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Grapheme-colour synaesthetes show increased grey matter volumes of parietal and fusiform cortex

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In synaesthesia, stimulation of a sensory modality triggers abnormal additional perceptions. Voxel-based morphometry (VBM) was used in 18 grapheme-colour synaesthetes to investigate the neuro-anatomical basis of their abnormal perceptions. More specifically, we tested the hypothesis that in synaesthesia altered connectivity in temporo-occipital and parietal areas may be associated with grey matter (GM) changes. The data reveal increased GM volumes in fusiform and intraparietal cortices. These findings are consistent with the two-stage model of grapheme-colour synaesthesia implying cross-activation at the level of the fusiform gyrus (FG) and 'hyperbinding' at the level of the parietal cortex. The observed structural differences in grapheme-colour synaesthetes with abnormal additional perceptions may also shed some light on the neural bases of abnormal perceptions in neurological and psychiatric disorders.

Keywords: voxel-based morphometry; parietal cortex; fusiform gyrus; colour area; V4/V8, grapheme area (VWFA)

Abbreviations: CIP = caudal intraparietal area; DTI = diffusion tensor imaging; FG = fusiform gyrus; GM = grey matter; IPS = intraparietal sulcus; MNI = Montrael Neurological Institute; ROI = Region of interest; VBM = Voxel-based morphometry; WM = white matter

Introduction

In synaesthesia, stimulation of one sensory modality results in abnormal additional percepts (Weiss *et al*., 2001), either within the same modality or across modalities. The best studied variant of synaesthesia, grapheme-colour synaesthesia, has a prevalence of about 2% in the population (Simner *et al*., 2006). In this condition, the presentation of a grapheme leads to an additional synaesthetic colour percept which causes clear psycho-physical effects (Dixon *et al*., 2000; Mattingley *et al*., 2001; Cohen Kadosh *et al*., 2007*b*). However, the neural basis of synaesthesia remains elusive to date. A better understanding of the neural mechanisms underlying synaesthetic experiences may also help to elucidate the pathophysiology of other abnormal perceptions observed in neurological or psychiatric conditions (Cohen Kadosh and Henik, 2007) such as, e.g. in Charles Bonnet syndrome or schizophrenia (Hubbard, 2007*b*). Specifically, one model of (grapheme-colour) synaesthesia proposes that over-activity in parietal regions, where the binding of different sensory information into coherent representations physiologically occurs, leads to stronger than normal binding of, e.g. colours and graphemes, resulting in the additional abnormal synaesthestic experiences (Esterman *et al*., 2006). Furthermore, investigations into the neural substrate of these abnormal binding mechanisms in synaesthesia may also shed some light on the neural bases of neuropsychological deficits resulting from lesions of the parietal cortex after stroke, e.g. Balint's syndrome and neglect, which may—at least in part—be caused by disturbed binding (Robertson, 2003).

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Integrating previous accounts (Hubbard and Ramachandran, 2005), a two-stage model of grapheme-colour synaesthesia has been proposed recently (Hubbard, 2007*a*, *b*). According to this model, synaesthetic experience may arise from abnormal cross-activation between the grapheme area and the colour area in the fusiform gyrus (FG) due to altered local connections. The synaesthetic colour perceptions generated in the FG are then bound together by parietal mechanisms resulting in a kind of 'hyperbinding'. Consistent with this two-stage model, previous functional imaging studies provided support for both an involvement of the FG (Nunn *et al*., 2002; Hubbard *et al*., 2005; Sperling *et al*., 2006; Cohen Kadosh *et al*., 2007*a*) and the parietal cortex (Weiss *et al*., 2005; Cohen Kadosh *et al*., 2007*a*) in grapheme-colour synaesthesia. Additional evidence that the parietal cortex may indeed be the locus of 'hyperbinding' in synaesthesia comes from studies using transcranial magnetic stimulation (TMS) (Esterman *et al*., 2006; Muggleton *et al*., 2007), in which TMS applied over caudal parietal cortex has been used to disrupt the (automatic) integration of grapheme processing and synaesthetic colour experience. Furthermore, using diffusion tensor imaging (DTI) and measures of fractional anisotropy (FA) in grapheme-colour synaesthetes, increased structural connectivity has recently been suggested for the white matter (WM) underlying the FG and the parietal cortex (Rouw and Scholte, 2007).

Thus, there is growing evidence for the organicity of synaesthesia. However, studies on grey matter (GM) changes in grapheme-colour synaesthesia, e.g. using voxel-based morphometry (VBM), are lacking so far. Therefore, we applied VBM in 18 grapheme-colour synaesthetes to further elucidate the neural basis of synaesthesia and to explore the two-stage model of synaesthesia. Specifically, in this study, we test the hypothesis that in grapheme-colour synaesthetes local changes of connectivity in temporo-occipital and intraparietal areas are associated with increased GM volumes in these areas.

Subjects and Methods

Subjects

Eighteen grapheme-colour synaesthetes and 18 control subjects without past or current neurological or psychiatric disease were investigated. The two groups were matched for age [synaesthetes 27.3 ± 8.1 years (mean ± SD), controls 26.8 ± 6.9 years], IQ as assessed by the MWT-B (Lehrl *et al*., 1995) (synaesthetes 116.9 ± 10.3, controls 116.3 ± 13.3), and handedness as assessed by the Oldfield handedness inventory (Oldfield, 1971) (synaesthetes' LQ: 62.6 ± 60, controls' LQ: 60 ± 69). All subjects performed within or above the normal range in a neuropsychological examination described in Weiss *et al*. (2005), including tests for colour vision and visuo-spatial abilities. As in Weiss *et al*. (2005), a test of consistency was used to verify the presence of genuine synaesthesia. For 129 items, the specific synaesthetic colour experience of each synaesthete was documented and re-tested without warning after at least 6 months. The colour responses of all synaesthetes were highly consistent over time (rate of consistent responses: 90.2 ± 7.6%).

Furthermore, we evaluated the individual patterns of synaesthetic experience in the 18 grapheme-colour synaesthetes participating in our study. Adopting the questionnaire developed by Rouw and Scholte (2007), which assesses whether a grapheme-colour synaesthete can be considered a 'projector' versus an 'associator', five of our subjects were classified as 'projectors' (questionnaire score above 0) and the remaining 13 subjects as 'associators' (questionnaire score below 0). Finally, the strength of the synaesthetic experiences in the grapheme-colour synaesthetes was assessed by a questionnaire adopted after Baron-Cohen and colleagues (1993).

MR imaging and analyses

High-resolution structural images were acquired on a 3T-whole body scanner (Siemens Trio, Erlangen, Germany) using a T_1-weighted 3D magnetization-prepared, rapid acquisition gradient echo (MP-RAGE) pulse sequence (TR = 2250 ms, TE = 3.03 ms, FOV = 256 mm, 176 sagittal slices of 1 mm thickness, flip angle = 9°, voxel size: 1 × 1 × 1). These high-resolution structural images were analysed by an optimized method of VBM using SPM2 as in Poettrich *et al*. (2008). This VBM protocol was based on the procedure proposed by Good *et al*. (2001) and special-purpose scripting tools provided by Dr Christian Gaser (http://dbm.neuro.uni-jena.de/vbm.html). For optimizing the stereotactic normalization procedure, the images were automatically segmented into GM, WM and cerebrospinal fluid probability maps. Afterwards, all nonbrain voxels were removed from the segmented images. The grey and WM maps obtained with this procedure were separately normalized to a grey and WM template representing the stereotactic standard space defined by the Montrael Neurological Institute (MNI) provided by SPM2. The transformation parameters derived from normalizing the individual GM map to the MNI templates were then used to normalize the individual anatomical images (T1). The normalized images of all participants (i.e. 36 subjects = 18 grapheme-colour synaesthetes and 18 control subjects) were averaged and smoothed to create a study-specific template with reduced scanner- and population-specific biases. In a second normalization step, we locally deformed the individual images to the study-specific template using non-linear spatial transformations. After correcting for non-uniformities in signal intensity, these normalized anatomical images were segmented into GM, WM, and cerebrospinal fluid maps. To correct for possible volume changes as a result of the non-linear spatial normalization, all images were modulated by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step (Good *et al*., 2001). The resulting modulated GM and WM maps were smoothed with a Gaussian kernel of 12 mm full-width at half-maximum. Furthermore, we assessed the effect of kernel size on the results of the VBM analysis using smoothing kernels of 10 and 8 mm. These analyses yielded the same pattern of results as the analysis with a smoothing kernel of 12 mm, which is part of the optimized VBM protocol by Good *et al*. (2001).

Consequently, global brain volume was calculated from the modulated images used for VBM. Differences in global brain volume between the two groups were assessed by a *t*-test. Regional (i.e. voxel-by-voxel) differences in GM between groups were assessed with an analysis of covariance (ANCOVA), considering mean corrected age and global brain volume as nuisance covariates. Differences in GM volume were expressed in percent change with respect to the study-specific template (cf. Gaser and Schlaug, 2003). In addition to a whole brain analysis with a threshold of $P < 0.05$, corrected, a region of interest (ROI) analysis, based on previous functional imaging data (Weiss *et al*., 2005) was applied to the VBM data to detect possible grey matter differences between the groups in the hypothesized target areas, i.e. intraparietal cortex and FG. These ROI-analyses were based on spherical search volumes centred on the respective activation peaks

of Weiss *et al*. (2005) for the intraparietal cortex (anterior intraparietal area, AIP: ±36, −50, +41; caudal intraparietal area, CIP: ±24, −65, +51) and the FG bilaterally (±34, −67, −15). Only two grapheme-colour synaesthetes who had participated in our previous fMRI study of synaesthesia (Weiss *et al*., 2005) also participated in the current morphometric study with 18 synaesthetes. We suggest that the high rate of new subjects (89%) justifies the use of ROI-analyses based upon the previous fMRI data in the current study, since the functional data set of the previous fMRI study can be considered unrelated to the current neuro-anatomical data set.

We included the corresponding ROIs of either hemisphere in our analyses, since previous studies have reported functional or structural differences in grapheme-colour synaesthetes for the FG and parietal cortex of either hemisphere. While some studies using fMRI to investigate the neural basis of grapheme-colour synaesthesia found activity differences in the colour-processing areas of the left FG (Nunn *et al*., 2002), a recent DTI study found structural differences in the right FG (Rouw and Scholte, 2007). Furthermore, other fMRI studies of grapheme-colour synaesthesia found activations in the FG bilaterally (Hubbard *et al*., 2005; Sperling *et al*., 2006). TMS applied over the right parietal cortex (Esterman *et al*., 2006; Muggleton *et al*., 2007) interfered with synaesthetic experiences, while functional and structural imaging with MRI revealed increased neural activity and increased structural connectivity in the left parietal cortex of grapheme-colour synaesthetes (Weiss *et al*., 2005; Rouw and Scholte, 2007).

Results

The global brain volumes did not differ significantly between grapheme-colour synaesthetes (1158 ± 73 ml) and control subjects (1115 ± 89 ml). For the whole brain analysis, VBM did not reveal significant differences in grey matter volume between the two groups. Consistent with the hypothesis, ROI-analyses revealed a significantly increased grey matter volume in the left caudal intraparietal sulcus (IPS) (−24, −64, +47; T = 3.84, $p_{SVC} < 0.05$) of the grapheme-colour synaesthetes (Fig. 1A–C). The anatomy toolbox by Eickhoff *et al*. (2005) confirmed that this region was located within the maximum probability map of human intraparietal area 3 (hIP3, see Fig. 1B, dark grey). Area hIP3, as characterized by

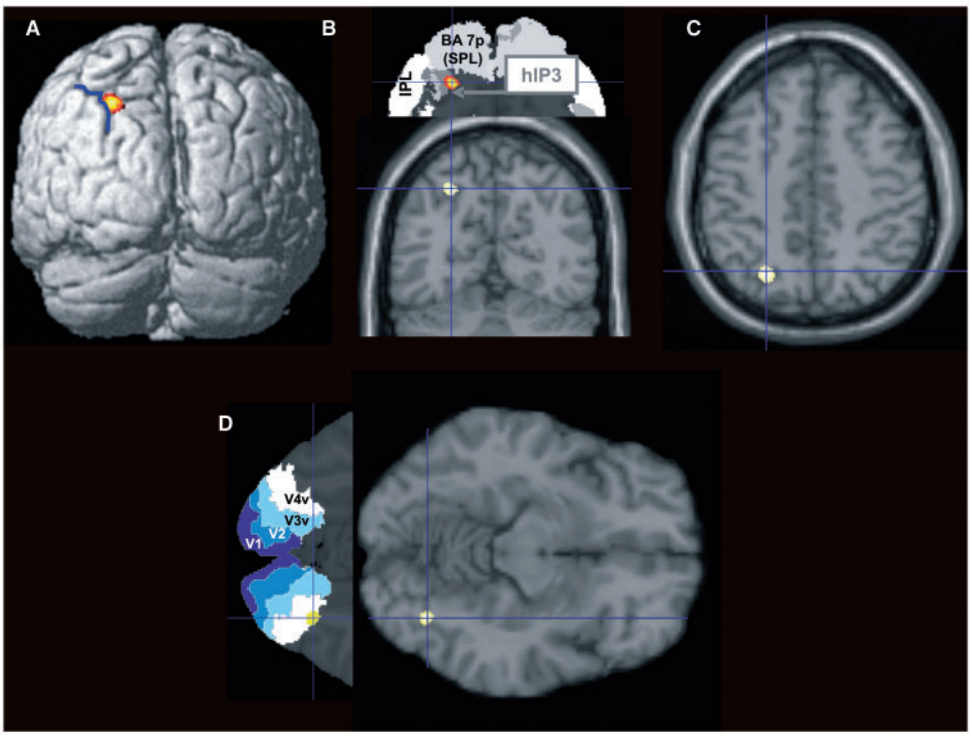

Fig. 1 Increased grey matter volumes in the left caudal IPS and the right fusiform gyrus (V4v) of grapheme-colour synaesthetes. (**A**) The area of increased GM volume in the left caudal IPS (maximum at −24, −64, +47) projected onto a 3D surface rendering of a single subject brain spatially normalized to the MNI space. The blue line indicates the IPS. (**B**) The area of GM difference in the left caudal IPS superimposed on a coronal section of the normalized standard single subject brain provided by SPM2 (lower part) to illustrate its location in the depth of the IPS. Furthermore, the upper part of Fig. 1B shows that the GM difference in the caudal IPS can be assigned to the maximum probability map of human intraparietal area 3 (hIP3, dark grey). Furthermore, the GM difference is located neither in the maximum probability map of Brodmann area (BA) 7p (posterior), which is part of the superior parietal lobe (SPL, light grey), nor in the areas comprising the inferior parietal lobe (IPL, white). (**C**) The area of GM difference in the caudal IPS superimposed on an axial section of the normalized standard single subject brain provided by SPM2. (**D**) The area of increased grey matter in the right fusiform gyrus (maximum at +34, −69, −11) is superimposed on an axial slice of an individual brain normalized to MNI space. The insert illustrates that this area is located within the maximum probability map of right V4v (white area) provided by the anatomy tool box (Eickhoff *et al*., 2005). The dark blue, blue and light blue areas indicate the maximum probability maps of V1, V2 and V3v, respectively.

(Scheperjans *et al*., 2008), is located in the caudal IPS, however, whether or not hIP3 comprises the CIP as defined in the macaque remains to be clarified (Shikata *et al*., 2003; Grefkes and Fink, 2005; Choi *et al*., 2006). The percent change in grey matter volume in the most significant voxel (−24, −64, +47) within the left caudal parietal cortex was (mean ± SD) 3.6 ± 0.9% for the grapheme-colour synaesthetes and −2.7 ± 1.1% for the control subjects.

Furthermore, in grapheme-colour synaesthetes, the grey matter volume in the right FG was increased (+34, −69, −11; T = 2.94, $p_{SVC} < 0.05$). This grey matter difference in the right FG was located within the maximum probability map of right V4v (Rottschy *et al*., 2007) as assessed with the anatomy toolbox (Eickhoff *et al*., 2005; see Fig. 1D). The percent change in grey matter volume in the most significant voxel (+34, −69, −11) within the right FG was (mean ± SD) 2.3 ± 1% for the grapheme-colour synaesthetes and −1.7 ± 0.7% for the control subjects.

Based on the above values from the VBM analysis, we performed correlation analyses (i) between the GM changes in the FG and the caudal IPS (cIPS/CIP) and the individual differences ('projector' versus 'associator') or strength of the synaesthetic experiences (see Methods section), as well as (ii) between the GM changes in the FG and the cIPS. The latter correlation was highly significant, i.e. the GM changes in the FG correlated with the GM changes in the cIPS across the group of grapheme-colour synaesthetes ($P < 0.001$). In contrast, no significant correlation could be observed between the individual pattern of synaesthetic experience or the strength of the synaesthetic experience and the GM changes in either FG or cIPS of the synaesthetes' brains.

The ROI-analyses for the corresponding areas in the right parietal cortex and left FG did not reveal significant grey matter differences. Furthermore, we examined *post hoc* whether any further grey matter differences could be observed in the whole brain analysis when employing a less strict *P*-value of $P < 0.001$, uncorrected (at the voxel-level). This analysis revealed an additional area of grey matter difference in the left superior temporal sulcus (STS; −45, −20, −8; T = 3.91) for the grapheme-colour synaesthetes. Since this area was detected only by a *post hoc* analysis with a liberal statistical threshold, we refrain from discussing this grey matter difference further.

Discussion

Consistent with, but extending previous findings of an increased structural connectivity in the WM underlying the parietal cortex and the FG in grapheme-colour synaesthetes (Rouw and Scholte, 2007), this study shows, for the first time, increased *grey* matter volumes of these brain regions in a different sample of grapheme-colour synaesthetes ($n = 18$). The data thereby are consistent with the recently proposed two-stage model of grapheme-colour synaesthesia (Hubbard, 2007*b*). At the first stage, this model postulates increased anatomical connections in grapheme-colour synaesthetes ('hyperconnectivity') at the level of the FG leading to an enhanced cross-activation of the grapheme and colour areas within that gyrus. At the second stage, the synaesthetic colour perceptions generated in the FG are supposed to be bound together by parietal mechanisms resulting in a kind of 'hyper-binding'. In accordance with this model, functional imaging studies of grapheme-colour synaesthetes showed increased neural activity both in the FG (Nunn *et al*., 2002; Hubbard *et al*., 2005; Sperling *et al*., 2006) and the intraparietal cortex (Weiss *et al*., 2005) during synesthetic colour experience. Our findings of localized alterations in the grey matter of the FG and the intraparietal cortex together with previously reported changes in the underlying WM of grapheme-colour synaesthetes (Rouw and Scholte, 2007) strongly suggest that synaesthesia is not only associated with altered brain function but also has a specific structural basis. The localization of the observed structural changes in grapheme-colour synaesthetes is thereby not only consistent with the two-stage model of synaesthesia but also suggests a specific neuroanatomical basis for it.

Thus, converging evidence is provided by previous DTI studies (Rouw and Scholte, 2007) and our current VBM study that there are structural differences in the WM and the GM of grapheme-colour synaesthetes. Note that FA measured by DTI only indicates changes in the coherence of the WM (Rouw and Scholte, 2007), but cannot assess connectivity patterns. Similarly, VBM studies revealing differences in the GM, i.e. volume differences in (cortical) brain areas, do not allow inferences about how these (enlarged) areas are connected. Therefore, further studies applying diffusion MRI and tractography (Le Bihan, 2003) are needed to assess differences in the functional network architecture of grapheme-colour synaesthetes.

Interestingly, while our current morphometric MRI study revealed structural differences in both the FG and the IPS of grapheme-colour synaesthetes, some previous functional imaging studies of synaesthesia showed significant activations in the FG or in the parietal cortex (Aleman *et al*., 2001; Elias *et al*., 2003; Weiss *et al*., 2005; Sperling *et al*., 2006). However, other fMRI studies found activations in both fusiform and parietal cortices (Nunn *et al*., 2002; Hubbard *et al*., 2005). Differences in the specific hypothesis tested, the experimental design, or the specific task employed in these fMRI studies may account for the divergent findings (Fink *et al*., 2002). When synaesthetes passively perceived the stimuli (Sperling *et al*., 2006), significant activation clusters were found in the FG. In contrast, when synaesthetes were required to (consciously) assess their synaesthetic experiences as in Weiss *et al*. (2005), differential activation was revealed in the parietal cortex. This pattern of activation is in accordance with the two-stage model of synaesthesia (Hubbard, 2007*b*) which suggests a rather automatic generation of synaesthetic experiences in the FG and the involvement of the parietal cortex in the conscious perception of these synaesthetic experiences (see also Cohen Kadosh and Henik, 2007). Furthermore, Cohen Kadosh and colleagues directly showed that activations in different brain areas (even at different times) can occur in the same (bi-directional) synaesthete as a function of task (Cohen Kadosh *et al*., 2007*a*). It should be noted, however, that Hubbard *et al*. (2005) and Nunn *et al*. (2002), who focused on the activations in the FG of grapheme-colour synaesthetes, also observed activations in the parietal cortex within the same task. Taken together, different patterns of significant activations (only in the FG, only

in the parietal cortex or in both cortices) have been observed in functional imaging studies of grapheme-colour synaesthetes. Whether these differences in activation patterns are due to differences in experimental tasks (Cohen Kadosh *et al*., 2007*a*) or rather due to individual differences in synaesthetic experiences (Hubbard *et al*., 2005) remains an interesting question for further research on the neural basis of grapheme-colour synaesthesia.

Obviously, our neuro-anatomical VBM study cannot speak to the temporal aspects of the two-stage model of synaesthesia (i.e. the temporal relationship between the generation of the synaesthetic experiences in the FG and the hyperbinding in the parietal cortex), which can be assessed by time-sensitive methods like EEG (see Schiltz *et al*., 1999; Beeli *et al*., 2008). However, the current neuro-anatomical data clearly supports the view that synaesthesia may occur at different levels, i.e. the lower-tier region FG and the higher-tier region IPS, and provides anatomical regions which may be used as source regions in future studies. A recent study which employed event-related potentials (ERPs) also supports a role of parietal and fusiform structures in synesthesia (Beeli *et al*., 2008). It should be noted, however, that (for the P2 component) the fusiform and parietal areas were found to be activated simultaneously in this ERP study.

The parietal grey matter difference observed in our sample of grapheme-colour synaesthetes was located in the caudal part of the IPS, more specifically, in the human intraparietal area 3 (hIP3; Scheperjans *et al*., 2008). The caudal IPS is known to be involved in polymodal form processing in humans and monkeys (Culham and Kanwisher, 2001; Grefkes and Fink, 2005) and shows enhanced neural activity in grapheme-colour synaesthesia (Weiss *et al*., 2005), suggesting a role of this parietal area in binding together form and colour in grapheme-colour synaesthesia (Sagiv and Robertson, 2005). Increased structural connectivity in the white matter underlying the caudal parietal cortex (Rouw and Scholte, 2007), where the current grey matter difference was found, supports the proposed 'hyperbinding' in grapheme-colour synaethesia (Robertson, 2003).

Using cytoarchitectonically defined maximum probability maps (Eickhoff *et al*., 2005), we were also able to confirm that the area of grey matter difference in the FG detected in our current study was located in the colour processing area V4v (Rottschy *et al*., 2007). This suggests that, in addition to changes in the local connectivity within the FG (Rouw and Scholte, 2007), the additional colour percepts of grapheme-colour synaesthetes are associated with specific grey matter differences in the colour processing area in the FG.

The current GM difference in the FG (+34, −69, −11) is close to the previously reported group mean coordinates of the visual word form area (VWFA; −43, −54, −12; McCandliss *et al*., 2003), i.e. a critical node in a hierarchy of areas involved in recognizing visually presented words (Dehaene *et al*., 2005; Vinckier *et al*., 2007). In fact, the GM difference observed in our study is located in the anterior part of the maximum probability map (MPM) of V4v (Fig. 1D) and the VWFA (or 'grapheme area') is assumed to be located just anterior to the colour processing area V4/V8 within the FG. However, while our data implicate a role for the right FG in grapheme-colour synaesthesia, most studies found the VWFA to be located in the left FG. Applying small volume correction (SVC) based on the adjusted mean coordinates of the VWFA to the current VBM analysis, no significant GM difference was found. Note, even in the absence of GM differences right around the traditional location of the VWFA, the current finding of GM differences in the FG of grapheme-colour synaesthetes is consistent with the notion that areas involved in (non-synaesthetic) reading processes (Dehaene *et al*., 2005; Vinckier *et al*., 2007) may also be implicated in synaesthesia. Thus, further functional and structural imaging studies are needed to elucidate the interplay of the colour- and grapheme-processing areas within the FG in synaesthesia (Ramachandran and Hubbard, 2001; Hubbard and Ramachandran, 2005; Hubbard, 2007*b*).

Taken together, the current and previous data suggest that synaesthetic colour experiences in grapheme-colour synaesthesia are associated with specific structural differences both in the fibre tracts of the white matter and in the cortical grey matter of the caudal parietal cortex and the FG. Developmental studies of grapheme-colour synaesthetes may now help to shed some light on the question whether the observed structural differences in the fusiform and intraparietal areas precede or result from synaesthetic experiences.

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