic priming, Chapter 3) and differences across the entire brain (Chapter 4). In some ways, synesthesia seems to be a very specific phenomenon considering that most forms of synesthesia are only shared by 1-2 percent or less of the human population. It has
been studied and defined mainly by identifying particular phenomenological differences of human experience that are unique, labeling these differences as “synesthetic”, and then using findings of significant differences in behavior and the brain within the synesthetic population to further define and categorize what synesthesia is. This means of selecting and defining synesthesia is clearly circular to the synesthete researcher, and hopefully to everyone else as well. A synesthete is someone who is defined as a synesthete. And synesthesia as it is defined by scientists is any blend of perceptual states or cognitive experiences that are unique or unusual, consistent, and automatic. What is synesthesia really? I do not know for sure, but I have contemplated this question, guided by my observation and participation in creating the definition of “synesthesia” alongside fellow synesthesia researchers, and as a synesthete myself. Here is the most accurate explanation and experience of what synesthesia is that I can give currently; synesthesia is a distinction within the domain of human perception.

Based on the findings from the literature and within this thesis, I suggest that synesthesia is a “real” phenomenon in the way it has been defined. In other words, synesthetic experiences are really experienced perceptually and they are not fantasy, memory reconstructions, etc. However, I suggest an additional or even alternative way to define what synesthesia is that is not based solely on the circular approach of identifying unique percepts of sensory or cognitive blendings. Synesthetes, appear to be unique in their general behavior with regard to visual imagery. This may extend to any form of imagery that relates to the forms of synesthesia experienced by the synesthete (e.g., taste imagery for a sound-taste or taste-shape synesthete, spatial imagery for a spatial sequence synesthete, etc). Likewise, synesthetes show unusual differences in globally distributed neuroanatomy (Chapter 4) and neurophysiology (e.g., Barnett et al 2008; Hänggi et al 2011). Synesthetic experiences are the result of a difference in “hard- and soft-wired” brain organization throughout the brain. In my opinion, a synesthete is someone whose brain has developed a pattern of globally increased arborization, most consistently in the parietal cortex and other associative regions (e.g., frontal cortex, thalamus), and who may exhibit phenomenological experiences that coincide with such a pattern of exuberant brain development. In other words, a synesthete by the common usage of the word, should be someone who shows both a pattern of unusually exuberant white matter connectivity and amplified neurophysiology throughout much of the brain, and at least one unique, automatic and consistent form of perceptual blending.

However, I wonder what of those humans who may show all of the differences in neuroanatomy and neurophysiology but do not show any phenomenological signs of classic synesthesia. In terms of modern science, if an individual has significantly different neuroanatomy and neurophysiology, they will also experience and/or interact with their world in a unique way consistent with the differences in the brain. It is possible that while such a person may not consciously experience a specific form of perceptual blending, they do show general behavioral characteristics common to synesthetes such as more vivid mental imagery, improved modally specific memory, enhanced creativity, more sensitive sensory perception, etc. Understanding the mechanisms of classic synesthesia (e.g., grapheme-color) may guide us in better understanding the perceptual systems involved in representing synesthetic phenomenology, and this is one boon of discovering what synesthesia is. Likewise, further research on the uniqueness of synesthetes may help us to discover the systemic patterns of brain wiring and development that result in a slightly more creative, imaginative, perceptive, cross-
wired and yet cognitively normal and healthy mind and brain, including synesthetes and those that do no experience such a distinction.

Synesthesia research has blossomed tremendously in the past 25 years, beginning with a few studies that rekindled a lost interest dating back over 100 years, and progressing into the field as it stands today on its own two feet. Scientists researching a number of different fields have aligned to the pursuit of understanding synesthetic phenomena and mechanisms that have begun to inform a wide range of topics within and beyond cognitive psychology and neuroscience. Indeed, synesthetes are cognitively normal adults and children who experience a reliably testable perceptual experience that can be selectively compared and contrasted to the minds and brains of other healthy individuals who are matched in seemingly every way except this one uniqueness. The development and phenomenology of synesthetic experience has thus informed language processing, brain development, cortical organization, perceptual binding, the interaction of internally and perceptually triggered experiences, multimodal sensory integration, genetic linkage to psychological experience, memory, creativity, studies of art and aesthetics, empathy, and mental illness. Synesthesia is also a curiosity in its own right to many scientists and non-scientists. The research in this thesis presents novel discoveries that synesthetic behavioral and neuroanatomical differences correlate with a standard metric of visual imagery that is common to the general population. A new model of perceptual binding of synesthetic color is proposed that can account for the paradox of synesthetic perception – seeing two colors bound to a single spatial location. Finally, it is shown that synesthetes may not simply lie on one end of a spectrum of phenomenological and neuroanatomical differences. Rather, this population of individuals may be categorically different than the general population in the relationship between cortical organization and behavioral performance.
6. References


