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The cross-activation theory at 10

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In 2001, Ramachandran and Hubbard introduced the cross-activation model of grapheme-colour synaesthesia. On the occasion of its 10-year anniversary, we review the evidence from experiments that have been conducted to test the model to assess how it has fared. We examine data from behavioural, functional magnetic resonance imaging (fMRI), anatomical studies (diffusion tensor imaging and voxel-based morphometry), and electroencephalography (EEG) and magnetoencephalography (MEG) studies of grapheme-colour synaesthesia. Although much of this evidence has supported the basic cross-activation hypothesis, our growing knowledge of the neural basis of synaesthesia, grapheme, and colour processing has necessitated two specific updates and modifications to the basic model: (1) our original model assumed that binding and parietal cortex functions were normal in synaesthesia; we now recognize that parietal cortex plays a key role in synaesthetic binding, as part of a two-stage model. (2) Based on MEG data we have recently collected demonstrating that synaesthetic responses begin within 140 ms of stimulus presentation, and an updated understanding of the neural mechanisms of reading as hierarchical feature extraction, we present a revised and updated version of the cross-activation model, the cascaded cross-tuning model. We then summarize data demonstrating that the cross-activation model may be extended to account for other forms of synaesthesia and discuss open questions about how learning, development, and cortical plasticity interact with genetic factors to lead to the full range of synaesthetic experiences. Finally, we outline a number of future directions needed to further test the cross-activation theory and to compare it with alternative theories.

In 2001, Ramachandran and Hubbard (2001a, 2001b) introduced the cross-activation model of grapheme-colour synaesthesia. Now, 10 years later, we take a look back at a number of experiments that have been conducted to test the model and assess how it has fared. We begin with a very brief history of synaesthesia research and review the state of knowledge in the late 1990s and early 2000s when we began this line of research in order to situate the cross-activation model relative to other models. We then briefly

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summarize some of the behavioural observations that we and others have made, which led us to propose the cross-activation model. We then review the model in detail and turn towards experimental tests using numerous converging neuroimaging methods that have been conducted in the past 10 years. Finally, we suggest updates to our original cross-activation theory that reflect changes in our understanding of the cortical basis of reading and discuss the interactions between genes and experience that lead to the full-blown synaesthesia phenotype.

A brief history

Although interest in various forms of synaesthesia – including coloured hearing – dates back to antiquity, synaesthesia research experienced its first wave of interest in the late 1800s and early 1900s. The first recognized medical description of synaesthesia dates to Georg Tobias Sachs in 1812 (Jewanski, Day, & Ward, 2009), but because it appeared in an unpublished doctoral thesis, made little impact on the field. In the early 1880s, Francis Galton published a number of studies of what we now refer to as grapheme-colour synaesthesia and number-form synaesthesia (Galton, 1880a, 1880b, 1883/1997), which led to a wave of interest surrounding the phenomenon.

In this initial movement, a variety of theories regarding the origins of synaesthesia were proposed; but given the limited knowledge of brain organization at the time, they often did not go beyond speculations and vague ideas of crosstalk. As early as 1893, Theodore Flournoy (1893) wrote dismissively of others who proposed models of synaesthesia based on 'the proximity or cycling of cortical centers that permits excitation to radiate from one to the other, the existence of exceptional forms of anastamoses linking nerve fibers or cells that are ordinarily separated, and so on'. (p. 18, translation by EMH). Interest in synaesthesia waned in the 1920s, for a variety of reasons (see Marks, 1975) and little new research was conducted until the mid-1970s.

In the wake of the cognitive revolution, which generated a renewed focus on internal states and the study of consciousness, scientists began to once again examine this fascinating phenomenon. Led by Lawrence E. Marks (1975) and Richard Cytowic (1989/2002) in the United States, and Baron-Cohen and Harrison (1997) in England, research into synaesthesia began by exploring the reality, consistency, and frequency of synaesthetic experiences. However, these early studies were primarily descriptive, rather than experimental, and did not include measures designed to test the perceptual reality of these unusual synaesthetic experiences. Consequently, they kindled little interest in the broader scientific community.

Indeed, even when Wollen and Ruggerio (1983) conducted a synaesthetic version of the Stroop interference paradigm with a single synaesthete, another 17 years passed before scientists once again addressed the topic of synaesthesia using Stroop paradigms (Dixon, Smilek, Cudahy, & Merikle, 2000; Mattingley, Rich, Yelland, & Bradshaw, 2001). These tests provided the first empirically motivated study of the phenomenon and demonstrated that synaesthesia was automatic and genuine. However, as Stroop interference can occur at any stage of processing (MacLeod, 1991), these results only demonstrated the presence of authentic associations in synaesthesia, not that it is a perceptual phenomenon. Indeed, as even non-synaesthetes trained on grapheme-colour correspondences show Stroop interference (Brang & Ramachandran, 2011; Meier & Rothen, 2009), Stroop by itself cannot distinguish between learned associations and actual synaesthetic experiences.

Behavioural studies (is it real?)

Against this backdrop, we began our research into grapheme-colour synaesthesia with the initial goal of demonstrating that it was a real, perceptual phenomenon, and attempting to identify the stages of processing at which it occurs. Our initial experiments built on the basic idea that, if synaesthesia were a perceptual phenomenon, it should affect behaviour even at early perceptual levels of processing, in addition to demonstrating Stroop-like interference. We devised a series of experiments in which synaesthetes would be expected to perform better than non-synaesthetes and demonstrated that grapheme-colour synaesthesia could lead to perceptual enhancement (Ramachandran & Hubbard, 2001a). These early results clearly demonstrated the perceptual reality of synaesthesia and were essential to establish that synaesthesia could be studied using psychophysical methods (see also Palmeri, Blake, Marois, Flanery, & Whetsell, 2002; Smilek, Dixon, Cudahy, & Merikle, 2001). These early papers helped trigger the explosion of interest in synaesthesia, as demonstrated by the numerous books and dozens of papers published since (e.g., see Cytowic & Eagleman, 2009).

Although some have contended that these results simply reflect greater motivation on the part of synaesthetes compared with non-synaesthetes (Gheri, Chopping, & Morgan, 2008), the overall patterns of improved (Palmeri *et al.*, 2002; Ramachandran & Hubbard, 2001a), impaired (Smilek *et al.*, 2001), and unaffected (Hong & Blake, 2008) performance are consistent with synaesthesia being elicited at intermediate levels of visual processing. Furthermore, perceptual enhancement has been independently replicated by other groups (Ward, Jonas, Dienes, & Seth, 2010), although the degree to which attention is critical for synaesthesia is still debated (Mattingley, Payne, & Rich, 2006; Sagiv, Heer, & Robertson, 2006).

The cross-activation theory

Building on these behavioural observations, we began to search for a possible neural basis for grapheme-colour synaesthesia and were struck by the fact that brain regions involved in letter and number processing (the 'grapheme area' or the 'visual word form area'; VWFA) lie adjacent to the V4 colour processing area (Ramachandran & Hubbard, 2001a, 2001b). Given that synaesthesia was known to run in families (Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Galton, 1883), we suggested that a genetic factor could lead to a failure of pruning, such that adjacent brain regions in the fusiform gyrus remain connected, even in adults, leading to 'cross-activation' between these regions in much the same way as had already been observed in phantom limb patients (Hubbard & Ramachandran, 2003; Ramachandran & Hubbard, 2001b). Although this theory shares certain key aspects with the neonatal synaesthesia theory, which suggests that everyone is born a synaesthete (Maurer, 1997) and the breakdown in modularity theory (Baron-Cohen, 1996; Baron-Cohen, Harrison, Goldstein, & Wyke, 1993), our original proposal went beyond these general notions of hyperconnectivity to suggest specific brain regions as the locus for a specific form of synaesthesia. Given that previous models were less precisely specified, our model was the first testable anatomical hypothesis for the neural basis of grapheme-colour synaesthesia. The cross-activation model makes three specific predictions: (1) the neural representations of the inducer and concurrent should lie in densely interconnected regions. These regions will often be adjacent to each other, but need not be; (2) genetic factors lead to a decrease in pruning, and such anatomical differences are responsible for synaesthetic experiences; and (3) activation passes directly from neurons that code for the inducer to neurons that code for the concurrent.

Comparison with other models

In addition to the cross-activation theory (see Figure 1A), two other main classes of model have been proposed to explain synaesthetic experiences: the disinhibited feedback model and the re-entrant processing model (for a thorough review of these issues, see Hubbard & Ramachandran, 2005). The disinhibited feedback theory (Figure 1C) suggests that synaesthesia may be due to disinhibited feedback from a 'multisensory nexus' such as the temporo-parietal-occipital junction and that synaesthetic concurrents arise because of disinhibited feedback from higher level visual areas in pathways common to synaesthetes and non-synaesthetes alike (Grossenbacher & Lovelace, 2001). Below, we discuss evidence from electroencephalography (EEG) and magnetoencephalography (MEG) studies that is inconsistent with the disinhibited feedback theory, or at the very least, the long-range version proposed by Grossenbacher and Lovelace.

The re-entrant processing model (Figure 1B) posits crosstalk between form and colour processing areas in the fusiform (as in the cross-activation model), but, as in the disinhibited feedback model, it also suggests that elicitation of synaesthetic colours requires neural activity from higher level areas in the temporal lobe (e.g., the anterior inferior temporal lobe) to feedback to V4 (Smilek *et al.*, 2001). One of the primary observations taken as evidence for the re-entrant theory is that synaesthetic colours are modulated by top-down categorization and context. Synaesthetes report that their colours alternate when they are presented with hierarchical stimuli depending on whether they focus on the global or local elements, and categorization of ambiguous graphemes (e.g., the H/A grapheme in the classic THE CAT demonstration) affects the experienced colours (Ramachandran & Hubbard, 2001b). Both the top-down modulation (Rich & Mattingley, 2003) and context effects (Dixon, Smilek, Duffy, Zanna, & Merikle, 2006; Myles, Dixon, Smilek, & Merikle, 2003) were subsequently confirmed by others using more rigorous experimental methods.

Top-down influences are not inconsistent with the cross-activation theory, as we would expect that the same top-down biasing mechanisms that are present in non-synaesthetes are also present in synaesthetes (for a more detailed discussion, see Hubbard

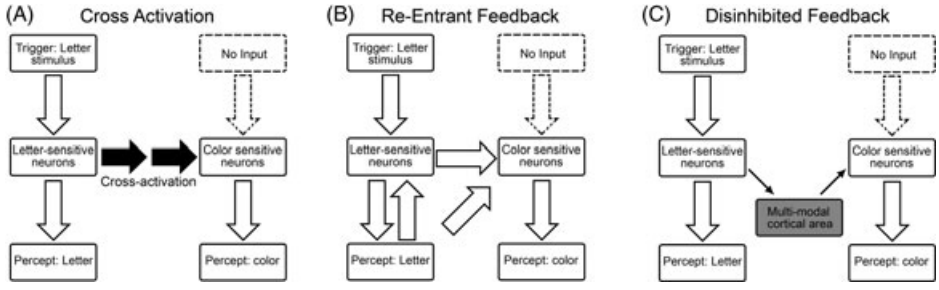

Figure 1. The main classes of neurophysiological theories of synaesthesia. Arrows indicate the flow of information, and boxes processing stages/areas. Solid lines indicate active regions and pathways, while dotted lines indicate non-active regions and pathways. (A) The cross-activation model. Letter input leads to cross-activation of colour areas (black arrows), which then leads to both the percept of letters and colours. (B) The re-entrant feedback model. Feedback from higher order conceptual areas involved in the conscious percept of the letter feeds back both to physical form areas and to colour areas, leading to the percept of a colour. (C) The disinhibited feedback model. Information propagates up from letter processing to a multi-modal cortical area (grey box) before feeding back to colour selective areas. Adapted from Mulvenna and Walsh, 2006.

& Ramachandran, 2005). Even in non-synaesthetes, top-down influences and context modify how stimuli are categorized. The key difference between the cross-activation and re-entrant feedback models is whether context plays an essential role in the genesis of synaesthesia, or whether it merely influences how ambiguous graphemes are categorized as in non-synaesthetes (McClelland & Rumelhart, 1981), leading to different populations of grapheme-selective neurons cross-activating different populations of colour-selective neurons. The same neural mechanisms that lead to top-down effects in non-synaesthetes will also alter grapheme categorization in synaesthetes, and this altered categorization will elicit different colour experiences, even without postulating additional anomalous feedback in synaesthetes.

From genotype to phenotype

Francis Galton (1883/1997) first noted that synaesthesia 'runs in families', an observation that has been confirmed multiple times in the modern literature (Bailey & Johnson, 1997; Barnett *et al.*, 2007; Baron-Cohen *et al.*, 1996; Simner *et al.*, 2006). We thus proposed that the anatomical specificity seen in synaesthesia could arise from the selective expression of synaesthesia genes through transcription factors in specific brain regions, which leads to three corollaries (Ramachandran & Hubbard, 2001b, p. 11). First, the genes for synaesthesia might be expressed in different brain regions, which could explain not only grapheme-colour synaesthesia, but also other forms of synaesthesia as well. Second, if this gene expression were to occur at multiple locations in the brain, it would explain why people who experience one type of synaesthesia are more likely to experience another form of synaesthesia, and third, it would explain why different forms of synaesthesia are present within the same family.

These predictions have been subsequently confirmed in a number of family studies. In one such study, eight of 22 synaesthetes reported multiple forms of synaesthesia (Simner *et al.*, 2006), while another study showed that grapheme-colour synaesthetes, but not lexical-gustatory synaesthetes, were more likely than non-synaesthetes to experience number forms (Sagiv, Simner, Collins, Butterworth, & Ward, 2006). Consistent with our suggestion of broad genetic expression, the types of synaesthesia reported within the same family can vary considerably (Ward & Simner, 2005). Baron-Cohen *et al.* (1996) reported that two of the families they tested included both grapheme- and music-colour synaesthesia. Similarly, lexical-gustatory synaesthetes often report family members who do not experience synaesthetic tastes, but who do experience synaesthetic colours (Ward, Simner, & Auyeung, 2005).

Based on early observations that a much larger number of women reported synaesthesia (between three and eight times more women than men) and the fact that no confirmed cases of father-to-son transmission were found (Baron-Cohen *et al.*, 1996), it was originally proposed that synaesthesia might be transmitted along the X-chromosome, perhaps even with lethality in males (Bailey & Johnson, 1997). However, as these studies relied on self-reported synaesthesia, we cannot rule out a reporting bias, and other studies that used random sampling demonstrated a female:male ratio of just greater than 1:1 (Simner *et al.*, 2006; Ward & Simner, 2005) contrary to the X-linked hypothesis. In addition, there are confirmed cases of identical twins who were discordant for grapheme-colour synaesthesia (Smilek, Dixon, & Merikle, 2005; Smilek *et al.*, 2002), although the authors did not test for other forms of synaesthesia, so it is unclear whether these twins simply had different *types* of synaesthesia or whether only one twin experienced any form of synaesthesia.

More recent genetic studies have therefore explored the possibility that synaesthesia arises through autosomal dominant (with incomplete penetrance) mechanisms. To date, only two genome-wide association studies of synaesthesia have been conducted. Asher *et al.* (2009) focused on 43 families with multiple members who experienced music-colour synaesthesia. Crucially, this study did not find any evidence of a genetic factor on the X-chromosome, and identified two confirmed cases of father-to-son transmission, which effectively rules out a purely X-linked hypothesis. Instead, Asher *et al.* found possible loci in four different locations, 2q24, 5q33, 6p12, and 12p12. These loci have generally been associated with genes involved in brain development, including genes that are known to be implicated in neuronal migration and pruning, sodium channel function, and NMDA receptor function. More recently, Tomson *et al.* (2011) studied five multiplex families with 'colored sequence synaesthesia' (CSS) in which numbers, letters, and other sequences are associated with colours. Based on their analysis, they identified a 23 Mb region on the long arm of chromosome 16 (16q12.2–23.1) that was present in two of the families, but not in the other three families, which the authors argue suggests that CSS may arise through diverse genetic mechanisms. Given the diversity of genes identified in these two studies, and the variety of roles they play, it is too early to use genetic data as evidence for or against any of the theories of synaesthesia.

Finally, in our 2001 paper, we also suggested why the gene is so prevalent and has not been weeded out through natural selection: more diffuse expression of the gene causes diffuse hyperconnectivity, which may confer a slight advantage in terms of creativity (Ramachandran & Hubbard, 2001b). For example, we suggested that the gene may confer a propensity for metaphor and that synaesthesia may be more common in artists and other creative professions (Dailey, Martindale, & Borkum, 1997; Domino, 1989; Rich, Bradshaw, & Mattingley, 2005) because of the patchy hyperconnectivity (but see Ward, Thompson-Lake, Ely, & Kaminski, 2008). If so, then the gene for synaesthesia would be mildly selected for, rather than against.

Functional neuroimaging data

One of the first direct tests of the predictions of the cross-activation theory came from functional neuroimaging studies (for reviews, see Hubbard, 2007a; Hubbard & Ramachandran, 2005; Rouw, Scholte, & Colizoli, 2011, in this issue). Based on the cross-activation model, we predicted that viewing of black graphemes on a white background would lead to greater activity in colour selective region V4. To test this theory, we conducted an fMRI experiment on six synaesthetes and six non-synaesthetes in which we compared neural activation for graphemes against non-grapheme stimuli matched for visual complexity (Hubbard, Arman, Ramachandran, & Boynton, 2005). Colour and grapheme regions of interest (ROIs) were defined *a priori* in a separate scan for each participant. We found greater modulation of V4 activity for graphemes versus non-graphemic stimuli in synaesthetes than in non-synaesthetes consistent with the predictions of the cross-activation theory (Figure 2A and 2B). Importantly, we did not observe differences in the responses to colours in the brains of synaesthetes compared with non-synaesthetes and did not observe differences in the response to graphemes outside of V4, arguing against generalized differences in the synaesthetes. Interestingly, we also found that performance on an independent perceptual task in which synaesthetic colours conferred a behavioural advantage correlated with V4 activation in the synaesthetes (Figure 2C), supporting the idea of a direct relationship between neural activity and perceptual experience (Hubbard, Arman, *et al.*, 2005). This

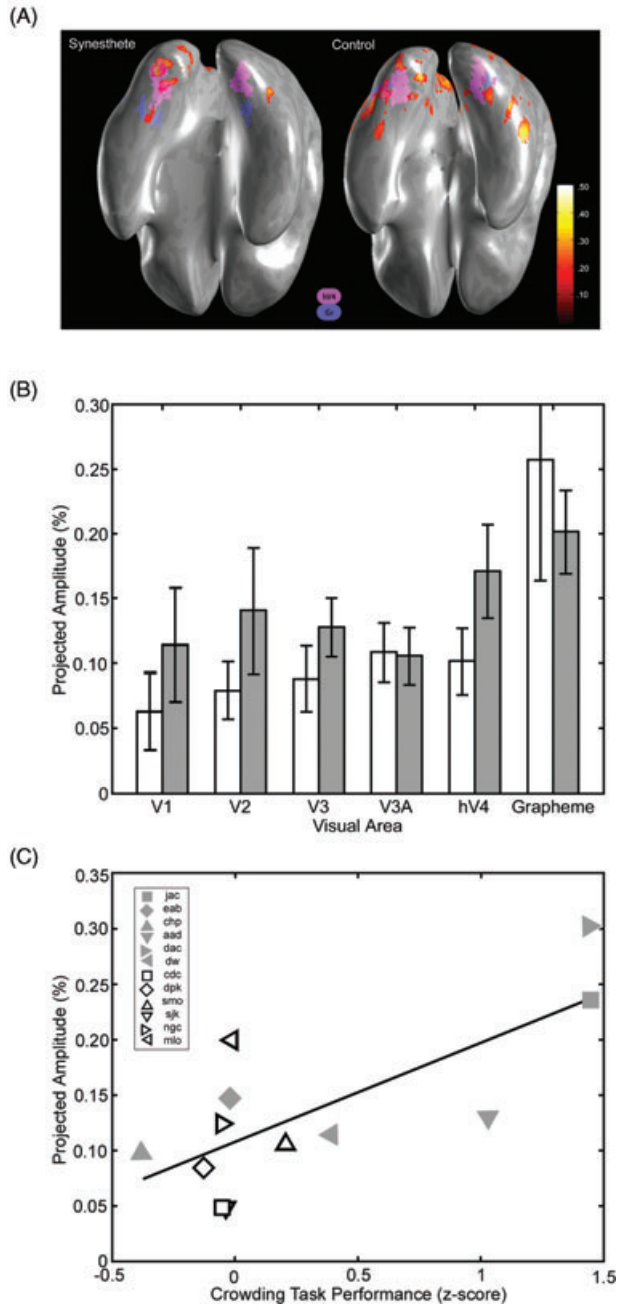

Figure 2. (A) Activation during grapheme viewing from a representative synaesthete and control subject. Retinotopic region V4 is indicated in pink and grapheme responsive areas are indicated in blue. (B) Average projected amplitude for synaesthetes and controls across early visual areas, showing significantly greater activation in synaesthetes than in controls in area V4. (C) Correlation between activation in V4 during grapheme viewing and performance enhancement on an independent perceptual task. Data reprinted from Hubbard, Arman, *et al.*, 2005 courtesy of Cell Press.

pattern of results has important implications for our understanding of the variability observed in behavioural studies (Dixon & Smilek, 2005).

A number of subsequent neuroimaging studies of grapheme-colour synaesthesia have also found increased activation in the region of V4 (Laeng, Hugdahl, & Specht, 2011; Rouw & Scholte, 2007; Specht & Laeng, 2011, in this issue; Sperling, Prvulovic, Linden, Singer, & Stirn, 2006; Steven, Hansen, & Blakemore, 2006; van Leeuwen, Petersson, & Hagoort, 2010; Weiss, Zilles, & Fink, 2005) (but see Rich *et al.*, 2006), which generally supports the cross-activation theory (for reviews, see Hubbard, 2007a; Hubbard & Ramachandran, 2005; Rouw *et al.*, 2011, in this issue). However, this is a weak test of the cross-activation theory. If activation differences had been found only in regions far outside the classical colour areas (e.g., in the hippocampus, see Gray *et al.*, 2006), this would have served to disconfirm the cross-activation model. Conversely, finding activation in these regions could be accounted for equally well by all three models. In particular, the lack of temporal resolution in fMRI makes it difficult to conclusively rule in favour of the cross-activation theory and against alternative theories such as the long-range feedback model (Grossenbacher & Lovelace, 2001) or the re-entrant feedback model (Smilek *et al.*, 2001).

Finally, although the model was not explicitly developed to account for additional aspects of synaesthetic experience, like the experience of textured colours (Eagleman & Goodale, 2009), they fit into the cross-activation model easily as V4 neurons code not only for colour but also for texture. This ability to account for new observations that were not part of the original motivation for proposing the cross-activation model lends additional support to our hypothesis.

Diffusion tensor imaging (DTI) and voxel-based morphometry (VBM)

Another source of evidence in favour of the cross-activation model comes from anatomical measures, such as DTI (Rouw & Scholte, 2007) and VBM (Jäncke, Beeli, Eulig, & Hanggi, 2009; Weiss & Fink, 2009). As the cross-activation theory suggests that there is decreased pruning in the fusiform gyrus, we would predict corresponding anatomical differences in this region. Consistent, repeated failures to find such anatomical differences would argue against the cross-activation model, while finding such anatomical differences is evidence against the strong versions of the disinhibited feedback theory that proposes only neural communication differences between synaesthetes and non-synaesthetes.

In an important study, Rouw and Scholte (2007) directly tested this prediction. They measured fMRI responses and fractional anisotropy (FA) using DTI in a group of 18 grapheme-colour synaesthetes. Their functional imaging data were consistent with previous studies, showing increased activation in the right fusiform gyrus in synaesthetes compared with controls. In addition, the authors found increased FA in the synaesthetes relative to the controls in three brain regions, right inferior temporal cortex and left frontal and parietal cortex (Figure 3A). No brain region showed greater FA in the controls than in the synaesthetes. In addition, Rouw and Scholte measured the subjective location of the synaesthetic experience (projector-associator distinction Dixon, Smilek, & Merikle, 2004) and found that FA in the fusiform gyrus correlated with the nature of the synaesthetic experience (Figure 3B), similar to what Hubbard, Arman, *et al.* (2005) found with fMRI. Although both the fMRI and DTI results were right lateralized in this study, other studies have found evidence for left-lateralized (Rich *et al.*, 2006) or bilateral

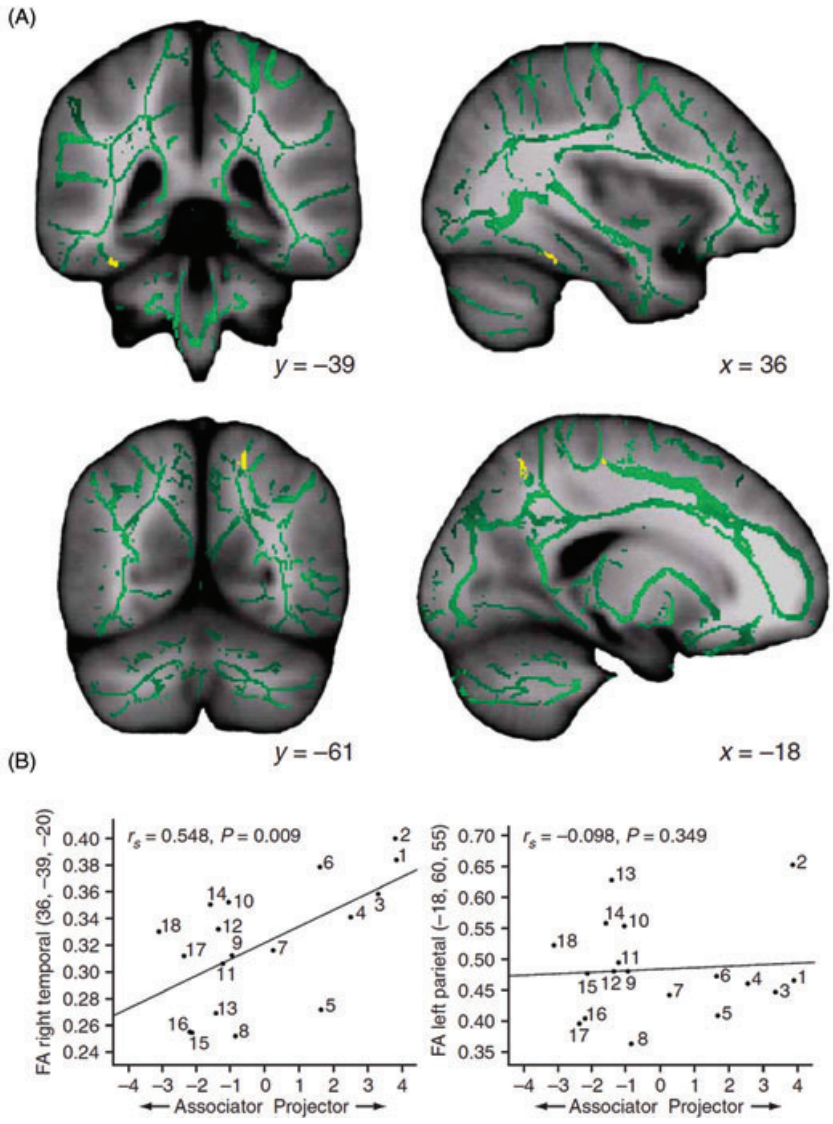

Figure 3. (A) Increased FA in parietal and fusiform regions in synaesthetes compared with non-synaesthetes. (B) Correlation between the self-reported intensity of synaesthetic experiences and FA in white matter tracts underlying inferior temporal regions. Data reprinted from Rouw and Scholte, 2007 courtesy of Nature Publishing Group.

fMRI differences (Hubbard, Arman, *et al.*, 2005), suggesting that such effects are bilateral, but may be difficult to detect, even in samples of this size.

This study provides clear evidence of anatomical differences between synaesthetes and non-synaesthetes, as predicted by the cross-activation theory. Other theories, such as the disinhibited feedback theory, would not have predicted this result. However, recent research has demonstrated that there are important links between local inhibition and pruning (Hensch, 2005) allowing the disinhibited feedback theory to explain these results *post hoc*: these anatomical differences may either be the cause of synaesthesia

or a secondary consequence of a lack of inhibition (Cohen Kadosh & Walsh, 2008; Hubbard, 2007b). Future studies using magnetic resonance spectroscopy (MRS) to test for differences in neurotransmitter balance in synaesthetes, especially in children, will be critical to shed light on these issues. Although the disinhibited feedback theory can explain these results *post hoc*, findings that are predicted by a theory are generally stronger evidence for a theory, as theories that survive empirical disconfirmation are to be preferred over theories that have not been directly tested in a similar manner.

VBM studies of cortical density in synaesthetes have also found results consistent with the predictions of the cross-activation theory (Jäncke *et al.*, 2009; Weiss & Fink, 2009). Weiss *et al.* contrasted a group of 18 grapheme-colour synaesthetes against a group of 18 controls. Whole-brain analyses did not yield significant differences. However, when using a small volume correction to identify *a priori* ROIs in the fusiform gyrus and parietal cortex based on their previous fMRI study (Weiss *et al.*, 2005), they found increased grey matter (GM) volume in the synaesthetic participants. Using probabilistic anatomical atlases, they compared the location of the increased GM against the locations of early retinotopic visual areas and found that the region of increased volume was right at the anterior border of V4, exactly as would be predicted by the cross-activation theory.

Jäncke *et al.* also found differences in a number of GM properties, including increased cortical thickness, cortical volume, and surface area in a number of early visual areas including the left and right fusiform gyri, lingual gyri, calcarine cortex, precuneus, and superior occipital cortex in a group of 24 synaesthetes compared against a group of 24 controls. In addition, when using a liberal statistical threshold ($p < .05$, uncorrected), the authors found increased FA in, among other areas, the white matter (WM) underlying the fusiform gyrus, consistent with the findings from Rouw and Scholte (2007).

The reasons for these differences in the strength of the findings are still unclear but may be due to individual differences in the synaesthetes tested across the studies (Rouw & Scholte, 2010). Rouw and Scholte measured fMRI responses and VBM in a group of 42 grapheme-colour synaesthetes (16 projectors and 26 associators) to identify (1) brain regions that showed differences across all synaesthetes compared with controls, (2) brain regions that showed differences between the two groups of synaesthetes. They found greater GM volume in superior parietal cortex, and decreased GM volume in the cingulate gyrus, in synaesthetes compared against non-synaesthetes. When the authors directly contrasted the two groups of synaesthetes, they found increased GM in anterior calcarine cortex (V1/V2) and precuneus, among other areas, for the projectors compared against the associators, and increased volume in the region of the hippocampus for associators compared against the projectors.

Finally, another recent study used surface-based morphometry and graph-theoretic approaches to examine the network properties in a group of 24 synaesthetes and 24 non-synaesthetes (Hanggi, Wotruba, & Jäncke, 2011). They find increased GM density in multiple regions throughout the brain. Using GM density as a proxy for connectivity, Hangii *et al.* infer a globally altered network organization in synaesthesia. The authors interpret this as evidence in favour of the idea that synaesthesia is but one phenotypic manifestation of a generally altered network connectivity (Bargary & Mitchell, 2008) and suggest that this is inconsistent with models that propose only localized differences. However, as discussed above, we suggested that part of the reason that the gene for synaesthesia may have survived is that it confers a selective advantage when expressed in multiple regions throughout the cortex (Ramachandran & Hubbard, 2001b), which would be consistent with Bargary and Mitchell, and with the widespread anatomical differences found by Hanggi *et al.*

Taken together, these studies demonstrate clear anatomical differences in the regions predicted by the cross-activation theory, including early visual areas, the fusiform gyrus, and the WM underlying the fusiform gyrus. However, anatomical differences are not limited to these areas and may differ between different groups of synaesthetes. Finally, although these findings are consistent with the predictions of the cross-activation theory, they do not conclusively rule out other possibilities, such as that the anatomical differences observed are the result of a lifetime of altered neural communication, which also gives rise to synaesthetic experiences (e.g., Cohen Kadosh & Walsh, 2008).

EEG and MEG studies

We now turn to the source of data that may shed the most light on the debate between the cross-activation theory and other theories of synaesthesia. Although functional neuroimaging studies have consistently demonstrated increased activation in V4, and neuroanatomical studies have demonstrated anatomical differences in the region of fusiform gyrus including the underlying WM, these methods cannot reveal the time course of activation in these regions when synaesthetes are presented with letters and numbers. However, EEG and MEG have the temporal resolution to address these questions.

One of the key predictions of the cross-activation model is that activation of V4 should occur early, since we predict that V4 will be directly activated by populations of neurons in the VWFA or grapheme area. Conversely, the disinhibited feedback model, especially as proposed by Grossenbacher and Lovelace (2001), would predict that activation of V4 should occur only after a substantial delay, as information must first propagate up through multiple levels of the cortical hierarchy before arriving at a 'multisensory nexus' and then propagating back down to V4. Thus, EEG and MEG data that show only late differences between synaesthetes and non-synaesthetes would, in principle disconfirm the cross-activation theory, while finding early differences would invalidate the long-range disinhibited feedback model.

To date, there have been only a few EEG studies of grapheme-colour synaesthesia. In general, these studies find that early ERP components, including the N1 and P2 components, which occur within 100 and 200 ms after stimulus presentation, respectively, are modulated by synaesthetic congruency (Brang, Edwards, Ramachandran, & Coulson, 2008; Brang, Kanai, Ramachandran, & Coulson, 2010; Sagiv & Ward, 2006) and similar results have been reported for auditory word- (Beeli, Esslen, & Jäncke, 2008) and tone-colour synaesthesia (Goller, Otten, & Ward, 2009). However, only one of these studies identified the probable cortical sources of the effects (Beeli *et al.*, 2008) using low-resolution brain electromagnetic tomography (LORETA) localizing the probable sources to inferior temporal regions, including regions near V4. Hence, although EEG data are consistent with the cross-activation model in showing early modulation by synaesthetic congruence, spatial localization has generally been limited.

In order to overcome the limited spatial resolution of EEG, we performed the only MEG study of synaesthesia to date (Brang, Hubbard, Coulson, Huang, & Ramachandran, 2010). We measured responses to graphemes in *a priori* defined ROIs, similar to the methods that we had used in our previous fMRI study (Hubbard, Arman, *et al.*, 2005) in a group of four projector synaesthetes and four controls. We defined V4 on the basis of well-characterized responses to patches in the upper and lower visual field, and the posterior temporal grapheme area (PTGA) on the basis of responses to graphemes within

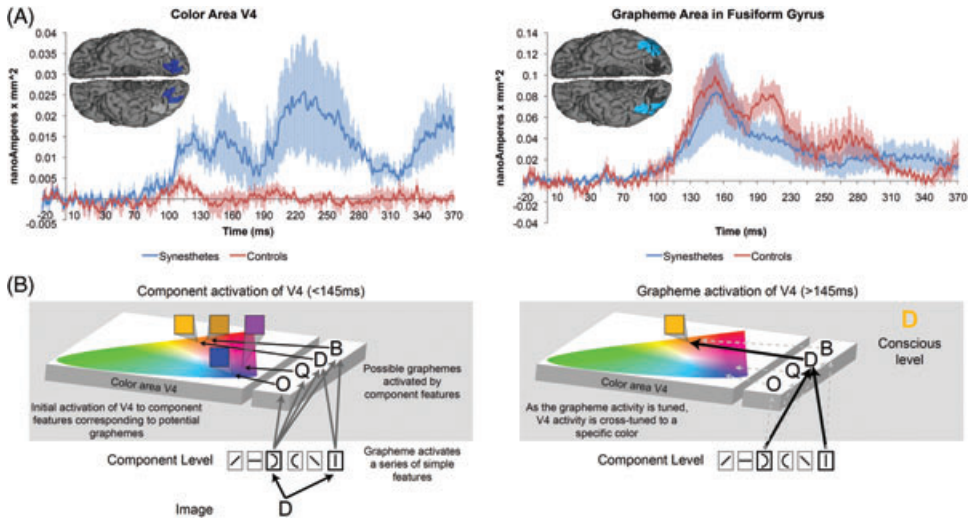

Figure 4. (A) MEG data from four synaesthetes and four matched controls in retinotopic area V4 and grapheme responsive areas (PTGA). (B) The Cascaded Cross-Tuning (CCT) model: initial activation of colours occurs via features, which after a process of competition is resolved to identify the specific letter being perceived, and which leads to a specific colour being elicited. From Brang *et al.*, 2010, courtesy of Neuroimage.

70–170 ms after stimulus onset, but excluding V4 (see Figure 4A). We then measured responses to graphemes and found that V4 was significantly more active in synaesthetes than in controls between 111 and 130 ms after stimulus onset. As additional confirmation of the cross-activation theory, activity within V4 reached significance only 5 ms after that of the PTGA, suggesting only a slight delay in the propagation of activity from grapheme to colour in synaesthesia. Critically, we did not observe any differences in the time course of activation or in the distribution of activity in the PTGA, again arguing against generalized differences between synaesthetes and non-synaesthetes.

Taken together, the results of EEG and MEG studies are consistent with the cross-activation model, but flatly contradict certain versions of the disinhibited feedback theory, particularly models like those proposed by Grossenbacher and Lovelace (2001), which suggest that information must pass through multiple stages of cortical processing before eliciting synaesthetic experiences. While models of local disinhibited feedback (e.g., Cytowic & Eagleman, 2009) or 'unmasking' (Cohen Kadosh, Henik, Catena, Walsh, & Fuentes, 2009; Cohen Kadosh & Walsh, 2008) may be able to account for such data *post hoc*, we again stress that this was a specific prediction made by the cross-activation theory, which has once again survived empirical disconfirmation, and which once again lends support to the our model.

Two-stage model

A growing awareness of the importance of binding and parietal mechanisms led to the first major modification of the cross-activation theory, the introduction of a 'two-stage model' of grapheme-colour synaesthesia (Hubbard, 2007a, 2007b). The cross-activation theory proposed that synaesthetic experiences are generated via cross-activation in the fusiform gyrus, but assumed that parietal binding and attention mechanisms were

similar in synaesthetes and non-synaesthetes. Conversely, the 'hyper-binding' theory of grapheme-colour synaesthesia suggested that synaesthetic experiences depend on increased binding between colour and form (Esterman, Verstynen, Ivry, & Robertson, 2006; Robertson, 2003).

Although the evidence reviewed above clearly demonstrates a critical role for early colour-selective visual areas in the genesis of synaesthetic experiences, a number of studies have also demonstrated the importance of parietal regions involved in attention and binding. For example, intra-parietal sulcus (IPS) regions are consistently more active in synaesthetes than in non-synaesthetes (Nunn *et al.*, 2002; Paulesu *et al.*, 1995; van Leeuwen *et al.*, 2010; Weiss *et al.*, 2005), suggesting a critical role for these regions. Inactivation of parietal regions using transcranial magnetic stimulation (TMS) reduces the synaesthetic Stroop effect (Esterman *et al.*, 2006; Muggleton, Tsakanikos, Walsh, & Ward, 2007) and can impair implicit bi-directional effects (Rothen, Nyffeler, von Wartburg, Muri, & Meier, 2010), which suggests that parietal activations are not merely epiphenomenal, but rather play a causal role in generating the experience of grapheme-colour synaesthesia. Finally, many of the anatomical studies described above have also found increased coherence (FA) in the WM underlying the IPS (Rouw & Scholte, 2007) and increased GM density overlapping with regions that demonstrate functional differences (Rouw & Scholte, 2010; Weiss & Fink, 2009). Curiously, the fMRI and TMS studies yield divergent results in terms of lateralization, with fMRI studies consistently suggesting that left hemisphere parietal mechanisms are critical to synaesthesia, while TMS studies suggest that right hemisphere mechanisms are critical. The reasons for this divergence remain unclear (see Hubbard, 2007b; Rouw *et al.*, 2011, in this issue).

Taken together, these results suggest that, while the activation of colour-specific visual areas may be the origin of synaesthetic experiences, these colour experiences must still be bound by (possibly overactive) parietal mechanisms. While anomalous binding may play an important role in the full explanation of the synaesthetic experiences, it is not sufficient to say that synaesthesia is a result of anomalous binding, since binding must have features upon which to act. We thus suggest that synaesthetic colours are first elicited in fusiform regions via cross-activation but are then bound by parietal mechanisms in the same way as other visual features. Consistent with this proposal, Specht & Laeng (2011, in this issue) applied independent components analysis (ICA) to fMRI data collected during a synaesthetic Stroop task. They identified three networks that showed increased activation in synaesthetes: one centered on the right fusiform gyrus, a second centered on parietal regions, and a third related to conflict monitoring regions including the anterior cingulate. Similarly, Jäncke & Langer (2011) find that parietal regions constitute a strong hub in resting state EEG of coloured-hearing synaesthetes.

Cascaded cross-tuning (CCT) model

Examination of our recent MEG data and an increased understanding of the neural mechanisms of reading led to the second major modification to the cross-activation theory. The differences observed between synaesthetes and non-synaesthetes in the MEG study described above were so early, in fact, that they pose a challenge to the original form of the cross-activation model and require some modification of our original proposal. Our original cross-activation model tacitly assumed a template-matching model of grapheme processing that was widely accepted at the time. In the intervening years, however, cognitive neuroscientists have increasingly come to view grapheme and word recognition as a process of hierarchical feature analysis (for reviews, see Dehaene,

Cohen, Sigman, & Vinckier, 2005; Grainger, Rey, & Dufau, 2008; Vinckier *et al.*, 2007). Building on this more detailed understanding of the neural mechanisms involved in reading, we have recently revised the cross-activation model (Brang, Hubbard, *et al.*, 2010) to account for the fact that features, rather than entire letters, may lead to a partial activation of V4 very early on (see Figure 4B). In parallel, grapheme identification occurs over time via competitive activation processes involving some combination of excitatory and inhibitory connections both within the grapheme level and between the grapheme level and other representational levels, both bottom-up and top-down. In this way, our modified cross-activation model, the CCT model, incorporates both early direct cross-activation and top-down influences. However, as we have noted previously (Hubbard & Ramachandran, 2005) as such top-down influences are present in everyone, synaesthete and non-synaesthete alike, there is no reason to assume that such top-down influences play a unique role in synaesthesia.

As a test of the CCT model, following on the suggestion that form-specific elements in graphemes initiate subconscious activity in V4, Brang and Ramachandran recently demonstrated a significant impairment in synaesthetes' ability to memorize novel shape-colour associations compared to controls. Critically, the inducing graphemes were non-linguistic characters that did not elicit conscious synaesthetic colours, suggesting the proscribed shape-colour correspondences conflicted with implicit synaesthetic associations (Brang & Ramachandran, 2011). In addition, letters and numbers that share similar basic visual features and form-specific elements elicit similar synaesthetic colours, providing a putative mechanism and import of the cross-activation theory at the stage at which colours first become bound with graphemes in a synaesthete (Brang, Rouw, Ramachandran, & Coulson, 2011; Hubbard, Ambrosio, Azoulai, & Ramachandran, 2005).

The cross-activation model applied to other forms of synaesthesia

Having reviewed the neuroimaging literature on grapheme-colour synaesthesia, we now turn to extensions of the cross-activation model to other forms of synaesthesia. A theory is strengthened if it can explain phenomena beyond those for which it was first proposed, thus making the generalizability of the theory another indirect test of the cross-activation theory. We thus briefly review the application of the basic cross-activation ideas, in particular the possibility that both the inducer and the concurrent in certain forms of synaesthesia are represented in adjacent brain areas, to other forms of synaesthesia. Clearly, the data in support of these extensions to the model are far less comprehensive than the data testing the cross-activation model of grapheme-colour synaesthesia (see Table 1). We hope that the various unexplored cells in this table will serve to spur future research into these questions, using neuroimaging methods similar to those used in the study of grapheme-colour synaesthesia. In some cases, such as grapheme-colour synaesthesia, a great deal of data has been collected, and the table is relatively complete. However, for most other forms of synaesthesia, a great deal more work is needed, and examination of some of these forms may require revising or even rejecting the cross-activation model for these forms.

Sequence-space synaesthesia

One of the first extensions of the cross-activation model was to attempt to explain number-form synaesthesia (Galton, 1880a, 1880b), in which numbers, and other ordinal sequences, including months of the year and days of the week (see e.g., Brang, Teuscher, Miller, Ramachandran, & Coulson, 2011; Jarrick, Jensen, Dixon, & Smilek,

Table 1. Summary of findings relevant to cortical models of synaesthesia. 'Yes' indicates positive evidence for the predictions of the cross-activation theory. 'No' indicates evidence contrary to the predictions of the cross-activation theory and question marks indicate an absence of data. Filling in these cells, both for the forms listed and for other forms not listed here, will be critical areas for future research.

Type of synaesthesia	Adjacent ?	Increased activation?	Anatomical differences?	Rapid co-activation?	Essential?
Grapheme-colour	Yes	Yes	Yes	Yes (1 study)	Yes (lesion)
Number-forms	Yes	Yes (1 study)	???	???	Yes (lesion)
OLP	Yes?	???	???	???	???
Taste-touch	Yes	???	???	???	???
Music-taste	Yes	???	Yes	???	???
Auras?	Yes	???	???	???	???
Lexical-gustatory	Yes	Yes (1 study)	???	???	???
Tone-colour	No	Yes	???	Yes	???
Swimming-colour (?)	???	???	???	???	???

2011) and letters of the alphabet (Jonas, Taylor, Hutton, Weiss, & Ward, 2011) are specifically associated with spatial locations and which often co-occurs with grapheme-colour synaesthesia (Sagiv, Simner, *et al.*, 2006; Seron, Pesenti, Noel, Deloche, & Cornet, 1992; but see Novich, Cheng, & Eagleman, 2011). Based on numerous patient and neuroimaging studies, parietal cortex is generally recognized as a key region for numerical and spatial processes (Dehaene, Piazza, Pinel, & Cohen, 2003; Hubbard, Piazza, Pinel, & Dehaene, 2005; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002) including processing of non-numerical ordinal sequences, including letters (Fias, Lammertyn, Caessens, & Orban, 2007) and months (Ischebeck *et al.*, 2008). Interestingly, even though classical univariate fMRI analyses show strict overlap between number and letter sequence processing in the mid-IPS (Fias *et al.*, 2007), multivariate classifiers can discriminate between number and letter responses (Zorzi, Di Bono, & Fias, 2011), showing that at the sub-voxel level, such responses may still be partially dissociable. These findings may account for differences in the degree to which different sequences are likely to be associated with space (see, Cytowic, 1989/2002; Flournoy, 1893; Hubbard, Ranzini, Piazza, & Dehaene, 2009).

Building on these observations, we proposed that this form of synaesthesia arises through cross-activation in parietal regions, and furthermore, that non-conscious numerical-spatial interactions that are present in everyone (e.g., the spatial-numerical association of response codes or SNARC effect; Dehaene, Bossini, & Giraux, 1993) are mediated by similar, albeit weaker connections in parietal cortex (Hubbard, Piazza, *et al.*, 2005). Preliminary support for this model comes from fMRI data showing increased posterior parietal activation in number-form synaesthetes when they perform an ordinal number task (Tang, Ward, & Butterworth, 2008). Consistent with this model, a patient who suffered a gunshot wound that entered near the right angular gyrus and lodged near the left temporal-parietal junction complained that his 'number plan' for months of the year, days of the week and letters of the alphabet, was no longer distinct (Spalding & Zangwill, 1950). An alternative model that suggests temporal regions, rather than parietal regions, as the locus of this form of synaesthesia (Eagleman, 2009) still incorporates key features of the cross-activation account such as adjacency.

Ordinal linguistic personification (OLP)

Similarly, we have proposed that OLP, in which people associate letters and numbers with personalities (Amin *et al.*, 2011; Simner, Gärtner, & Taylor, 2011; Simner & Holenstein, 2006) may depend on the same types of local cross-activation between brain regions involved in sequence representations, such as the inferior parietal cortex and regions involved in personality attribution (Simner & Hubbard, 2006), while other models have suggested numerous anatomical substrates in a 'personification network' (Smilek *et al.*, 2007) including the angular gyrus, but also including extrastriate and fusiform regions, the amygdala and medial frontal cortex. To date, these models have not been directly tested using neuroimaging methods, but the fact that the essential features of the cross-activation model can be extended to different types of synaesthesia by examining different patterns of adjacency in the brain lends additional support to the cross-activation theory, as these models have demonstrated that the cross-activation theory can be extended beyond the forms of synaesthesia for which it was first proposed.

Musical interval-taste synaesthesia

In a single-case study, Hanggi, Beeli, Oechslin, & Jäncke (2008) demonstrated anatomical differences in insular regions in an unusual musical interval-taste synaesthete, ES. The authors report increased GM in auditory and gustatory areas in the insula and increased FA and WM volume in the fibre tracts underlying these regions. Crucially, the authors compared ES against groups of non-synaesthetic controls, and non-synaesthetic musicians, as a lifetime of musical training has also been shown to lead to changes in cortical organization. The application of the cross-activation model to this unusual form of synaesthesia, and the clear anatomical differences observed, further demonstrates the general applicability of this model.

As noted above, these are only a few examples of the many forms of synaesthesia. In many cases, the only data we have is that the inducer and concurrent regions lie next to each other, or a single study showing functional and/or anatomical differences (e.g., for lexical-gustatory synaesthesia, see Jones *et al.*, 2011). These early results suggest that it may be possible to expand the cross-activation theory to a large variety of forms of synaesthesia, but a great deal more work will be required, using all of the methods described above (and others, see below) to fully test the application of the cross-activation theory to these other forms of synaesthesia.

Development, learning, and neuronal recycling

Finally, we turn to questions about how genetic factors interact with learning in synaesthesia. Systematic study of the associations in grapheme-colour synaesthesia suggests that individual differences in synaesthetic colours are not simply due to random differences in wiring between synaesthetes (Beeli, Esslen, & Jäncke, 2007; Cohen Kadosh, Henik, & Walsh, 2007;Simner *et al.*, 2005; Simner & Ward, 2008; Smilek, Carriere, Dixon, & Merikle, 2007). Interestingly, the rules that govern these trends may be different in different forms of synaesthesia. For letters, frequency appears to be the cricital factor, as high-frequency letters are generally associated with high-frequency colours (Simner *et al.*, 2005; Simner & Ward, 2008). For digits, however, numerical magnitude is associated with brightness (Cohen Kadosh *et al.*, 2007) and for week-day names, frequency is associated with hue and saturation in the same subjects

(Cohen Kadosh, Henik, & Walsh, 2009). In addition, in a comparison of lexical-gustatory and grapheme-colour synaesthesia, different forms of synaesthesia follow different rules (Ward *et al.*, 2005).

This leads to the question of whether synaesthesia reflects differences in learning or in brain maturation. One recent proposal (Cohen Kadosh *et al.*, 2009) suggests that both play a role, building on the interactive specialization framework (Johnson, 2001, 2011), which proposes that 'specialization of a cortical region is determined within the context of its neighbours and connection patterns' (Johnson, 2011, p. 10) through a combination of intrinsic self-organizing and activity-dependent processes. These processes lead to gradual refinement of cortical regions through development, such that cortical biases generally lead to specific regions being specialized for certain functions, but without necessitating a one-to-one mapping between brain regions and specific cognitive processes.

However, interactive specialization is intended as a domain-general account of brain development, and as such does not distinguish between evolutionarily ancient systems and modern cultural systems. Why, for example, is grapheme-colour synaesthesia more common than face colour synaesthesia if adjacency and brain wiring are the only factors that count? One possible explanation is that face and grapheme processing depend on slightly different brain regions, with face processing depending on temporal regions further from V4 than the VWFA (Hasson, Harel, Levy, & Malach, 2003). A more theoretically interesting possibility is that the degree to which cortex must reorganize during learning is greater for novel culturally acquired systems such as graphemes (Dehaene & Cohen, 2007) and ordinal sequences (Cohen Kadosh *et al.*, 2009) than for items that have a long evolutionary history, such as faces or colours. This greater degree of cortical reorganization for novel cultural artefacts might provide greater opportunities for cross-activation in the cortical recycling process. This would also provide an account of some of the trends in synaesthetic colours noted above. For example, the presence of shared sub-letter features such as junctions and curvature (Brang, Hubbard, *et al.*, 2010) might help account for why similarly shaped letters are associated with similar colours (Brang *et al.*, 2011), why certain pairings are easier to learn than others (Brang & Ramachandran, 2011) and might also help to account for learning in multi-lingual synaesthetes (Mills *et al.*, 2002) and instances of rapid learning in synaesthesia (Mroczko, Metzinger, Singer, & Nikolic, 2009).

Similarly, such an account might help to explain the directionality seen in synaesthesia. As letters and numbers are learned later than colours, and as greater cortical reorganization is required to learn these culturally invented systems, it is possible that this asymmetry in the learning process leads colour neurons to be committed to colour processing early in development, prior to learning to read. Learning to read then attempts to piggy back on some of these dedicated neurons, leading to the experience of colours when viewing graphemes, but not vice versa. However, our knowledge of the interactions between the genetic factors discussed above and the process of learning to read is still in its infancy, and much more work will be needed to understand how these interactions lead to the full range of synaesthetic experiences.

Future directions

Although the past 10 years have seen great progress in our understanding of the neural basis of synaesthesia, there is still much work to be done. First, many different types of evidence have been brought to bear on the neural basis of grapheme-colour synaesthesia,

but similar studies have not yet been carried out on the other forms of synaesthesia, and so far none of the studies demonstrating anatomical and functional differences in other forms of synaesthesia have been replicated (see Table 1). Clearly, more work will be required to better understand the neural basis of these other forms of synaesthesia, and to test whether the cross-activation theory successfully generalizes to these other forms.

Second, there are no studies of the neural development of synaesthesia. Methods for neuroimaging with children are becoming widespread and have been applied to a number of questions in cognitive and perceptual development. Similar methods, combined with methods of identifying and tracking children who are synaesthetic or who are likely to become synaesthetic will be critical to understanding the development of synaesthesia, and how genes and experience interact.

Finally, we must address the relative absence of neuroimaging data directly testing the predictions of the disinihibited feedback theory. Other sources of data have been suggested as evidence for disinhibition, but this evidence is largely anecdotal. For example, Grossenbacher and Lovelace (2001) note that experiences similar to synaesthesia can sometimes be elicited with psychedelics. However, this superficial similarity may be misleading, as synaesthetic percepts are often simple, while psychedelic-induced visualizations are often complex (compare Cytowic & Eagleman, 2009; Shanon, 2002). Building on this same point, other authors have also suggested that synaesthesia may arise through mechanisms of cortical disinhibition (Cytowic & Eagleman, 2009) or even through specific genetic anomalies in the 2a form of the serotonin receptor (Brang & Ramachandran, 2008).

However, none of these pharmacological hypotheses of synaesthesia have been tested with neuroimaging methods such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) or MRS. Future studies using these methods will help to identify whether there are any differences in neurotransmitters concentrations, receptor density or other alterations in synthesis, or breakdown of specific neurotransmitters involved with cortical inhibition and excitation. Radioactive tracer molecules developed for use with PET and SPECT, called radioligands, can show striking specificity, differentially binding to specific neurotransmitter receptors within specific brain regions. For example, one of the most common radioligands, [^{11}C]raclopride, selectively binds to dopamine D2/D3 receptors in the striatum, whereas others ([^{11}C]SCH 23390 and [^{11}C] NNC 112) bind to D1/D5 receptors in the cortex. Other radioligands have been developed to measure other neurotransmitter system properties, such as dopamine synthesis and use, serotonin receptor density (in particular, 5-HT1A and 5-HT2A receptors), and GABA-A benzodiazapine receptor families. All of these PET and SPECT methods are ideally suited to test differences in these neurotransmitter families in synaesthesia.

Based on the hypothesis that synaesthesia results from differences in cortical excitability, and in particular, from disinhibited feedback, we might also predict imbalances in the primary neurotransmitter systems involved in cortical excitation and inhibition, glutamate and GABA, respectively. MRS methods are ideally suited to measuring levels of these neurotransmitters. MRS uses a standard MRI scanner to identify shifts in the frequency with which protons precess after being energized by a radiofrequency (RF) pulse in the presence of a magnetic field. Because of their electron structure, protons in different molecules are more or less affected by the RF pulse, leading to characteristic changes in spin rate. These shifts can be used as markers for the concentration of a number of different biochemical substances, including GABA and glutamate/glutamine. MRS methods have shed considerable light on the processes of glutamate and GABA

synthesis use and reuptake, including the role of GAD65 and GAD67 in epilepsy (for a review, see Petroff, 2002) and could shed similar light on the relative role of these neurotransmitters, if any, in the increased cortical excitability thought to be associated with synaesthesia.

These methods are no more difficult to use than standard fMRI methods and have been around in various forms since before the development of fMRI and DTI. Thus, the absence of information from these methods is a striking gap in the experimental literature. Models based on disinhibited feedback and neurotransmitter differences have been around for as long as the cross-activation model, and yet not one neuroimaging study has directly tested these ideas with suitable methodology. Future studies using these methods will be critical to evaluating the possibility that differences in neurotransmitter function underlie synaesthesia.

Conclusions

Here, we have reviewed the history of the cross-activation theory, especially for grapheme-colour synaesthesia, and provided evidence from numerous studies, using a variety of methodologies, in favour of this model. We have shown that specific predictions made by the cross-activation model, including the location of functional differences, the presence of anatomical differences, and even the time course of synaesthetic activation of these brain regions, have been repeatedly confirmed. The cross-activation theory has survived repeated empirical disconfirmation, and as such, we conclude that it is on solid empirical ground. From this, we cannot conclude that other models are incorrect: in many cases, they simply have not been subjected to the same empirical tests that the cross-activation theory has.

We have additionally demonstrated that the basic lessons from the cross-activation theory can be generalized to account for other forms of synaesthesia, such as number-forms, OLP, and even a unique musical interval-taste synaesthete. Although these extensions are preliminary, we are optimistic that future empirical studies will demonstrate the wide applicability of the cross-activation model, ranging from low-level forms to higher level cognitive forms. Indeed, it is precisely the fact synaesthesia spans the whole spectrum from low-level cross-activation to higher order associations that make synaesthesia such a valuable probe for understanding the neural basis of the mind. The past 10 years have seen incredible progress in our understanding of the neural basis of synaesthesia, and we are optimistic that the next 10 years will see even greater progress.

References

Amin, M., Olu-Lafe, O., Claessen, L. E., Sobczak-Edmans, M., Ward, J., Williams, A. L., & Sagiv, N. (2011). Understanding grapheme personification: A social synaesthesia? *Journal of Neuropsychology*, *5*, 255–282. doi:10.1111/j.1748-6653.2011.02016.x

Asher, J. E., Lamb, J. A., Brocklebank, D., Cazier, J. B., Maestrini, E., Addis, L., ... Monaco, A. P. (2009). A whole-genome scan and fine-mapping linkage study of auditory-visual synesthesia reveals evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12. *American Journal of Human Genetics*, *84*(2), 279–285. doi:10.1016/j.ajhg.2009.01.012

Bailey, M. E. S., & Johnson, K. J. (1997). Synaesthesia: Is a genetic analysis feasible? In S. Baron-Cohen & J. E. Harrison (Eds.), *Synaesthesia: Classic and Contemporary Readings* (pp. 182–207). Oxford, England: Blackwell.

Bargary, G., & Mitchell, K. J. (2008). Synaesthesia and cortical connectivity. *Trends in Neuroscience*, *31*(7), 335–342. doi:10.1016/j.tins.2008.03.007

Barnett, K. J., Finucane, C., Asher, J. E., Bargary, G., Corvin, A. P., Newell, F. N., & Mitchell, K. J. (2007). Familial patterns and the origins of individual differences in synaesthesia. *Cognition*, *106*(2), 871–893. doi:10.1016/j.cognition.2007.05.003

Baron-Cohen, S. (1996). Is there a normal phase of synaesthesia in development? *Psyche*, *2*(27).

Baron-Cohen, S., Burt, L., Smith-Laittan, F., Harrison, J., & Bolton, P. (1996). Synaesthesia: Prevalence and familiality. *Perception*, *25*(9), 1073–1079. doi:10.1068/p251073

Baron-Cohen, S., & Harrison, J. E. (Eds.). (1997). *Synaesthesia: Classic and Contemporary Readings*. Malden, MA, US: Blackwell Publishers Inc.

Baron-Cohen, S., Harrison, J. E., Goldstein, L. H., & Wyke, M. (1993). Coloured speech perception: Is synaesthesia what happens when modularity breaks down? *Perception*, *22*(4), 419–426. doi:10.1068/p220419

Beeli, G., Esslen, M., & Jäncke, L. (2007). Frequency correlates in grapheme-color synaesthesia. *Psychological Science*, *18*(9), 788–792. doi:10.1111/j.1467-9280.2007.01980.x

Beeli, G., Esslen, M., & Jäncke, L. (2008). Time course of neural activity correlated with colored-hearing synesthesia. *Cerebral Cortex*, *18*(2), 379–385. doi:10.1093/cercor/bhm072

Brang, D., Edwards, L., Ramachandran, V. S., & Coulson, S. (2008). Is the sky 2? Contextual priming in grapheme-color synaesthesia. *Psychological Science*, *19*(5), 421–428. doi:10.1111/j.1467-9280.2008.02103.x

Brang, D., Hubbard, E. M., Coulson, S., Huang, M., & Ramachandran, V. S. (2010). Magnetoencephalography reveals early activation of V4 in grapheme-color synesthesia. *Neuroimage*, *53*(1), 268–274. doi:10.1016/j.neuroimage.2010.06.008

Brang, D., Kanai, S., Ramachandran, V. S., & Coulson, S. (2010). Contextual Priming in Grapheme-Color Synesthetes and Yoked Controls: 400 msec in the Life of a Synesthete. *Journal of Cognitive Neuroscience*, *23*(7), 1681–1696. doi:10.1162/jocn.2010.21486

Brang, D., & Ramachandran, V. S. (2008). Psychopharmacology of synesthesia; the role of serotonin S2a receptor activation. *Medical Hypotheses*, *70*(4), 903–904. doi:10.1016/j.mehy.2007.09.007

Brang, D., & Ramachandran, V. S. (2011). *Novel symbols show implicit associations in synesthesia*. Manuscript in preparation.

Brang, D., Rouw, R., Ramachandran, V. S., & Coulson, S. (2011). Similarly shaped letters evoke similar colors in grapheme-color synesthesia. *Neuropsychologia*, *49*(5), 1355–1358. doi:10.1016/j.neuropsychologia.2011.01.002

Brang, D., Teuscher, U., Miller, L. E., Ramachandran, V. S., & Coulson, S. (2011). Handedness and calendar orientations in time-space synaesthesia. *Journal of Neuropsychology*, *5*, 323–332. doi:10.1111/j.1748-6653.2011.02012.x

Cohen Kadosh, R., Henik, A., Catena, A., Walsh, V., & Fuentes, L. J. (2009). Induced cross-modal synaesthetic experience without abnormal neuronal connections. *Psychological Science*, *20*(2), 258–265. doi:10.1111/j.1467-9280.2009.02286.x

Cohen Kadosh, R., Henik, A., & Walsh, V. (2007). Small is bright and big is dark in synaesthesia. *Current Biology*, *17*(19), R834–R835. doi:10.1016/j.cub.2007.07.048

Cohen Kadosh, R., Henik, A., & Walsh, V. (2009). Synaesthesia: Learned or lost? *Developmental Science*, *12*(3), 484–491. doi:10.1111/j.1467-7687.2008.00798.x

Cohen Kadosh, R., & Walsh, V. (2008). Synaesthesia and cortical connections: Cause or correlation? *Trends in Neuroscience*, *31*(11), 549–550; author reply 550–541. doi:10.1016/j.tins.2008.08.004

Cytowic, R. E. (1989/2002). *Synesthesia: A Union of the Senses*. New York: Springer-Verlag.

Cytowic, R. E., & Eagleman, D. M. (2009). *Wednesday Is Indigo Blue: Discovering the Brain of Synesthesia*. Cambridge, MA: MIT Press.

Dailey, A. R., Martindale, C., & Borkum, J. (1997). Creativity, synesthesia and physiognomic perception. *Creativity Research Journal*, *10*(1), 1–8.

Dehaene, S., Bossini, S., & Giraux, P. (1993). The mental representation of parity and numerical magnitude. *Journal of Experimental Psychology: General*, *122*, 371–396.

Dehaene, S., & Cohen, L. (2007). Cultural recycling of cortical maps. *Neuron*, *56*(2), 384–398. doi:10.1016/j.neuron.2007.10.004

Dehaene, S., Cohen, L., Sigman, M., & Vinckier, F. (2005). The neural code for written words: A proposal. *Trends in Cognitive Sciences*, *9*(7), 335–341. doi:10.1016/j.tics.2005.05.004

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, *20*(3/4/5/6), 487–506. doi:10.1080/02643290244000239

Dixon, M. J., & Smilek, D. (2005). The importance of individual differences in grapheme-color synesthesia. *Neuron*, *45*(6), 821–823. doi:10.1016/j.neuron.2005.03.007

Dixon, M. J., Smilek, D., Cudahy, C., & Merikle, P. M. (2000). Five plus two equals yellow: Mental arithmetic in people with synaesthesia is not coloured by visual experience. *Nature*, *406*(6794), 365. doi:10.1038/35019148

Dixon, M. J., Smilek, D., Duffy, P. L., Zanna, M. P., & Merikle, P. M. (2006). The role of meaning in grapheme-colour synaesthesia. *Cortex*, *42*(2), 243–252. doi:10.1016/S0010-9452(08)70349-6

Dixon, M. J., Smilek, D., & Merikle, P. M. (2004). Not all synaesthetes are created equal: Projector versus associator synaesthetes. *Cognitive Affective and Behavioral Neuroscience*, *4*(3), 335–343. doi:10.3758/CABN.4.3.335

Domino, G. (1989). Synesthesia and creativity in fine arts students: An empirical look. *Creativity Research Journal*, *2*(1–2), 17–29.

Eagleman, D. M. (2009). The objectification of overlearned sequences: A new view of spatial sequence synesthesia. *Cortex*, *45*(10), 1266–1277. doi:10.1016/j.cortex.2009.06.012

Eagleman, D. M., & Goodale, M. A. (2009). Why color synesthesia involves more than color. *Trends in Cognitive Sciences*, *13*(7), 288–292. doi:10.1016/j.tics.2009.03.009

Esterman, M., Verstynen, T., Ivry, R. B., & Robertson, L. C. (2006). Coming unbound: Disrupting automatic integration of synesthetic color and graphemes by transcranial magnetic stimulation of the right parietal lobe. *Journal of Cognitive Neuroscience*, *18*(9), 1570–1576. doi:10.1162/jocn.2006.18.9.1570

Fias, W., Lammertyn, J., Caessens, B., & Orban, G. A. (2007). Processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. *Journal of Neuroscience*, *27*(33), 8952–8956. doi:10.1523/JNEUROSCI.2076-07.2007

Flournoy, T. (1893). *Des phénomènes de synopsie [On the phenomena of synopsia]*. Genève: Charles Eggimann & Co.

Galton, F. (1880a). Visualised numerals. *Nature*, *22*, 494–495. doi:10.1038/021494e0

Galton, F. (1880b). Visualised numerals. *Nature*, *21*, 252–256. doi:10.1038/021252a0

Galton, F. (1883). *Inquiries into human faculty and its development*. London: Dent & Sons.

Galton, F. (1883/1997). Colour associations. In S. Baron-Cohen & J. E. Harrison (Eds.), *Synaesthesia: Classic and Contemporary Readings* (pp. 43–48). Oxford, England: Blackwell.

Gheri, C., Chopping, S., & Morgan, M. J. (2008). Synaesthetic colours do not camouflage form in visual search. *Proceedings of the Royal Society Biological Sciences Series B*, *275*(1636), 841–846. doi:10.1098/rspb.2007.1457

Goller, A. I., Otten, L. J., & Ward, J. (2009). Seeing sounds and hearing colors: An event-related potential study of auditory-visual synesthesia. *Journal of Cognitive Neuroscience*, *21*(10), 1869–1881. doi:10.1162/jocn.2009.21134

Grainger, J., Rey, A., & Dufau, S. (2008). Letter perception: From pixels to pandemonium. *Trends in Cognitive Sciences*, *12*(10), 381–387. doi:10.1016/j.tics.2008.06.006

Gray, J. A., Parslow, D. M., Brammer, M. J., Chopping, S., Vythelingum, G. N., & Ffytche, D. H. (2006). Evidence against functionalism from neuroimaging of the alien colour effect in synaesthesia. *Cortex*, *42*(2), 309–318. doi:10.1016/S0010-9452(08)70357-5

Grossenbacher, P. G., & Lovelace, C. T. (2001). Mechanisms of synesthesia: Cognitive and physiological constraints. *Trends in Cognitive Sciences*, *5*(1), 36–41. doi:10.1016/S1364-6613(00)01571-0

Hanggi, J., Beeli, G., Oechslin, M. S., & Jäncke, L. (2008). The multiple synaesthete E.S.: Neuroanatomical basis of interval-taste and tone-colour synaesthesia. *Neuroimage*, *43*(2), 192–203. doi:10.1016/j.neuroimage.2008.07.018

Hanggi, J., Wotruba, D., & Jäncke, L. (2011). Globally altered structural brain network topology in grapheme-color synesthesia. *The Journal of Neuroscience*, *31*(15), 5816–5828. doi:10.1523/JNEUROSCI.0964-10.2011

Hasson, U., Harel, M., Levy, I., & Malach, R. (2003). Large-scale mirror-symmetry organization of human occipito-temporal object areas. *Neuron*, *37*(6), 1027–1041. doi:10.1016/S0896-6273(03)00144-2

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience*, *6*(11), 877–888. doi:10.1038/nrn1787

Hong, S. W., & Blake, R. (2008). Early visual mechanisms do not contribute to synesthetic color experience. *Vision Research*, *48*(8), 1018–1026. doi:10.1016/j.visres.2008.01.024

Hubbard, E. M. (2007a). Neurophysiology of synesthesia. *Current Psychiatry Reports*, *9*(3), 193–199. doi:10.1007/s11920-007-0018-6

Hubbard, E. M. (2007b). A real red-letter day. *Nature Neuroscience*, *10*(6), 671–672. doi:10.1038/nn0607-671

Hubbard, E. M., Ambrosio, P., Azoulai, S., & Ramachandran, V. S. (2005). *Grapheme and letter name based patterns in synesthetic colors*. Paper presented at the Cognitive Neuroscience Society, San Francisco, CA.

Hubbard, E. M., Arman, A. C., Ramachandran, V. S., & Boynton, G. M. (2005). Individual differences among grapheme-color synesthetes: Brain-behavior correlations. *Neuron*, *45*(6), 975–985. doi:10.1016/j.neuron.2005.02.008

Hubbard, E. M., Piazza, M., Pinel, P., & Dehaene, S. (2005). Interactions between number and space in parietal cortex. *Nature Reviews Neuroscience*, *6*(6), 435–448. doi:10.1038/nrn1684

Hubbard, E. M., & Ramachandran, V. S. (2003). Refining the experimental lever: A reply to Shannnon and Pribram. *Journal of Consciousness Studies*, *10*(3), 77–84.

Hubbard, E. M., & Ramachandran, V. S. (2005). Neurocognitive mechanisms of synesthesia. *Neuron*, *48*(3), 509–520. doi:10.1016/j.neuron.2005.10.012

Hubbard, E. M., Ranzini, M., Piazza, M., & Dehaene, S. (2009). What information is critical to elicit interference in number-form synesthesia? *Cortex*, *45*(10), 1200–1216. doi:10.1016/j.cortex.2009.06.011

Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., ... Delazer, M. (2008). Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. *Human Brain Mapping*, *29*(8), 894–909. doi:10.1002/hbm.20433

Jäncke, L., Beeli, G., Eulig, C., & Hanggi, J. (2009). The neuroanatomy of grapheme-color synesthesia. *European Journal of Neuroscience*, *29*(6), 1287–1293. doi:10.1111/j.1460-9568.2009.06673.x

Jäncke, L., & Langer, N. (2011). A strong parietal hub in the small-world network of coloured-hearing synaesthetes during resting state EEG. *Journal of Neuropsychology*, *5*, 178–202. doi:10.1111/j.1748-6653.2011.02004.x

Jarick, M., Jensen, C., Dixon, M. J., & Smilek, D. (2011). The automaticity of vantage point shifts within a synaesthetes' spatial calendar. *Journal of Neuropsychology*, *5*, 333–352. doi:10.1111/j.1748-6653.2011.02011.x

Jewanski, J., Day, S. A., & Ward, J. (2009). A colorful albino: The first documented case of synaesthesia, by Georg Tobias Ludwig Sachs in 1812. *Journal of the History of Neuroscience*, *18*(3), 293–303. doi:10.1080/09647040802431946

Johnson, M. H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience 2*, 475–483. doi:10.1038/35081509

Johnson, M. H. (2011). Interactive Specialization: A domain-general framework for human functional brain development? *Developmental Cognitive Neuroscience*, *1*(1), 7–21. doi:10.1016/j.dcn.2010.07.003

Jonas, C. N., Taylor, A. J. G., Hutton, S., Weiss, P. H., & Ward, J. (2011). Visuo-spatial representations of the alphabet in synaesthetes and non-synaesthetes. *Journal of Neuropsychology*, *5*, 302–322. doi:10.1111/j.1748-6653.2011.02010.x

Jones, C. L., Gray, M. A., Minati, L., Simner, J., Critchley, H. D., & Ward, J. (2011). The neural basis of illusory gustatory sensations: Two rare cases of lexical-gustatory synaesthesia. *Journal of Neuropsychology*, *5*, 243–254. doi:10.1111/j.1748-6653.2011.02013.x

Laeng, B., Hugdahl, K., & Specht, K. (2011). The neural correlate of colour distances revealed with competing synaesthetic and real colours. *Cortex*, *47*(3), 320–331. doi:10.1016/j.cortex.2009.09.004

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin*, *109*(2), 163–203.

Marks, L. E. (1975). On colored-hearing synesthesia: Cross-modal translations of sensory dimensions. *Psychological Bulletin*, *82*(3), 303–331.

Mattingley, J. B., Payne, J., & Rich, A. N. (2006). Attentional load attenuates synaesthetic priming effects in grapheme-colour synaesthesia. *Cortex*, *42*(2), 213–221. doi:10.1016/S0010-9452(08)70346-0

Mattingley, J. B., Rich, A. N., Yelland, G., & Bradshaw, J. L. (2001). Unconscious priming eliminates automatic binding of colour and alphanumeric form in synaesthesia. *Nature*, *410*(6828), 580–582. doi:10.1038/35069062

Maurer, D. (1997). Neonatal synaesthesia: Implications for the processing of speech and faces. In S. Baron-Cohen & J. E. Harrison (Eds.), *Synaesthesia: Classic and Contemporary Readings* (pp. 224–242). Malden, MA, US: Blackwell Publishers Inc.

McClelland, J. L., & Rumelhart, D. E. (1981). An interactive activation model of context effects in letter perception: Part I. An account of basic findings. *Psychological Review*, *89*, 60–94.

Meier, B., & Rothen, N. (2009). Training grapheme-colour associations produces a synaesthetic Stroop effect, but not a conditioned synaesthetic response. *Neuropsychologia*, *47*(4), 1208–1211. doi:10.1016/j.neuropsychologia.2009.01.009

Mills, C. B., Viguers, M. L., Edelson, S. K., Thomas, A. T., Simon-Dackô, S. L., & Innis, J. A. (2002). The color of two alphabets for a multilingual synesthete. *Perception*, *31*(11), 1371–1394. doi:10.1068/p3429

Mroczko, A., Metzinger, T., Singer, W., & Nikolic, D. (2009). Immediate transfer of synesthesia to a novel inducer. *Journal of Vision*, *9*(12), 25 21–28. doi:10.1167/9.12.25

Muggleton, N., Tsakanikos, E., Walsh, V., & Ward, J. (2007). Disruption of synaesthesia following TMS of the right posterior parietal cortex. *Neuropsychologia*, *45*(7), 1582–1585. doi:10.1016/j.neuropsychologia.2006.11.021

Myles, K. M., Dixon, M. J., Smilek, D., & Merikle, P. M. (2003). Seeing double: The role of meaning in alphanumeric-colour synaesthesia. *Brain and Cognition*, *53*(2), 342–345. doi:10.1016/S0278-2626(03)00139-8

Novich, S., Cheng, S., & Eagleman, D. M. (2011). Is synaesthesia one condition or many? A large-scale analysis reveals subgroups. *Journal of Neuropsychology*, *5*, 353–371. doi:10.1111/j.1748-6653.2011.02015.x

Nunn, J. A., Gregory, L. J., Brammer, M., Williams, S. C. R., Parslow, D. M., Morgan, M. J., … Gray, J. A. (2002). Functional magnetic resonance imaging of synesthesia: Activation of V4/V8 by spoken words. *Nature Neuroscience*, *5*(4), 371–375. doi:10.1038/nn818

Palmeri, T. J., Blake, R. B., Marois, R., Flanery, M. A., & Whetsell, W. O. (2002). The perceptual reality of synesthetic color. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 4127–4131. doi:10.1073/pnas.022049399

Paulesu, E., Harrison, J. E., Baron-Cohen, S., Watson, J. D. G., Goldstein, L., Heather, J., … Frith, C. D. (1995). The physiology of coloured hearing: A PET activation study of colour-word synaesthesia. *Brain*, *118*, 661–676. doi:10.1093/brain/118.3.661

Petroff, O. A. (2002). GABA and glutamate in the human brain. *The Neuroscientist*, *8*(6), 562–573. doi:10.1177/1073858402238515

Ramachandran, V. S., & Hubbard, E. M. (2001a). Psychophysical investigations into the neural basis of synaesthesia. *Proceedings of the Royal Society Biological Sciences Series B*, *268*(1470), 979–983. doi:10.1098/rspb.2000.1576

Ramachandran, V. S., & Hubbard, E. M. (2001b). Synaesthesia: A window into perception, thought and language. *Journal of Consciousness Studies*, *8*(12), 3–34.

Rich, A. N., Bradshaw, J. L., & Mattingley, J. B. (2005). A systematic, large scale study of synaesthesia: Implications for the role of early experience in lexical-colour associations. *Cognition*, *98*(1), 53–84. doi:10.1016/j.cognition.2004.11.003

Rich, A. N., & Mattingley, J. B. (2003). The effects of stimulus competition and voluntary attention on colour-graphemic synaesthesia. *Neuroreport*, *14*(14), 1793–1798. doi:10.1097/01.wnr.0000091135.75061.aa

Rich, A. N., Williams, M. A., Puce, A., Syngeniotis, A., Howard, M. A., McGlone, F., & Mattingley, J. B. (2006). Neural correlates of imagined and synaesthetic colours. *Neuropsychologia*, *44*(14), 2918–2925. doi:10.1016/j.neuropsychologia.2006.06.024

Robertson, L. C. (2003). Binding, spatial attention and perceptual awareness. *Nature Reviews Neuroscience*, *4*(2), 93–102. doi:10.1038/nrn1030

Rothen, N., Nyffeler, T., von Wartburg, R., Muri, R., & Meier, B. (2010). Parieto-occipital suppression eliminates implicit bidirectionality in grapheme-colour synaesthesia. *Neuropsychologia*, *48*(12), 3482–3487. doi:10.1016/j.neuropsychologia.2010.07.032

Rouw, R., & Scholte, H. S. (2007). Increased structural connectivity in grapheme-color synesthesia. *Nature Neuroscience*, *10*(6), 792–797. doi:10.1038/nn1906

Rouw, R., & Scholte, H. S. (2010). Neural basis of individual differences in synesthetic experiences. *Journal of Neuroscience*, *30*(18), 6205–6213. doi:10.1523/JNEUROSCI.3444-09.2010

Rouw, R., Scholte, H. S., & Colizoli, O. (2011). Brain areas involved in synaesthesia: A review. *Journal of Neuropsychology*, *5*, 214–242. doi:10.1111/j.1748-6653.2011.02006.x

Sagiv, N., Heer, J., & Robertson, L. C. (2006). Does binding of synesthetic color to the evoking grapheme require attention? *Cortex*, *42*(2), 232–242. doi:10.1016/S0010-9452(08)70348-4

Sagiv, N., Simner, J., Collins, J., Butterworth, B., & Ward, J. (2006). What is the relationship between synaesthesia and visuo-spatial number forms? *Cognition*, *101*(1), 114–128. doi:10.1016/j.cognition.2005.09.004

Sagiv, N., & Ward, J. (2006). Cross-modal interactions: Lessons from synesthesia. In S. Martinez-Conde, S. L. Macknik, L. M. Martinez, J.-M. Alonso & P. U. Tse (Eds.), *Progress in Brain Research* (Vol. 155, pp. 263–275). London: Elsevier Science.

Seron, X., Pesenti, M., Noel, M.-P., Deloche, G., & Cornet, J.-A. (1992). Images of numbers: Or "When 98 is upper left and 6 sky blue". *Cognition*, *44*(1–2), 159–196. doi:10.1016/0010-0277(92)90053-K

Shanon, B. (2002). Ayahuasca visualizations: A structural typology. *Journal of Consciousness Studies*, *9*(2), 3–30.

Simner, J., Gärtner, O., & Taylor, M. D. (2011). Cross-modal personality attributions in synaesthetes and non-synaesthetes. *Journal of Neuropsychology*, *5*, 283–301. doi:10.1111/j.1748-6653.2011.02009.x

Simner, J., & Holenstein, E. (2007). Ordinal linguistic personification as a variant of synesthesia. *Journal of Cognitive Neuroscience*, *19*(4), 694–703.

Simner, J., & Hubbard, E. M. (2006). Variants of synesthesia interact in cognitive tasks: Evidence for implicit associations and late connectivity in cross-talk theories. *Neuroscience*, *143*(3), 805–814. doi:10.1016/j.neuroscience.2006.08.018

Simner, J., Mulvenna, C., Sagiv, N., Tsakanikos, E., Witherby, S. A., Fraser, C., . . . Ward, J. (2006). Synaesthesia: The prevalence of atypical cross-modal experiences. *Perception*, *35*(8), 1024–1033. doi:10.1068/p5469

Simner, J., & Ward, J. (2008). Synaesthesia, color terms, and color space: Color claims came from color names in Beeli, Esslen, and Jäncke (2007). *Psychological Science*, *19*(4), 412–414. doi:10.1111/j.1467-9280.2008.02101.x

Simner, J., Ward, J., Lanz, M., Jansari, A. S., Noonan, K., Glover, L., & Oakley, D. A. (2005). Non-random associations of graphemes to colours in synaesthetic and non-synaesthetic populations. *Cognitive Neuropsychology*, *22*(8), 1069–1085. doi:10.1080/02643290500200122

Simon, O., Mangin, J. F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, *33*(3), 475–487. doi:10.1016/S0896-6273(02)00575-5

Smilek, D., Carriere, J. S., Dixon, M. J., & Merikle, P. M. (2007). Grapheme frequency and color luminance in grapheme-color synaesthesia. *Psychological Science*, *18*(9), 793–795. doi:10.1111/j.1467-9280.2007.01981.x

Smilek, D., Dixon, M. J., Cudahy, C., & Merikle, P. M. (2001). Synaesthetic photisms influence visual perception. *Journal of Cognitive Neuroscience*, *13*(7), 930–936. doi:10.1162/089892901753165845

Smilek, D., Dixon, M. J., & Merikle, P. M. (2005). Synaesthesia: Discordant male monozygotic twins. *Neurocase*, *11*(5), 363–370. doi:10.1080/13554790500205413

Smilek, D., Malcolmson, K. A., Carriere, J. S., Eller, M., Kwan, D., & Reynolds, M. (2007). When "3" is a Jerk and "E" is a King: Personifying Inanimate Objects in Synesthesia. *Journal of Cognitive Neuroscience*, *19*(6), 981–992. doi:10.1162/jocn.2007.19.6.981

Smilek, D., Moffatt, B. A., Pasternak, J., White, B. N., Dixon, M. J., & Merikle, P. M. (2002). Synaesthesia: A case study of discordant monozygotic twins. *Neurocase*, *8*(4), 338–342. doi:10.1076/neur.8.3.338.16194

Spalding, J. M. K., & Zangwill, O. (1950). Disturbance of number-form in a case of brain injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *12*, 24–29.

Specht, K., & Laeng, B. (2011). An Independent Component Analysis of fMRI data of grapheme-color synaesthesia. *Journal of Neuropsychology*, *5*, 203–213. doi:10.1111/j.1748-6653.2011.02008.x

Sperling, J. M., Prvulovic, D., Linden, D. E. J., Singer, W., & Stirn, A. (2006). Neuronal correlates of graphemic colour synaesthesia: A fMRI study. *Cortex*, *42*(2), 295–303. doi:10.1016/S0010-9452(08)70355-1

Steven, M. S., Hansen, P. C., & Blakemore, C. (2006). Activation of color selective areas of visual cortex in a blind synesthete. *Cortex*, *42*(2), 304–308. doi:10.1016/S0010-9452(08)70356-3

Tang, J., Ward, J., & Butterworth, B. (2008). Number forms in the brain. *Journal of Cognitive Neuroscience*, *20*(9), 1547–1556. doi:10.1162/jocn.2008.20120

Tomson, S. N., Avidan, N., Lee, K., Sarma, A. K., Tushe, R., Milewicz, D. M., ... Eagleman, D. M. (2011). The genetics of colored sequence synesthesia: Suggestive evidence of linkage to 16q and genetic heterogeneity for the condition. *Behavioural Brain Research*, *223*(1), 48–52. doi:10.1016/j.bbr.2011.03.071

van Leeuwen, T. M., Petersson, K. M., & Hagoort, P. (2010). Synaesthetic colour in the brain: Beyond colour areas. A functional magnetic resonance imaging study of synaesthetes and matched controls. *PLoS One*, *5*(8), e12074. doi:10.1371/journal.pone.0012074

Vinckier, F., Dehaene, S., Jobert, A., Dubus, J. P., Sigman, M., & Cohen, L. (2007). Hierarchical coding of letter strings in the ventral stream: Dissecting the inner organization of the visual word-form system. *Neuron*, *55*(1), 143–156. doi:10.1016/j.neuron.2007.05.031

Ward, J., Jonas, C. N., Dienes, Z., & Seth, A. (2010). Grapheme-colour synaesthesia improves detection of embedded shapes, but without pre-attentive 'pop-out' of synaesthetic colour. *Proceedings of the Royal Society Biological Sciences Series B*, *277*(1684), 1021–1026. doi:10.1098/rspb.2009.1765

Ward, J., & Simner, J. (2005). Is synaesthesia an X-linked dominant trait with lethality in males? *Perception*, *34*(5), 611–623. doi:10.1068/p5250

Ward, J., Simner, J., & Auyeung, V. (2005). A comparison of lexical-gustatory and grapheme-colour synaesthesia. *Cognitive Neuropsychology*, *22*(1), 28–41. doi:10.1080/02643290442000022

Ward, J., Thompson-Lake, D., Ely, R., & Kaminski, F. (2008). Synaesthesia, creativity and art: What is the link? *British Journal of Psychology*, *99*(1), 127–141. doi:10.1348/000712607X204164

Weiss, P. H., & Fink, G. R. (2009). Grapheme-colour synaesthetes show increased grey matter volumes of parietal and fusiform cortex. *Brain*, *132*(Pt 1), 65–70. doi:10.1093/brain/awn304

Weiss, P. H., Zilles, K., & Fink, G. R. (2005). When visual perception causes feeling: Enhanced cross-modal processing in grapheme-color synesthesia. *Neuroimage*, *28*(4), 859–868. doi:10.1016/j.neuroimage.2005.06.052

Wollen, K. A., & Ruggiero, F. T. (1983). Colored-letter synesthesia. *Journal of Mental Imagery*, *7*(2), 83–86.

Zorzi, M., Di Bono, M. G., & Fias, W. (2011). Distinct representations of numerical and non-numerical order in the human intraparietal sulcus revealed by multivariate pattern recognition. *Neuroimage*, *56*(2), 674–680. doi:10.1016/j.neuroimage.2010.06.035

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