Grapheme-Colour and Tone-Colour Synaesthesia is Associated with Structural Brain Changes in Visual Regions Implicated in Colour, Form and Motion

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Abstract

Synaesthesia is a rare condition in which stimulation in one modality leads to a secondary experience in another sensory modality. Varying accounts attribute the condition to either neuroanatomical differences between the synaesthetes and non-synaesthetes or functional differences in how sensory brain regions interact. This study employed voxel-based-morphometry to examine whether synaesthetes who experience both grapheme-colour and tone-colour synaesthesia as their evoked sensation show neuroanatomical differences in gray matter volume compared to non-synaesthetes. We observed that synaesthetes showed an increase in gray matter volume in left posterior fusiform gyrus, but a concomitant decrease in anterior regions of left fusiform gyrus and left MT / V5. These findings imply that synaesthesia for colour is linked to neuroanatomical changes between adjacent regions of the visual system.

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Introduction

Synaesthesia is a condition in which one property of a stimulus results in conscious experiences of an additional attribute (Cohen Kadosh & Henik, 2007; Ramachandran & Hubbbard, 2001). For example, in grapheme-colour synaesthesia a visually presented grapheme results in synaesthetic experiences of colour (Ramachandran & Hubbbard, 2001). The developmental form of the condition is thought to occur in approximately 4% of the population (Simner et al., 2006), with the most common variants occurring in 1.5-2% of people (Simner et al., 2006; Banissy, Cohen Kadosh, Maus, Walsh, & Ward, 2009). The authenticity of synaesthesia is now well established (e.g. Baron-Cohen, Harrison, Goldstein and Wyke, 1993; Cohen Kadosh & Henik, 2007; Ramachandran & Hubbbard, 2001; Ward and Simner, 2003) and there is growing interest in using the condition to shed light on basic mechanisms of perception and cognition (e.g. Banissy, Garrido, Kusnir, Duchaine, Walsh, & Ward, 2011; Banissy & Ward, 2007; Sagiv & Ward, 2006; Simner, 2007).

Despite this, the neural mechanisms which underpin synaesthesia are a subject of debate. A current area of dispute in the synaesthesia literature is whether synaesthetic experience is due to differences in brain structure (e.g. structural connectivity) or brain function (e.g. changes in cortical inhibition/excitability) (Bargary & Mitchell, 2008; Cohen Kadosh & Walsh, 2008; Eagleman, 2009; Hubbard & Ramachandran, 2005; Smilek et al., 2001). In support of structural connectivity accounts, grapheme-colour synaesthetes have been reported to show increased gray matter in the fusiform gyrus (FG) and intraparietal sulcus (IPS) (Weiss & Fink, 2009) and more coherent white matter in inferior-temporal, parietal and frontal brain regions (Rouw & Scholte, 2007). Evidence for functional accounts has been provided by

findings that synaesthetic-like experiences can be induced following hallucinogenic drugs (Aghajanian & Marek, 1999), that the phenomenology of grapheme-colour synaesthesia can be induced in non-synaesthetes (individuals without aberrant connectivity) using post-hypnotic suggestion (Cohen Kadosh, Henik, Catena, & Walsh, 2009), and that linguistic-colour synaesthetes show differences to non-synaesthetes in visual cortex excitability (Barnett et al., 2008).

In addition to debates on the neurophysiological mechanisms of synaesthesia, there is further debate concerning functional models of the condition. These can be divided by the neurophysiological substrates which each model favours. Cross-activation models contend that synaesthesia arises from cross activity between adjacent brain regions and consider synaesthesia in terms of excess anatomical connections between those brain regions - e.g. in grapheme-colour synaesthesia, neural activity in anterior regions of the fusiform gyrus involved in processing grapheme meaning and form leading to direct cross-activation of adjacent areas of the fusiform gyrus involved in processing colour (Hubbard & Ramachandran, 2005; Ramachandran & Hubbbard, 2001). Disinhibition of feedback accounts contend that synaesthesia arises from disinhibition of long range feedback from multisensory (e.g. temporal-parietal junction; intraparietal sulcus) to sensory-specific (e.g. colour selective regions of the fusiform gyrus) brain areas, and consider synaesthesia in terms of differences in cortical inhibition between multisensory and sensory-specific brain regions (Grossenbacher & Lovelace, 2001). Local perceptual unmasking accounts contend that synaesthesia arises from unmasking of unimodal neurons that exist in another unimodal area and consider synaesthesia in terms of differences of cortical inhibition / excitability within sensory-specific brain regions (Cohen Kadosh & Henik, 2007; Cohen Kadosh & Walsh, 2008). Hyper-binding accounts suggest that

over-activity in parietal regions results in stronger than normal binding of sensory attributes leading to synaesthetic experience (e.g. Esterman, Verstynen, Ivry, & Robertson, 2006; Hubbard, 2007). Finally, re-entrant processing models combine mechanisms of cortical connectivity and differences in cortical inhibition to account for the condition, contending that synaesthesia arises through local feedback connections between regions involved in processing the meaning of the stimulus which evokes synaesthesia and sensory-specific regions of the cortex - e.g. in grapheme-colour synaesthesia, neural activity involved in processing the meaning and form of the grapheme within anterior fusiform and posterior inferior temporal cortex feedback to adjacent areas of the fusiform gyrus involved in processing colour (Smilek, Dixon, Cudahy, & Merikle, 2001).

In an attempt to address the neural mechanisms of synaesthesia further we used voxel-based morphometry (VBM) to assess structural brain correlates in a group of nine synaesthetes who experience grapheme-colour synaesthesia and tone-colour synaesthesia (in which tones evoke visual experiences of colour and form), in comparison to a larger group of forty-two non-synaesthetes. Specifically, we investigated whether their synaesthesia was linked to differences in gray matter volumes in brain regions known to be involved in multisensory integration and in regions linked to synaesthetic experience.

Methods

Participants

Nine synaesthetic participants (4 males, 5 females; mean age = 38 years, SD = 8 years) and forty-two non-synaesthetic controls (21 male, 21 female; mean age = 32 years, SD = 7 years) took part. Two synaesthete participants were left-handed, all

other participants were right-handed. For all synaesthetes, grapheme-colour associations were confirmed with tests of consistency over 2-3 months. Eight of the nine synaesthetes had participated in a previous study on tone-colour synaesthesia in which the consistency of synaesthetic associations for sounds (including single tones of different pitch and timbre) was confirmed over a 2-3 month retest. The automaticity of their tone-colour synaesthesia was also assessed using a synaesthetic Stroop paradigm in which participants had to name the real colour of a coloured patch and ignore the synaesthetic colour of a simultaneously presented tone. Synaesthetes showed interference when the colour of the tone was incongruent with the real colour (Ward, Huckstep, & Tsakanikos, 2006).

MRI data acquisition

MR images were acquired on a 1.5-T Siemens Sonata MRI scanner (Siemens Medical, Erlangen, Germany). High-resolution anatomical images were acquired using a T1-weighted 3-D Modified Driven Equilibrium Fourier Transform (MDEFT) sequence (voxel size = 1 x 1 x 1.5 mm).

Data analyses

Voxel-based morphometry: T1-weighted MR images were first segmented for gray matter and white matter using the segmentation tools in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Subsequently, we performed Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007) in SPM8 for inter-subject registration of the GM images. The registered images were then transformed to MNI stereotactic space using affine and non-linear spatial normalisation implemented in SPM8 for statistical analysis. Voxel-wise t-tests were

conducted to detect differences in local gray matter concentration between synaesthetes and control groups. The gender and age of the participants were included in the design matrix as covariates of no interest to regress out any effects of these factors. We employed small volume correction for multiple comparisons within a sphere (12mm radius) for coordinates of: ± 34, -67, -15 (bilateral fusiform gyrus), ± 50 -62 4 (human MT / V5), ± 50 -55 7 (middle temporal gyrus), and ± 24 -64 +47 (intraparietal sulcus). The regions were selected based on a previous VBM study documenting gray matter differences in the fusiform gyrus and intraparietal sulcus of grapheme-colour synaesthetes relative to non-synaesthetes (Weiss & Fink, 2009), on a functional brain imaging study examining regions involved in audiovisual integration in non-synaesthetes (Beauchamp, Lee, Argall, & Martin, 2004), and a functional brain imaging study of tone-colour synaesthesia (Stewart et al., in prep). For each of the pre-defined loci, we used $p < 0.05$ family-wise error (FWE) corrected for the small volume (see Worsley et al. 1996) as the criterion to detect voxels with a significant difference between the synaesthetes and control groups. Outside those regions we used a threshold of $p < 0.05$, corrected for multiple comparisons across the whole brain volume.

Results

Region of interest analysis

Regional (i.e. voxel-by-voxel) differences in gray matter between groups were assessed, with age and gender included as covariates of no interest. Region of interest (ROI) analyses were then conducted to detect possible differences in gray matter volumes between groups. This ROI-analysis revealed that synaesthetes displayed significant increases in gray matter volume in the left posterior fusiform gyrus (-33, -

72, -12; T = 2.99, p small volume corrected [psvc] = < .05), but reduced volume in left MT / V5 (-45, -61, 4; T = 3.13, psvc = < .05) and left anterior fusiform gyrus (-29 -63 -9; T = 2.90, psvc = < .05; Figure 1). No significant differences between the gray matter volumes of synaesthetes and controls were found at our regions of interest in middle temporal gyrus and intraparietal sulcus.

The region of increased gray matter in the left posterior fusiform was determined as being located in the maximum probability map of left V4 (Eickhoff et al., 2005) and is consistent with previous anatomically delineated coordinates for the posterior sub-region of human V4 (Bartels & Zeki, 2000) and functional brain imaging identifying posterior left V4 (Morita, Kochiyama, Okado, Yonekura, Matsumura, & Sadato, 2004). It is also in line with a previous report of increased gray matter volume between grapheme-colour synaesthetes and non-synaesthetes in left posterior fusiform gyrus (Weiss & Fink, 2009). The region of decreased gray matter volume in the left anterior fusiform gyrus is in accordance with previous functional brain imaging studies identifying anterior left V4 (Morita et al., 2004) and regions of the fusiform gyrus involved in processing grapheme meaning and form (termed by some as the visual word form area -- e.g. Cohen, Jobert, Le Bihan, & Dehaene, 2004; also see McCandliss, Cohen, & Dehaene, 2003 for review). The regional differences in left MT / V5 were also confirmed to be located within the maximum probability map of this region (Eickhoff et al., 2005) and the peak coordinates are consistent with previous functional brain imaging of human MT / V5 (e.g. Watson et al., 1993; Dumoulin et al. 2000).

To examine the extent of the difference in gray matter density between synaesthetes and non-synaesthetes, we also calculated receiver operation curves (ROC; Figure 2) at each region that significantly differed between the groups. This

analysis provides a standardised estimate of the size of the difference in volume for synaesthetes relative to controls, which can be inferred by the area under the ROC (AUC). Permutation tests revealed that the AUC significantly differed from chance level (0.5) at the left posterior fusiform gyrus (AUC = 0.218, p = 0.005); left MT/V5 (AUC = 0.828, p = 0.0002); and left anterior fusiform gyrus (AUC = 0.783, p = 0.003).

(FIGURE 1 HERE)

(FIGURE 2 HERE)

Whole brain analysis

We did not observe any significant differences between groups at a threshold of P<0.05, corrected for multiple comparisons. Post-hoc analysis at a liberal statistical threshold (p < .005 uncorrected at the voxel level; Table 1) revealed that, in addition to left posterior fusiform gyrus, synaesthetes displayed significant increases in gray matter volume in right precentral gyrus (42, -4, 42; T = 3.59,), left anterior middle temporal gyrus (-57 -18 -15, T = 3.33) and right supramarginal gyrus (53, -21, -24; T = 2.73). These regions may be useful for future studies of synaesthesia that find differences in similar brain regions and may offer new lines of enquiry, however we refrain from discussion of these findings given the liberal statistical threshold used and that we did not have a priori hypotheses about them. The whole brain analysis examining reduced gray matter volume at a threshold of p <.005 uncorrected was also consistent with our ROI analysis and revealed that synaesthetes showed reduced gray matter volume in left anterior fusiform gyrus and left MT/V5 (Table 2).

(INSERT TABLE 1 AND 2 HERE)

Discussion

This study used voxel-based morphometry to assess the structural brain correlates of a group of synaesthetes who experience colour for graphemes and tones. The findings show that the presence of grapheme and tone-colour synaesthesia is associated with increased gray matter volume in the left posterior fusiform gyrus, but a decrease in cortical volume at a region corresponding to left V5 / MT and left anterior fusiform gyrus. These results are consistent with reports of altered gray and white matter in grapheme-colour synaesthesia (Rouw & Scholte, 2007; Rouw & Scholte, 2010; Weiss & Fink, 2009). They also provide a key addition, by demonstrating for the first time that synaesthesia involving colour is not only linked to an increase in regions of the visual cortex involved in colour processing, but is also linked to a concomitant decrease in adjacent regions of the visual system.

Varying accounts of synaesthesia attribute the condition to differences in brain structure (e.g. Rouw & Scholte, 2007; Bargary & Mitchell, 2008), changes in brain function (e.g., Cohen Kadosh & Walsh, 2008; Grossenbacher & Lovelace, 2001), or a combination of both (Smilek et al., 2001). Moreover, different models have highlighted a role for cross-activity between adjacent brain regions involved in processing the synaesthetic inducer (e.g. graphemes) and the synaesthetic experience (e.g. colour) (Hubbard & Ramachandran, 2001); re-entrant feedback mechanisms (e.g. between anterior fusiform gyrus / posterior inferior temporal regions and human V4; Smilek et al., 2001); disinihibited feedback between multisensory and sensory-specific regions of the cortex (Grossenbacher & Lovelace, 2001); or differences in local mechanisms of inhibition/excitation within sensory-specific cortices (Cohen

Kadosh & Henik, 2007; Cohen Kadosh & Walsh, 2008). While it is difficult to directly infer function from a study of differences in neuroanatomy, our findings could be explained by at least three of these accounts. Clearly, the adjacent increase and decrease within the fusiform gyrus is consistent with cross-activation and re-entrant accounts of grapheme-colour synaesthesia that posit a role for structural variation and adjacency in the condition. They could also be explained by inhibition/excitation accounts, as the structural changes reported may be a consequence of sustained differences in cortical excitability/inhibition within the visual system. Moreover, as has been shown in other domains (e.g. studies into sensory deprivation) sustained changes in cortical inhibition / excitation can result in local and widespread anatomical changes in the brain (e.g. Pascual-Leone et al., 2005). There is no reason to assume that synaesthetes should deviate from this and delineating the contribution that any differences in cortical excitability have on structural alterations in synaesthesia is an important challenge for future studies.

The reduced gray matter volume in the region corresponding to left V5 / MT is also a particularly striking finding. In non-synaesthetes, suppressing neural activity in V5 / MT disrupts motion processing but facilitates responses to colour and form targets (Ellison, Battelli, Cowey, & Walsh, 2003; Walsh, Ellison, Battelli, & Cowey, 1998; Morland, Ogilvie, Ruddock, & Wright, 1996). These findings have been interpreted as evidence of a mutual inhibition between visual areas involved in colour and form processing (e.g. V4) and motion processing (e.g. V5 /MT); with V5 / MT responsiveness modulating V4 and vice versa (Ellison et al., 2003; Walsh et al., 1998). While some caution is warranted in inferring physiology from neuroanatomy (especially because we did not functionally localize motion and colour regions on an individual subjects basis), we suggest that one possibility for the increase in cortical

volume within the posterior fusiform gyrus but reduction in motion-selective regions of the visual cortex, may reflect a prioritizing of areas involved in colour and form processing (e.g. facilitated V4 activity) leading to an inhibition and concomitant decrease in motion selective brain region sensitivity. In accordance with this, Barnett and colleagues (2008) report that linguistic-colour synaesthetes show increased cortical responsiveness to simple visual stimuli which bias activation of parvocellular pathways sensitive to colour perception and visual recognition processes (Kaplan, 1991), but a decreased response to stimuli which bias activation of magnocellular pathways sensitive to motion perception and action-related behaviours (Kaplan, 1991). Previous work also indicates that synaesthetes who experience colour show heightened colour sensitivity (Banissy, Walsh, & Ward, 2009; Yaro & Ward, 2007), implying facilitated activity in colour-selective brain regions. Based on our findings and those of Barnett et al. (2008) we are now assessing whether colour synaesthetes show a parallel decrease in motion perception abilities.

A further factor of interest for future studies is to consider the extent to which the differences reported here are functions of synaesthetes experiencing grapheme-colour synaesthesia, tone-colour synaesthesia, or a combination of both. While all of the synaesthetes in the current study experience both variants of synaesthesia, it is reasonable to assume that the pattern of results would not differ were they all only grapheme-colour synaesthetes or only tone-colour synaesthetes because the likelihood is that the differences are a function of abnormal responses to colour rather than the specific variants of synaesthesia per se. Nevertheless, this is an interesting avenue to explore with future studies.

In sum, our findings show that colour synaesthesia is linked to increased gray matter volume in posterior regions of the fusiform gyrus involved in processing

colour, but a parallel reduction in volume for adjacent anterior fusiform regions and in regions of the visual cortex linked to processing motion. These findings are consistent with other studies reporting neuoranatomical changes in synaesthesia and provide new anatomical substrates that can inform future studies.

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Figure 1. Synaesthetes who experience colour show increased gray matter volume in left posterior fusiform gyrus (shown in red), but decreased volume in left anterior fusiform gyrus (shown in green) and left MT / V5 (shown in blue). Clusters are thresholded at $p < 0.001$ (uncorrected) for display purposes.

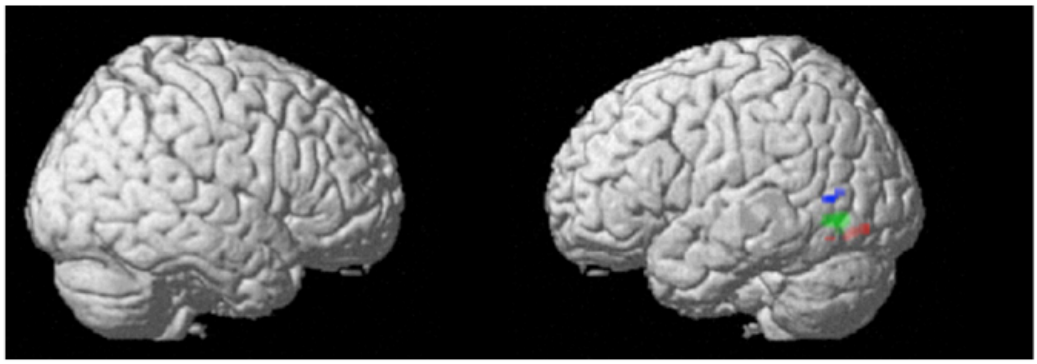

Figure 2. a) Independent samples t-tests showing significant differences between synaesthetes (S) and controls (C) in gray matter volume at the peak voxel location of left posterior fusiform gyrus, left MT/V5 and left anterior fusiform gyrus (** = p <.001). **b)** Receiver operating curve analysis showing a standardised estimate of the size of the difference in volume for synaesthetes relative to controls at posterior left fusiform gyrus, left MT/V5 and left anterior fusiform gyrus. The cumulative probability density functions (c.d.f.) of gray matter density for synaesthetes are plotted against those for controls. The AUC significantly differed from chance level at each site (p <.05).

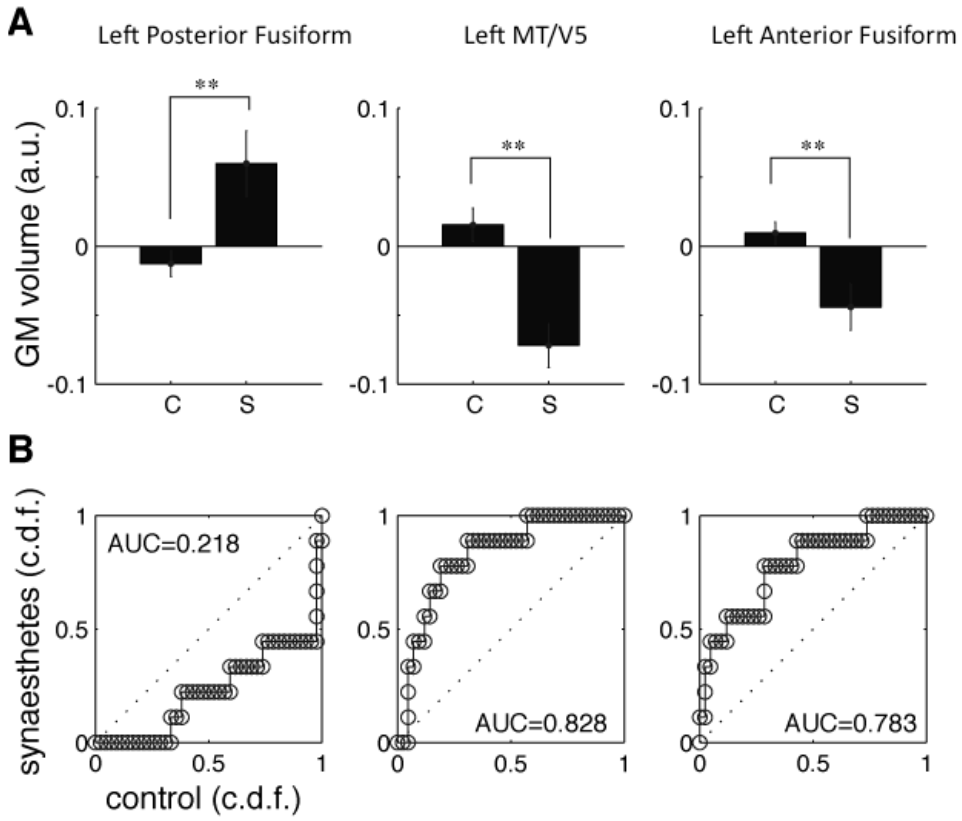

Table 1. Whole brain analysis (p = <.005 uncorrected) examining regions of increased grey matter volume in synaesthetes relative to non-synaesthetic controls. For each cluster, from left to right, we describe: the anatomical description of that cluster based on the anatomy toolbox (Eickhoff et al., 2005); the hemisphere containing the cluster; the cluster size (mm^2); the MNI coordinates of the peak voxel; and the uncorrected p value.

Anatomical Location	Hemisphere	Cluster Size (mm^2)	MNI Coordinates			*P* value (df = 1, 47)
			x	Y	z	
Precentral Gyrus	Right	59	42	-4	42	< 0.001
Middle Temporal Gyrus	Left	42	-57	-18	-15	0.001
Fusiform Gyrus	Left	50	-33	-72	-12	0.002
Inferior-occipital Gyrus	Left		-32	-79	-9	0.002
Fusiform Gyrus	Left		-35	-63	-14	0.004
Supramarginal Gyrus	Right	16	53	-21	24	0.003

Table 2. Whole brain analysis (p = <.005 uncorrected) examining regions of decreased grey matter volume in synaesthetes relative to non-synaesthetic controls. For each cluster, from left to right, we describe: the anatomical description of that cluster based on the anatomy toolbox (Eickhoff et al., 2005); the hemisphere containing the cluster; the cluster size (mm^2); the MNI coordinates of the peak voxel; and the uncorrected p value.

Anatomical Location	Hemisphere	Cluster Size (mm^2)	MNI Coordinates			*P* value (df = 1, 47)
			x	y	z	
Fusiform Gyrus	Left	147	-30	-64	-5	< 0.001
Middle Temporal Gyrus	Left	97	-45	-61	4	0.002
Middle Temporal Gyrus	Left		-36	-64	6	0.003