



## Pathways to seeing music: Enhanced structural connectivity in colored-music synesthesia

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### ABSTRACT

Synesthesia, a condition in which a stimulus in one sensory modality consistently and automatically triggers concurrent percepts in another modality, provides a window into the neural correlates of cross-modal associations. While research on grapheme–color synesthesia has provided evidence for both hyperconnectivity–hyperbinding and disinhibited feedback as potential underlying mechanisms, less research has explored the neuroanatomical basis of other forms of synesthesia. In the current study we investigated the white matter correlates of colored–music synesthesia. As these synesthetes report seeing colors upon hearing musical sounds, we hypothesized that they might show unique patterns of connectivity between visual and auditory association areas. We used diffusion tensor imaging to trace the white matter tracts in temporal and occipital lobe regions in 10 synesthetes and 10 matched non-synesthete controls. Results showed that synesthetes possessed hemispheric patterns of fractional anisotropy, an index of white matter integrity, in the inferior fronto-occipital fasciculus (IFOF), a major white matter pathway that connects visual and auditory association areas to frontal regions. Specifically, white matter integrity within the right IFOF was significantly greater in synesthetes than controls. Furthermore, white matter integrity in synesthetes was correlated with scores on audiovisual tests of the Synesthesia Battery, especially in white matter underlying the right fusiform gyrus. Our findings provide the first evidence of a white matter substrate of colored–music synesthesia, and suggest that enhanced white matter connectivity is involved in enhanced cross-modal associations.

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### Introduction

One question central to cognitive neuroscience is how humans make associations between sensory modalities. Synesthesia, a condition in which external stimuli trigger consistent and involuntary concurrent percepts in another modality, provides a window into the neural underpinnings of cross-modal association. Synesthesia is estimated to occur in 1–4% of the population (Simner et al., 2006). Existing theories of synesthesia separately posit hyperconnectivity (or hyperbinding) (Hubbard, 2007; Hubbard and Ramachandran, 2005; Hubbard et al., 2011; Ramachandran and Hubbard, 2001a, 2001b), and disinhibited feedback (Grossenbacher and Lovelace, 2001) between modality-specific processing regions as mechanisms underlying synesthetic perception. However, conflicting evidence makes it unclear which model provides the more accurate description of synesthesia, or even whether the mechanisms of hyperconnectivity and disinhibited feedback are mutually exclusive (Cytowic and Eagleman, 2009).

Evidence from neuroimaging sheds light on structural and functional differences in the synesthetic brain. Structural neuroimaging

using diffusion tensor imaging (DTI; Jancke et al., 2009; Rouw and Scholte, 2007) and cortical thickness (Hanggi et al., 2011; Jancke et al., 2009; Weiss and Fink, 2009) has demonstrated increased connectivity and right-lateralized fractional anisotropy in grapheme–color synesthetes in inferior temporal cortex, and in regions in left frontal and parietal cortices. Additionally, functional MRI studies showed increased activation in area V4 in grapheme–color synesthesia (van Leeuwen et al., 2010; Weiss et al., 2005), as well as stronger functional connectivity in synesthetes between sensory integration regions in the parietal lobe and primary sensory regions (Neufeld et al., 2012). EEG and MEG studies of grapheme–color synesthesia showed synesthesia-modulated activation (Brang et al., 2008, 2010; Sagiv and Ward, 2006) localized to V4 and inferior temporal regions (Beeli et al., 2008). While these structural and functional differences in the synesthete brain provide clear evidence for a neural basis of synesthetic perception, most of these findings come from grapheme–color synesthesia, in which inducer and concurrent processing regions may be anatomically adjacent. Thus, these findings may not generalize to other forms of synesthesia, in which inducer and concurrent are processed in non-adjacent regions in the cortex (Neufeld et al., 2012).

Colored–music synesthesia, a form of synesthesia in which musical sounds such as tones, chords, and instrumental timbres elicit colored

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percepts (Cytowic and Eagleman, 2009), provides a good test for the hypothesis of different patterns of connectivity in inducer and concurrent processing regions. A handful of studies so far have begun to examine this form of synesthesia. For example, resting state EEG studies have identified increased functional connectivity centered around the parietal lobe and auditory cortex of colored-music synesthetes (Jancke and Langer, 2011). Goller et al. (2009) showed early differences in auditory event-related potentials (ERPs) in auditory–visual synesthetes, suggesting that sound processing differences in auditory–visual synesthesia involve the auditory cortex and superior temporal regions. This difference in auditory areas was also found in a multiple-form synesthete who had tone–color as well as interval–taste synesthesia (Hänggi et al., 2008). Functional MRI provided further evidence for increased visual activation in V4/V8 during processing of speech in speech–color synesthetes (Gaschler-Markefski et al., 2011; Nunn et al., 2002). Taken together, these findings from synesthetes whose inducers and concurrents come from different sensory modalities suggest that regions of the cortex involved in processing the inducer and concurrent may be different from controls in morphology and/or connectivity.

The previous studies lead us to a new hypothesis: If color processing in visual association regions (V4/V8) and music or auditory processing in auditory association regions (superior temporal gyrus, superior temporal sulcus, middle temporal gyrus) are more closely connected, possibly with the inclusion of other, additional regions, then the white matter pathways that pass through these regions might be different in colored-music synesthetes. The current study tests the hypothesis that connections between visual association regions in the occipital lobe and auditory association regions in the temporal lobe may be differently structured in colored-music synesthetes. We used diffusion tensor imaging to trace the major white matter pathways that contain fibers that traverse both temporal and occipital lobe regions in colored-music synesthetes and matched non-synesthete controls. These white matter pathways include (1) the inferior fronto-occipital fasciculus (IFOF), which connects the occipital pole to the frontal lobe through temporal lobe regions (Catani et al., 2002; Kier et al., 2004), and (2) the inferior longitudinal fasciculus (ILF), which connects the occipital cortex with the temporal pole (Catani et al., 2002). To address the possibility of group connectivity differences in areas not thought to be involved in audiovisual integration, we also traced the arcuate fasciculus (AF), which connects the superior and middle temporal gyri in the temporal lobe with the frontal lobe (Loui et al., 2009). We then quantified the relationship between behavioral measures of synesthetic associations and white matter integrity in the white matter where we found connectivity differences between synesthetes and controls.

## Materials and methods

### Subjects

Twenty healthy volunteers (10 music–color synesthetes and 10 non-synesthete controls) participated in the current study. Both groups of participants were recruited through online advertisements and fliers posted at local schools and conservatories. Synesthete and Control groups were matched for age, gender, ethnicity, handedness (as assessed using the Edinburgh Handedness Inventory; Oldfield, 1971), IQ (as assessed using the Shipley Institute of Living Scale; Shipley, 1940), years of musical training, and age of onset of musical training (see Table 1 for subject demographic information). All subjects gave written informed consent, and the Beth Israel Deaconess Medical Center Institutional Review Board approved the study.

### Behavioral screening

Before testing, all subjects completed a questionnaire assessing their musical and linguistic backgrounds. To control for the possibility of group differences in IQ, we administered Shipley's verbal and

**Table 1**  
Demographic information and mean Synesthesia Battery scores (averaged across tone–color, chord–color, and instrument–color tests) for subjects included in analyses.

	Synesthetes	Controls
Gender		
Male	7	7
Female	3	3
Handedness		
Left	1	1
Right	9	9
Age	22.6 (SD = 3.9)	24.32 (SD = 4.2)
Age of onset of musical training	8.4 (SD = 2.9)	9.3 (SD = 2.9)
Years of musical training	12.6 (SD = 4.1)	12.8 (SD = 5.8)
Ethnicity		
White	8	8
Black	1	1
Hispanic	1	1
Shipley scores		
Abstract	17.6 (SD = 2.5)	17.7 (SD = 1.6)
Verbal	33.3 (SD = 6.4)	33.78 (SD = 2.6)
Total	120 (SD = 5.3)	118.10 (SD = 4.8)
Mean Synesthesia Battery scores	0.66 (SD = .18)	1.37 (SD = .29)

abstract tests (Shipley, 1940), which have been shown to correlate highly with overall IQ (Paulsen and Lin, 1970).

Although synesthetes were recruited based on self-report of seeing colors when hearing music, to confirm the presence or absence of synesthesia each subject also completed three subtests of The Synesthesia Battery ([www.synesthete.org](http://www.synesthete.org)): the tone–color, chord–color, and instrument–color subtests (Eagleman et al., 2007). On each trial of every subtest, subjects were presented with an auditory stimulus and an accompanying color palette (consisting of 16.7 million colors), and were asked to select the color that they most closely associated with the given stimulus. Stimuli comprised 13 individual pitches for the tone–color test, 12 three-note chords for the chord–color test, and 18 instrumental timbres for the instrument–color test. Each stimulus was presented three times in randomized order. Subjects' color selections were recorded as RGB values, and the geometric distance between color selections for each presentation of a single test-item was calculated and averaged across all items for a total stimulus–color consistency score. Subjects who scored below a consistency threshold on the battery were classified as synesthetic (Eagleman et al., 2007). T-tests confirmed significant group differences in scores on the chord–color ( $t(16) = 4.5046$ ,  $p < .01$ ), tone–color ( $t(14) = 4.36$ ,  $p < .01$ ), and instrument–color ( $t(16) = 4.8118$ ,  $p < .01$ ) subtests, with synesthetes showing greater overall behavioral consistency of sound–color associations than controls. Two non-synesthete subjects reported not experiencing any sound–color associations for any of the subtests of the Synesthesia Battery, and therefore did not receive scores on any of these tests. As the report of not experiencing any sound–color associations was consistent with non-synesthetes' behavior, these two subjects were included in the group analyses as control subjects, but were excluded from brain–behavioral correlational analyses. Two additional subjects in the control group reported not experiencing any sound–color associations in the tone–color test only; these subjects were included in all analyses with their mean score on the Synesthesia Battery computed as a mean between the two remaining (chord–color and instrument–color) subtests. Two additional subjects in the control group scored close to 1.0 on the battery but did not report automatically perceiving colors in response to sounds; as automaticity is a prerequisite characteristic of synesthesia (Ward, 2012) we did not consider the Synesthesia Battery score as a criterion for exclusion of these two subjects from the control group.

### Image acquisition

High-resolution anatomical and diffusion-weighted images were acquired in a 3-T General Electric scanner. Anatomical images were

obtained using a T1-weighted, three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo (MPRAGE) volume acquisition with a voxel resolution of  $0.93 \times 0.93 \times 1.5$  mm. Diffusion-weighted images were obtained with a single-shot, spin-echo, EPI sequence (echo time = 86.9 ms, repetition time = 10,000 ms, field of view = 240 mm, slice thickness = 2.5 mm resulting in voxel size =  $2.5 \text{ mm}^3$ , no skip, NEX = 1, axial acquisition). Thirty noncollinear directions with a b value of  $1000 \text{ s/mm}^2$  and five directions with a b-value of  $0 \text{ s/mm}^2$  were acquired. Fractional anisotropy (FA) values, a measure of the degree of directional preference of water diffusion (Basser, 1995), were calculated within each brain voxel. This diffusion sequence lasted 10 min.

#### Data analysis

All pre-processing of raw data was conducted using FMRIB FSL software (Smith et al., 2004). Images were corrected for eddy distortion and head motion using a 3D affine transformation (Jenkinson and Smith, 2001), and brain extraction was applied to motion-corrected images using the BET tool. A diffusion model was subsequently fit to each voxel of the brain using *dtifit*, and eigenvalues, eigenvectors, and FA were estimated. Probability distributions for diffusion parameters were estimated at each voxel of the brain using *bedpostx* (Behrens et al., 2007) with two directions permitted per voxel.

#### ROI definition

To identify the IFOF in each hemisphere of each subject's brain, we applied probabilistic tractography between seed regions of interest (ROIs) that are known anatomical landmarks of the IFOF based on a white matter atlas (Wakana et al., 2004). ROIs were drawn bilaterally on axial slices over the external capsule and fusiform gyrus of each subject's native space FA map, in accordance with established methods for regional definition of IFOF seed and waypoint masks (Catani et al., 2002) (Fig. 1). Specifically, the first ROI was placed at the anterior floor of the external capsule, and the second ROI was drawn over the fusiform gyrus with a low probability of crossing fibers from the closely neighboring uncinate fasciculus (also see Catani et al., 2002). All ROIs were drawn by a first coder and verified by a second coder; both coders were blind to subject and group identity. Mean ROI volumes were  $452 \text{ mm}^3$  ( $SD = 62.7056 \text{ mm}^3$ ) for ROIs drawn on the external capsule, and  $425 \text{ mm}^3$  ( $SD = 101 \text{ mm}^3$ ) for ROIs drawn on the fusiform gyrus. ROI volumes and locations (center-of-gravity coordinates) did not differ between subject groups (all  $t(18) < 2$ , and  $p > .1$ ), ruling out the possibility that any between-group differences in tract volume or diffusion measures might be confounded by group differences in ROI volume or location (see Fig. 2 and Table 2 for size and center-of-gravity location of ROIs).

In addition to the IFOF, we also traced the inferior longitudinal fasciculus (ILF) and the dorsal and ventral components of the arcuate fasciculus (AF). Seed and waypoint ROIs for the ILF were defined bilaterally in a coronal slice over white matter underlying the occipital pole and white matter underlying the temporal pole respectively (Catani et al., 2002). Mean ROI volume over the occipital pole was  $219 \text{ mm}^3$  ( $SD = 55 \text{ mm}^3$ ) whereas mean ROI volume over the temporal pole was  $143 \text{ mm}^3$  ( $SD = 36 \text{ mm}^3$ ). Seed ROIs for both AF branches were defined bilaterally on white matter underlying gray matter in the posterior inferior frontal gyrus (pIFG). Waypoint regions for the ventral and dorsal AF branches were defined bilaterally on white matter underlying the posterior middle temporal gyrus (pMTG) and posterior superior temporal gyrus (pSTG) respectively (Halwani et al., 2011; Loui et al., 2009). Mean ROI volume in the IFG was  $141 \text{ mm}^3$  ( $SD = 23 \text{ mm}^3$ ),  $102 \text{ mm}^3$  ( $SD = 16.37 \text{ mm}^3$ ) in the pSTG, and  $98 \text{ mm}^3$  ( $SD = 14.98 \text{ mm}^3$ ) in the pMTG. There were no group differences in ROI volume or location (all  $t(18) < 2$ , and  $p > .1$ ), ensuring that any resulting tract differences could not be due to differences in ROI volume or location.

#### DTI tractography

To trace the inferior frontal-occipital fasciculi (IFOF), probabilistic tractography was conducted using FSL software, and was initiated from seed regions of interest of the fusiform gyrus in each hemisphere of each brain, to waypoint masks in the external capsule of the same hemisphere in each brain. Resulting tracts between ipsilateral ROIs were identified in each hemisphere for each subject, and were labeled Left and Right IFOF, in accordance with previous studies (Catani et al., 2002). To remove extraneous fiber projections, all tracts were thresholded at 10% of the robust range for non-zero voxels. Thresholded tracts were binarized, masked with FA images, and mean volume and FA values were extracted from the resulting tracts for statistical comparisons.

Probabilistic tractography for control AF tracts was conducted from pIFG seed regions as defined in each hemisphere of each individual brain, and waypoint regions in the pSTG (dorsal AF), and pMTG (ventral AF) respectively. Resulting tracts between pIFG–pSTG, and pIFG–pMTG were identified in each hemisphere of each subject's brain. Probabilistic tractography for control ILF tracts was conducted from seed regions in the occipital pole in each hemisphere, to waypoint regions in the temporal pole. The same post-tractography processing pipeline used for IFOF was applied to AF and ILF tracts: tracts were thresholded at 10% of the robust range for non-zero voxels, binarized, and masked with FA images. Mean volume and FA were extracted from thresholded, binarized, masked tracts, and exported for statistical analyses.

To allow images to be visualized and compared directly between subjects, all subjects' tracts and FA images were aligned and normalized

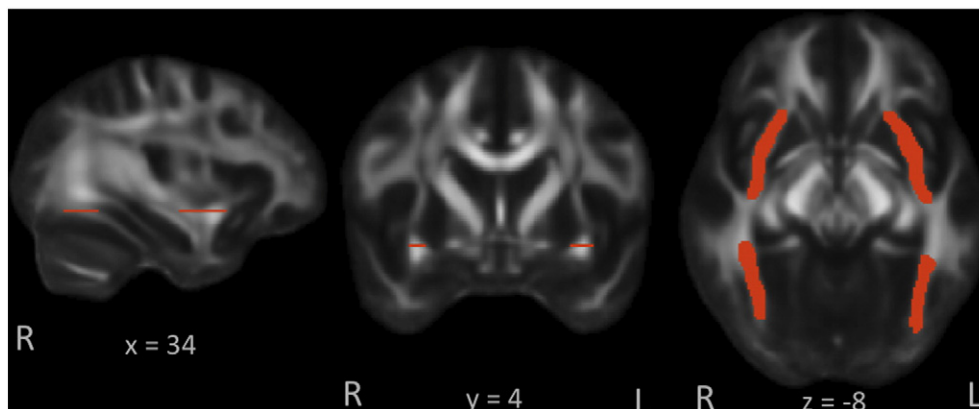


Fig. 1. 3D-view of external capsule and fusiform gyrus ROIs, as visualized on FSL's FMRIB58 1 mm FA template.

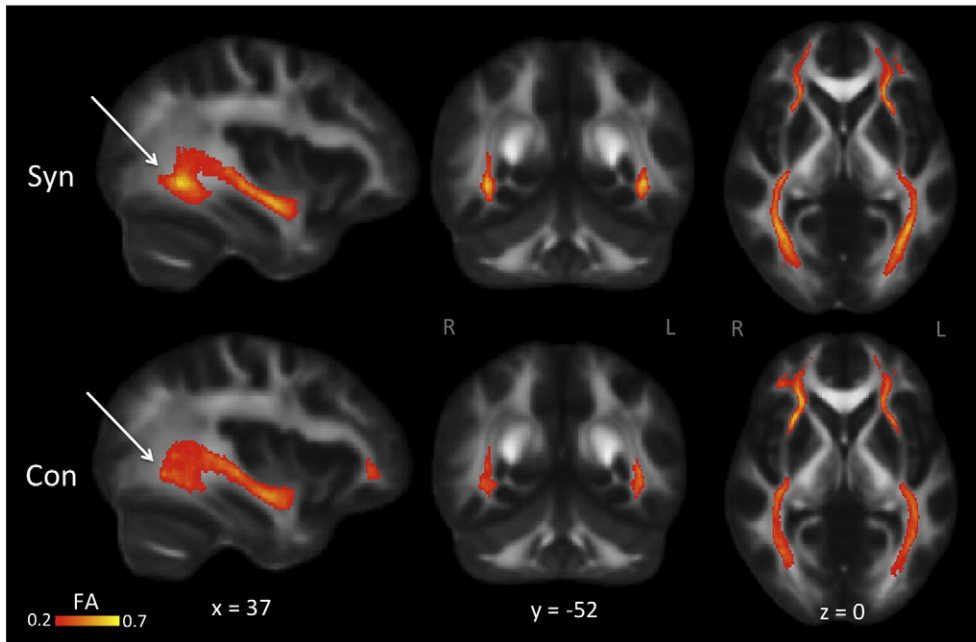


Fig. 2. Sagittal, coronal, and axial views of IFOF canonical tract for synesthetes (top row) and controls (bottom row).

to the FSL 1 mm FA template using both linear registration (FLIRT) (Jenkinson and Smith, 2001) and nonlinear registration tools (FNIRT) in the FSL library. To enable a regression analysis of FA values within the IFOF with Synesthesia Battery scores across all subjects, the IFOF was summed between subjects to obtain a canonical tract traversed by the IFOF. All subjects' normalized FA images were then regressed on the average Synesthesia Battery consistency score in SPM5, using the canonical tract as an explicit mask. This regression analysis yielded voxels within the IFOF with FA values that were significantly correlated with behavioral performance at a corrected level. The use of the canonical tract as a mask improves statistical power by reducing the number of statistical comparisons to the hypothesized search space, while avoiding biasing our between-subject comparisons by constraining the search space to be the same for all subjects.

#### Whole-brain volume and FA

To address the possibility that tract differences might result from increased global connectivity and/or brain volume, we extracted mean global FA and volume statistics from each subject's FA map for group statistical comparisons.

## Results

#### White matter integrity of IFOF

A comparison of white matter integrity in the IFOF between the left and right hemispheres showed different patterns between synesthetes and controls. A two-way ANOVA on the dependent

Table 2

Mean volume ( $\text{mm}^3$ ) and center of gravity voxel coordinates for ROIs drawn on the fusiform gyrus (posterior ROI) and external capsule (anterior ROI). Voxel coordinates are given in standard FSL space.

	Anterior ROI		Posterior ROI	
	Left	Right	Left	Right
Volume ( $\text{mm}^3$ )	483.15	499.95	546.15	545.85
X	-29	30	-35	35
Y	8	9	-29	-56
Z	-9	-9	-5	-5

variable of FA for right and left IFOF, with group (Synesthete vs. Control) and hemisphere (left vs. right) as factors, showed a significant interaction between group and hemisphere ( $F(1, 36) = 4.8237$ ,  $p < .05$ ). Planned contrasts on tract FA comparing the two groups confirmed that the synesthete group possessed significantly higher FA in the right IFOF compared to the control group,  $t(18) = 2.207$ ,  $p < .05$ , Cohen's  $d = 1.04$ . This between-group difference was not observed for the left IFOF ( $t(18) = 0.86$ , n.s.). Furthermore, control subjects showed significantly higher FA in the left IFOF ( $p < 0.01$ , Tukey's HSD, Cohen's  $d = 0.82$ ) whereas synesthetes did not show any significant difference in FA in the IFOF between the two hemispheres (Fig. 3).

#### White matter integrity of right IFOF reflects Synesthesia Battery scores

While the two-way ANOVA comparing left and right IFOF between synesthete and control groups showed significant inter-hemispheric differences between groups, the precise relationship between left and right IFOF and synesthetic behavior had yet to be determined. To assess the possibility of a linear relationship between observed group differences in mean FA of the IFOF and synesthetic behavior, we correlated FA values in the IFOF of each hemisphere with mean Synesthesia Battery scores. Results confirmed a significant correlation

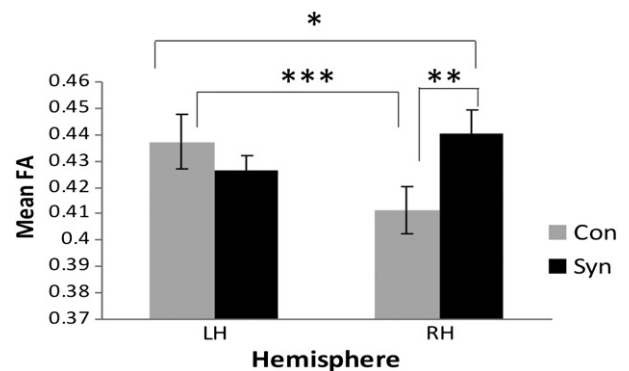


Fig. 3. Main comparisons in mean FA of the IFOF. Bars represent means. Error bars represent standard error. \*Group  $\times$  hemisphere interaction:  $p < 0.05$ ; \*\*between-group difference:  $p < 0.05$ ; \*\*\*inter-hemispheric difference:  $p < 0.01$  (post-hoc Tukey's HSD).

between FA of the right IFOF and mean Synesthesia Battery scores for all subjects  $r = -0.62, p = .0055$ . We found no significant relationship between FA of the left IFOF and behavioral measures ( $r = .01, n.s.$ ).

To determine whether FA of the IFOF is related to individual differences within the synesthete group, we also correlated mean scores on the Synesthesia Battery with mean FA of the IFOF among subjects in the synesthete and control groups separately (Fig. 4). Results showed that among the synesthete group, there was a significant correlation between right IFOF FA and mean Synesthesia Battery score,  $r = -.75, p = .012$ , corrected using Bonferroni adjusted alpha levels of .0125 per test (0.05/4 for two hemispheres and two groups). In the left IFOF, the correlation within the synesthete group was also significant ( $r = -.648, p = 0.043$ ), but did not survive correction. This correlation within the synesthete group indicates an association between the consistency of sound–color associations for synesthetes and white matter integrity in the IFOF, especially in the right hemisphere. This correlation was not observed within the control group for either the left ( $r = .41, n.s.$ ) or the right IFOF ( $r = .18, n.s.$ ).

To identify specific points along the IFOF that might be most correlated with synesthetic behavior, we regressed the FA values of all voxels within the IFOF on the average score on the Synesthesia Battery (see Materials and methods). This regression yielded a single cluster of seven voxels (centered around  $x = 22, y = -77, z = -1$ ) that was significantly correlated with scores on the synesthesia battery at the  $p < 0.05$  (FWE-corrected) level (Fig. 5). This significant cluster was located within the inferior fronto-occipital fasciculus as defined by the JHU white-matter tractography atlas (Mori et al., 2008). This cluster lies in white matter in fusiform gyrus within the posterior portion of the IFOF in the occipital lobe, suggesting that the structural integrity of white matter in the posterior portion of the right IFOF, specifically in the fusiform gyrus, is most important for the relationship between white matter and synesthetic behavior.

*Inferior longitudinal fasciculus, arcuate fasciculus, and whole brain measures*

To address the possibility that group differences in IFOF might be due to larger differences in global connectivity, we tested for between-group differences in mean FA in the whole brain. Additionally, because differences in IFOF might not be specific to the IFOF but may extend to other tracts that are associated with visual and auditory areas in the cortex, we compared mean FA of other white matter tracts with fibers in the occipital and temporal lobes. Specifically, we compared the inferior longitudinal fasciculus and the dorsal and ventral branches of the arcuate fasciculus.

A two-way ANOVA was conducted on the dependent variable of FA in the left and right ILF, with factors of group (Synesthete vs. Control) and hemisphere (left vs. right). Results showed no significant main

effect of group ( $F(1,36) = 1.9, n.s.$ ) or hemisphere ( $F(1,36) = 0.17, n.s.$ ) and no significant interaction ( $F(1,36) = 0.21, n.s.$ ), suggesting that the results observed in the IFOF did not extend to other tracts that connect the visual and temporal cortices.

Two-way ANOVAs were conducted on the dependent variable of FA in the dorsal and ventral branches of the AF tract. Results showed no main effect of group on FA for either the ventral ( $F(1,36) = .45, n.s.$ ) or dorsal ( $F(1,36) = .04, n.s.$ ) branches of the AF. There was, however, a main effect of hemisphere on FA, with both groups showing left-lateralization of FA in the ventral and dorsal AF branches: ventral AF  $F(1,36) = 13.89, p < .01$ ; dorsal AF  $F(1,36) = 9.0, p < .01$ . This finding is in keeping with literature on leftward asymmetry of the arcuate fasciculus in healthy populations (Buchel et al., 2004; Powell et al., 2006; Vernooij et al., 2007). Taken together with results on the ILF showing no between-group differences in FA, results from the AF suggest that observed differences in the IFOF are not generalizable to other major white matter pathways.

Separate one-way ANOVAs were conducted on mean global FA and mean global volume, with factors of group (Synesthete vs. Control) and hemisphere (left vs. right). Results confirmed no difference between groups in either global FA or volume (all  $F < 2$ , and  $p > .1$ ), suggesting that between-group differences in the IFOF are not due to global differences in volume or connectivity.

**Discussion**

Results show that people with colored-music synesthesia possess enhanced structural connectivity between frontal lobe and visual and auditory association areas. Compared to controls, colored-music synesthetes possess different hemispheric patterns of white matter integrity in the inferior fronto-occipital fasciculus, with increased rightward asymmetry in synesthetes. In addition to showing between-group differences, fractional anisotropy in the right IFOF also correlates with behavioral measures of synesthesia across all subjects. Furthermore, FA correlates with behavioral measures within the synesthete group, but not within the control group. Synesthetic individuals, who show highly consistent sound-to-color mappings on the tone-color, chord-color, and instrument-color subtests of the Synesthesia Battery, possess higher FA values in the right IFOF, as well as increased rightward asymmetry in white matter integrity of the IFOF. Voxelwise comparisons within the IFOF further pinpoint the association between behavioral consistency and white matter integrity to the white matter underlying the fusiform gyrus. As the current samples are well matched for age, ethnicity, handedness, IQ, and onset and duration of musical training, results observed are not due to demographics, musical training, or general cognitive ability. Two subjects from the control group did score better on colored-music subtests of the Synesthesia Battery

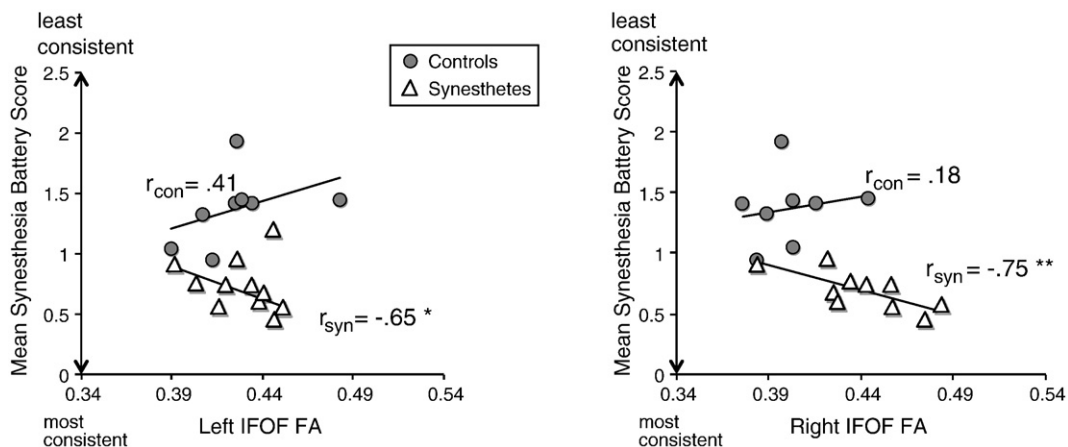
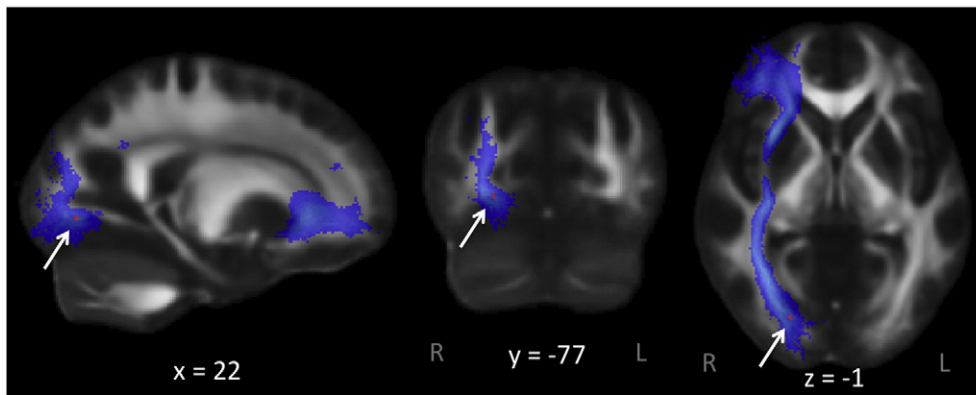


Fig. 4. Correlations between FA in the left IFOF (A) and right IFOF (B) and mean Synesthesia Battery scores. \* $p < .05$  uncorrected; \*\* $p < .05$  Bonferroni-corrected.



**Fig. 5.** A cluster of seven voxels within the occipital portion of the right IFOF was most highly correlated with consistency score on the Synesthesia Battery (averaged across subtests for each individual). The right IFOF as defined by the JHU white matter atlas (Wakana et al., 2007) is shown in blue. The red cluster (indicated with arrows) is significantly correlated with subjects' average scores on the synesthesia battery at the  $p < 0.05$  (FWE-corrected) level.

than previously-reported scores from control subjects (Eagleman et al., 2007); however the group differences between synesthete and control groups are highly significant, and the two control subjects who showed consistent auditory–visual associations did not report automatic experiences of associations between sounds and colors. This high internal consistency in sound–color associations may be because the control group was matched with the synesthete group with respect to musical training; as persons with musical training have enhanced audiovisual encoding (Musacchia et al., 2007), musical training may have led to stronger audiovisual associations (but not automatized synesthesia) in these control subjects.

Results in the IFOF are not generalizable to whole-brain connectivity or volume measures, or to other tracts with fibers in the temporal and occipital lobes (inferior longitudinal fasciculus and arcuate fasciculus). This specificity of results suggests that increased white matter integrity in colored-music synesthetes is unique to the IFOF. The IFOF has been implicated in multimodal integration, visual information processing, and processing of speech and language input (Baggio et al., 2012; Duffau et al., 2005; Martino et al., 2010; Sarubbo et al., in press; Vandermosten et al., 2012). While the ILF is a white matter pathway directly between occipital and temporal lobes and the AF is a white matter pathway between temporal and frontal lobes, the IFOF is a white matter tract that connects visual and auditory association areas in the occipital and temporal lobes with the frontal lobe (Kier et al., 2004). The present finding of associations between synesthesia and the IFOF, rather than the ILF or the AF, suggests that top-down input from the frontal lobe towards both auditory and visual association areas is involved in the colored-music synesthetic experience.

Disconnection of the IFOF is associated with numerous white matter pathologies, including obsessive–compulsive disorder (Garibotto et al., 2010; Koch et al., 2012), schizophrenia, and bipolar disorder (Cheung et al., 2008; Lin et al., 2011; Szezeko et al., 2008). Disconnection of the IFOF has also been linked to attention deficits (Silk et al., 2009), and to developmental dyslexia (Odegard et al., 2009; Rollins et al., 2009; Vandermosten et al., 2012), with degree of white matter integrity of the IFOF correlating with behavioral measures of phonological decoding during reading (Odegard et al., 2009). Despite mounting evidence for the role of the IFOF in processing visual and auditory associations, less is known about the behavioral implications of hyperconnectivity or hyperbinding in the IFOF. Thus, results from the current study inform our understanding of the functional implications of increased connectivity of the IFOF.

The correlation between fractional anisotropy of the right IFOF and behavioral performance on the Synesthesia Battery was significant across our entire sample of participants, as well as within the synesthete group, but not within the control group. A non-significant correlation in

the controls might result from an increased likelihood for non-synesthetes to select colors randomly on the Synesthesia Battery (as they do not automatically perceive associations between auditory and visual stimuli), or from the non-synesthetic controls having adopted a different strategy from synesthetes (e.g. based on short-term memory rather than long-term audiovisual association) to make their ratings consistent between various presentations of the same stimuli. Alternately, the observed within-group correlation results might reflect a categorically different mechanism for auditory–visual associations that exists in synesthetes, but not controls. In any case, the current findings raise the question of whether synesthesia is a distinct category or whether it reflects one end of a spectrum (Eagleman, 2012; Simner, 2012). While the present results cannot answer this question conclusively, the present findings of between-group differences in the right IFOF, that show a linear correlation with behavioral consistency—both between groups and among synesthetes—suggest that synesthetes and non-synesthetes may lie along the same neurologically defined continuum (Eagleman, 2012; Simner, 2012).

Hemispheric differences in the IFOF, especially driven by higher FA in the right IFOF among synesthetes, may play a role in enhanced sensory perception as modeled by colored-music synesthesia. Leftward asymmetry of the IFOF as seen in our control sample has been found in previous studies of white matter connectivity in normal individuals (Hugdahl and Westerhausen, 2010; Powell et al., 2006). In contrast, we observed rightward FA asymmetry in the IFOF of the synesthetes, with the differences mainly driven by higher FA in the right IFOF. These structural differences in the IFOF may provide support for the hyperconnectivity/hyperbinding model of synesthesia in showing enhanced connectivity between auditory and visual association regions, providing a neuroanatomical substrate for colored-music synesthesia. Furthermore, brain–behavior correlations between white matter integrity in the right IFOF and behavioral measures on colored-music subtests of the synesthesia battery demonstrate an association between structural differences and consistency of cross-modal associations. Voxelwise regression of FA values in the right IFOF on Synesthesia Battery scores pinpoint the effect of increased white matter integrity in synesthetes to visual association areas, specifically white matter underlying the fusiform gyrus in the occipital lobe. This finding suggests that synesthetic associations may arise from increased white matter integrity in the occipital lobe, and raises the possibility that heightened associativity between sounds and colors may be associated with the extent to which an individual's right IFOF extends into the fusiform gyrus in the occipital lobe.

These results link colored-music synesthesia to different hemispheric asymmetry in the IFOF. Specifically, results show behavioral associations with the right IFOF, in contrast to the left IFOF, the inferior

longitudinal and arcuate fasciculi, and global volume and FA measures. As the IFOF connects visual and auditory association cortices—regions that are involved in processing color and music respectively—to the frontal lobe, these results may be specific to colored-music synesthesia. However, the IFOF also includes white matter underlying the middle temporal gyrus, which codes for overlearned sequences in (Eagleman, 2009; Pariyadath et al., 2012). Thus, to the extent that different forms of synesthesia rely on overlearned sequencing, the IFOF may be an important white matter pathway for other forms of synesthesia as well.

Although results appear to be specific to rightward asymmetry in the IFOF, we cannot exclude the possible involvement of other regions that were not tested in this study, such as regions in the parietal lobe that might contribute to the binding process (Neufeld et al., 2012). While future experiments may take a whole-brain or template-driven approach, in the present study we adopted a tract-based approach in conducting tractography between individually defined seed regions of interest in order to identify the most accurate white matter pathways for each individual. By identifying a behaviorally relevant and anatomically accurate white matter tract within each individual, and then regressing the white matter integrity of the tract on synesthetic behavior, we were able to identify the white matter underlying the fusiform gyrus as a specific subregion within the right IFOF that is most predictive of synesthetic associations.

While FA is an index of white matter integrity that has been linked to increased structural connectivity including myelination and axonal coherence, it could also be related to other biological factors, including increased intra-axonal viscosity and decreased crossing fibers. The present diffusion imaging methods cannot tease apart which of these factors may be driving the current results. If the enhanced FA in the right IFOF of synesthetes is a result of decreased crossing fibers that are inhibitory, then disinhibited feedback might be a mechanism underlying synesthesia; this would change the theoretical implications of our results. However, disinhibited feedback and hyperconnectivity/hyperbinding are not mutually exclusive (Cytowic and Eagleman, 2009), and it is possible that both may underlie the current findings.

In conclusion, we have found increased structural connectivity in the white matter tracts connecting visual and auditory association areas in people with colored-music synesthesia. Results are driven by enhanced white matter connectivity in the right hemisphere IFOF, especially in white matter underlying the right fusiform gyrus. This suggests that the enhanced perceptual experience of synesthesia may involve enhanced white matter connectivity. These results offer a link between synesthesia and other populations characterized by enhanced local white matter connectivity, such as absolute pitch possessors (Loui et al., 2011a, 2011b) and individuals with high cognitive intelligence, high emotional intelligence, and exceptional creativity (Chiang et al., 2009; Jung et al., 2010; Takeuchi et al., 2011), as well as in patients with auditory verbal hallucinations and autistic spectrum disorders (Fletcher et al., 2010; Hoffman and Hampson, 2011).

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## Conflict of interest statement

The authors declare no competing financial interests.

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