

Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words

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In 'colored-hearing' synesthesia, individuals report color experiences when they hear spoken words. If the synesthetic color experience resembles that of normal color perception, one would predict activation of parts of the visual system specialized for such perception, namely the human 'color center', referred to as either V4 or V8. Using functional magnetic resonance imaging (fMRI), we here locate the region activated by speech in synesthetes to area V4/V8 in the left hemisphere, and demonstrate overlap with V4/V8 activation in normal controls in response to color. No activity was detected in areas V1 or V2, suggesting that activity in primary visual cortex is not necessary for such experience. Control subjects showed no activity in V4/V8 when imagining colors in response to spoken words, despite over-training on word-color associations similar to those spontaneously reported by synesthetes.

In synesthesia, a stimulus in one sensory modality triggers, involuntarily and automatically, a sensation in another: thus, in 'colored hearing', hearing words induces sensations of color¹. Positron-emission tomography (PET) has shown in colored-hearing synesthetes the activation by speech of regions of visual association cortex not activated in controls, without significant activation of lower visual areas, including areas V1, V2 or V4/V8 (ref. 2). If synesthetic color experience is similar to true color percepts, however, one can more specifically predict activation of the human 'color center', called V4 (refs. 3, 4) or V8 (ref. 5). Using the greater spatial resolution and sensitivity of fMRI, we tested this prediction by comparing brain activation patterns elicited by spoken words versus tones in synesthetes and controls. We also determined whether primary visual cortex (areas V1 and V2) was active during colored-hearing synesthesia. Lack of V1/V2 activity would suggest the generation of conscious visual percepts without contribution from primary visual cortex⁶⁻⁸. Specifically, we compared the activation pattern in synesthetes hearing words to those observed in response to seen colors both in a group of non-synesthetes for whom the latter data were already⁹ available (Experiment 1) and, in a within-subject design, in synesthetes themselves (Experiment 2). To control for the possibility that synesthetes might have an unusual topography of the visual areas, we also compared the regions activated by seen colors in these subjects and in non-synesthetes. In Experiment 3, we investigated whether normal subjects imagining colors show activation of a similar kind to that observed when synesthetes spontaneously

experience colors in response to heard words. To maximize the stringency of this comparison, we first overtrained subjects on word-color associations modeled on those reported by the synesthetes. Subjects were then presented with the words in the scanner, instructed to predict or imagine the associated colors, retrained in the scanner (to eliminate associative loss due to contextual change) and retested. Our findings demonstrate activation by spoken words of left V4/V8 (not V1/V2) in synesthetes but not controls.

RESULTS

Hearing words compared with tones showed (Experiment 1), in both synesthetes and controls, activation of language areas of the perisylvian regions: superior temporal gyrus bilaterally, and left inferior frontal gyrus (Tables 1 and 2). Synesthetes showed additional activation in the color-selective region^{5,10}. We compared this to that elicited by color (colored versus monochromatic 'Mondrians') previously reported in normal subjects⁹. The only significant overlap was in the left fusiform gyrus, with coordinates closely similar to those reported as V4 (ref. 10) or V8 (ref. 5) (Figs. 1 and 2). Despite this left lateralization, the synesthetes did not report color experiences confined to the right visual field. Localization to particular parts of the visual field was not generally possible or was centered. Given the left lateralization of cortical language systems, lateralized V4/V8 activation may reflect the elicitation by speech, rather than sounds in general, of synesthetic color experiences. PET² similarly revealed subthreshold activation of left but not right V4/V8



Table 1. Cerebral structures activated by word minus tone perception in synesthetic subjects.

Cluster size (voxels)	Talairach coordinates (mm)			Max effect size	Area of activation	BA
	x	y	z			
85	-45	2	32	0.089	inferior frontal/premotor	6/44
33	-50	-45	11	0.075	superior temporal gyrus	22/39
25	-48	-24	6	0.075	superior temporal gyrus	22/42
18	-22	-43	-9	0.041	anterior fusiform gyrus ^a	19
17	-40	-58	35	0.053	angular gyrus	39/40
17	53	-17	1	0.103	mid/sup temporal gyrus	21/22
15	-33	-66	-13	0.045	V4/V8 fusiform gyrus	19
15	-33	-67	9	0.048	middle occipital lobe	19
11	7	42	-7	0.046	medial frontal gyrus	10
11	-19	-55	15	0.047	posterior cingulate	23/31
10	-32	-75	15	0.041	medial occipital gyrus	19
10	-6	-61	26	0.045	posterior cingulate	31
8	22	27	48	0.041	superior frontal gyrus	8
7	33	-6	4	0.034	claustrum	-
6	-16	-60	9	0.037	posterior cingulate	23
6	-27	-27	53	0.036	inferior parietal lobule	40
6	-56	-19	9	0.066	auditory association cortex	42

^aThese coordinates fall within the region denoted V4 α (see Table 1 in ref 10). Maximum effect size and the Talairach and Tournoux³⁹ coordinates at which this level of response was observed in each cluster. All activations shown are at voxel-wise $p \leq 0.0005$ by randomization testing. The data were obtained in Experiment 1; all regions listed were replicated in Experiment 2. BA, Brodmann area.

in colored-hearing synesthetes. Besides V4/V8, we saw further activation in left anterior fusiform gyrus (area V4 α) in synesthetes (Table 1), perhaps reflecting experience of colored percepts with shape or object-related properties^{10,11}. Colored Mondrians and objects versus their monochromatic counterparts activate anterior fusiform gyrus^{9,12}, as do orientation-contingent color after-images¹³.

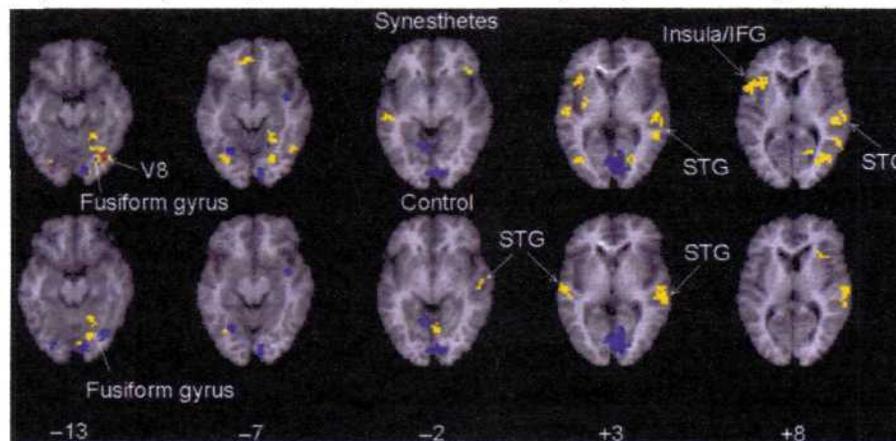
No V1/V2 activation was observed, even at a lenient threshold ($p = 0.01$; data not shown), although this occurs in normal controls in response to color⁹. Nor was there activation of the posterior inferior temporal region in synesthetes, observed in a previous PET study² and perhaps reflecting the shape aspects of

episodic memory processes and posterior cingulate activation in synesthetes relative to controls.

The location of the activation patterns elicited (Experiment 2) by colors (chromatic minus achromatic Mondrians) in the right hemisphere was consistent with previous reports^{4,5,9,10,12} and similar between controls (center of mass of cluster: 28 (x), -56 (y), -13 (z); 30 voxels) and synesthetes (40, -52, -13; 43 voxels). Controls showed a corresponding area of activation in the left hemisphere (-32, -73, -13; 4 voxels). However, no left V4/V8 activation was seen in the synesthetes. As in Experiment 1, there was no activation of V4/V8 in controls in response to heard

synesthetic percepts¹¹. However, this region can not be imaged properly using fMRI, because of inhomogeneity effects. Controls showed less activation overall than synesthetes (Tables 1 and 2), for whom words were possibly more arousing as a result of the color percepts elicited. Activation of the right claustrum in synesthetes alone is consistent with proposals that this region functions as a multi-modal convergence area¹⁴. We also observed activation in left posterior cingulate selectively in synesthetes. PET studies consistently find activation of this region associated with episodic memory processes^{15,16}, perhaps specifically due to encoding of auditory-verbal material¹⁷. Incidental encoding of episodic memory occurs under many conditions, and greater incidental episodic memory for emotionally meaningful words has been associated with left posterior cingulate activation¹⁸. Because synesthesia is memorable and emotional¹⁹, these findings are compatible with enhancement of

Fig. 1. Activation maps of synesthetes and controls, combined with a color activation mapping study⁹. The data shown are 5.5-mm axial slices between Talairach z planes -13 mm and +8 mm at a voxel-wise type I error probability (by randomization testing) of 0.0005, for synesthetes (upper row) and controls (lower row). Data for Experiment 1 are shown in yellow (words minus tones), and the color activation mapping study in blue. The cluster common to both these studies is shown in red. The Talairach and Tournoux³⁹ coordinates of the center of mass of this cluster are -35, -64, -13. The data from Experiment 2 (not illustrated) yielded a similar center of mass for the cluster activated by words in synesthetes: -40, -69, -13 (6 voxels). Foveal left V8 (as defined retinotopically) centers on -33, -65, -14 (ref. 5). Data are superimposed onto a high-resolution volumetric image mapped into the same space. Right side of image corresponds to left hemisphere of the brain. STG, superior temporal gyrus. IFG, inferior frontal gyrus.



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Table 2. Cerebral structures activated by word minus tone perception in control subjects.

Cluster size (voxels)	Talairach coordinates (mm)			Max effect size	Area of activation	BA
	x	y	z			
49	-55	-21	5	0.060	superior temporal gyrus	22
23	-39	10	30	0.043	inferior frontal	44/9
23	-37	24	13	0.039	inferior frontal	44/45
13	57	-17	4	0.058	superior temporal gyrus	22
11	-55	-10	26	0.040	premotor area	6
9	-2	-58	-2	0.033	lingual gyrus/brainstem	-
9	6	14	37	0.033	cingulate gyrus	24
8	-24	-76	26	0.045	occipital cortex	19
8	-19	-49	-13	0.033	cerebellum	-
8	-17	-66	-13	0.039	cerebellum	-
7	3	-2	53	0.048	supplementary motor area	6
7	-46	3	42	0.044	premotor area	6

Maximum effect size and the Talairach and Tournoux³⁹ coordinates at which this level of response was observed in each cluster. All activations are at voxel-wise $p \leq 0.0005$ by randomization testing. The data shown were obtained in Experiment 1; all regions listed were replicated in Experiment 2. BA, Brodmann area.

words. Also confirming Experiment 1, the words elicited V4/V8 activity in the synesthetes, activating the same area (Fig. 1 legend), including its left lateralization. Given the lack of left V4/V8 activity in the synesthetes in response to color in the Mondrian task (tested in the same session), the left lateralized response to spoken words cannot be attributed either to a greater sensitivity of left V4/V8 to stimuli in general or to methodological artifact. Taken together with the replicated observation of preferential left V4/V8 activation by spoken words in synesthetes, the lack of activation in response to colors raises the possibility that participation in synesthetic color perception reduces the availability of this region for normal color processing.

Four sets of activation patterns in response to words were gathered from non-synesthetes in Experiment 3. Two were gathered before retraining: 'pre-predict' (with instructions to predict the associated colors) and 'pre-imagine' (with instructions to imagine them). Two further sets were gathered after retraining in the scanner: 'post-predict' and 'post-imagine'. All subjects were tested in the order pre-predict, pre-imagine, post-predict, post-imagine. Because the aim of this experiment was to determine whether imagining colors might, in normal subjects, activate the same color-selective region activated in colored-hearing synesthesia, we analyzed the region of interest (ROI) established in Experiment 1 as the 10-voxel overlap between the color region in normal subjects⁹ and the response to heard words in synesthetes (Figs. 1 and 2).

We performed four sets of comparisons (pre-imagine versus pre-predict, post-predict versus post-imagine, pre-imagine versus post-imagine and pre-predict versus post-predict) by analysis of variance at a voxel-wise p value of 0.05, and examined significant differences within the ROI. The total number of observed differences was 1. As 40 tests were carried out (10 voxels \times 4 experiments), the expectation of false positives at $p = 0.05$ would have been two. Thus we conclude that there

are no significant differences. To account for mapping errors, an area of 5 mm surrounding the mask was included in the comparisons, increasing the number of voxels tested and so strengthening this result. All four data sets were then combined, yielding one large group map. The overlap between this map and the ROI was just one voxel, with a chance expectation of 0–1 voxels (10 voxels tested at $p = 0.05$). Thus there is no evidence that non-synesthetes activate V4/V8 under any of the conditions tested.

In the combined map, there were five clusters of voxels in the middle/superior temporal gyrus and auditory cortex: -40, -17, 4 (12 voxels); 52, -25, -7 (12 voxels); 49, -31, -2 (11 voxels); -55, -47, 9 (8 voxels); -58, -11, -2 (7 voxels). These were observed at a voxel-wise p value of 0.001. Thus, the combined data confirmed the expected activation in auditory cortex. There were also large clusters of activated voxels both in true Broca's area (-35, 36, -2, 51 voxels, inferior frontal gyrus) and its right-sided analogue (43, 17, -2, 36 voxels), presumably reflecting the active processing of heard words.

DISCUSSION

Our data validate subjective reports of colored hearing by synesthetes. Experimental evidence for the long-term specificity and stability of these reports exists^{1,20}, as does psychophysical evidence for the perceptual quality of the experience²¹. The data reported here, demonstrating differences between synesthetes and controls in activation of a color-selective region by spoken words, lend such phenomena an authenticity beyond reasonable doubt. Synesthetic color experiences have been related to the activation of visual association cortex². Our data related them specifically to a region (the V4 complex¹⁰: that is, V4/V8 together with V4 α) specialized for color vision. In Experiment 3, despite overtraining on synesthete-like word-color associations and retraining in the scanner, non-synesthetes showed no activation in the V4/V8 region activated in synesthetes; nor did specific instructions to imagine the associated color increase V4/V8 activation over the zero level observed with instructions simply to predict it. These results confirm an earlier report that V4/V8 was not differentially activated in a color imagery task compared to a spatial orientation control task⁹. Thus, the neural substrate of synesthetic color experience is closer to that of a true color percept than to color imagery, resembling hallucinations of color in patients with the Charles

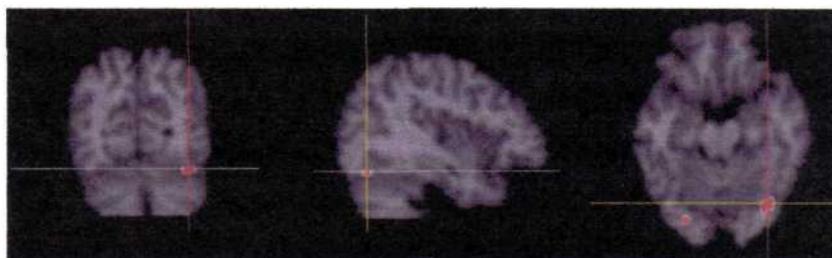


Fig. 2. Orthogonal views of the site of overlap between the current experiment and a color activation mapping study⁹. Coronal, sagittal and axial planes are shown.

Bonnet syndrome²². The earlier PET data² have provided support for the hypothesis that synesthetic color experiences 'result from partial activation of higher-order visual cortical networks, rather than arising at the earliest levels of cortical visual processing' (ref. 23). Our findings, in contrast, like those of recent psychophysical experiments²¹, support the latter hypothesis.

One difference between the activations observed in synesthetes experiencing color in response to words and induced by colored visual stimuli, respectively, lies in the absence of primary visual cortex activation in the former case. We cannot exclude the possibility that such activation does occur during synesthetic color experiences, but cannot be detected easily using current neuroimaging techniques. Thus, color after-images produced relatively less prominent activation in V1 and V2 than did color stimuli⁵. Area V8, however, responded clearly to both color after-images and color stimuli. Thus color after-images are apparently more functionally selective than direct visual stimulation, as found also for the visual motion after-effect²⁴ and illusory motion⁷, in which activation of V5 but not V1 has been observed. Percepts of these kinds, then, may share neurobiological characteristics with those specific to colored-hearing synesthesia. If there is genuinely no V1/V2 activation during synesthetic color experiences, then the brain appears to be capable of generating conscious visual percepts without contribution from primary visual cortex^{2,6,8} (but see ref. 25). Thus our results provide support for previous suggestions that activity in V1/V2 may be neither sufficient⁸ nor necessary⁶ for conscious visual experience.

One account of colored-hearing synesthesia attributes it to abnormal neuronal connectivity between auditory and visual cortical areas^{21,23,26}. The lack of activation of V4/V8 in controls imagining colors in response to words, despite extensive over-training on the relevant word-color associations, is inconsistent with the major alternative account, that synesthesia results from strong associative learning²⁶. Direct testing of the former, 'hard-wiring' account would require invasive connectivity studies not possible with human subjects. However, our results allow us to state the hard-wiring hypothesis more precisely. We observed V4/V8 activation by words in the synesthetes in the left hemisphere only, and no activation of regions occupying an earlier point in the stream of visual processing^{12,27}. We saw no topographic differences in the location of the color-specialized region of the visual system between synesthetes and controls in the right hemisphere. However, we did not see left V4/V8 activation in response to colors in the synesthetes, indicating that normal color perception may compete with synesthetic perception in this region. Thus any hard-wired specialization in the brains of colored-hearing synesthetes is likely to take the form of a left-lateralized direct projection from auditory speech areas to V4/V8, in addition to such more indirect connections between these regions as are present in the normal brain. This might happen because a genetic mutation gives rise to the development of, or a failure to prune, such a projection—in the latter case, one perhaps transiently present during development in non-synesthetes as well²⁸. A genetic account along these lines is plausible, given that synesthesia runs in families and is strongly sex limited^{29,30}. Irrespective of how it arises, any hard-wiring basis for synesthesia poses problems for widely accepted functionalist accounts of consciousness^{26,31}.

METHODS

Subjects. Subjects (all female) were 12 right- and 1 left-handed (by self-report of handedness) word-color synesthetes^{1,30}, with no similar experiences for other auditory stimuli as assessed by the test of genuineness for synesthesia¹; and 27 right- and 1 left-handed controls. Controls had never

experienced synesthesia and were not told the purpose of the study. No subject had a history of neurological or psychiatric disease or was taking psychoactive drugs. Synesthetes and controls were matched for age (synesthetes: Experiment 1, mean 50.2 yrs, range 23–72, and Experiment 2, 44.5, 23–56; controls: 51.1, 32–70, and 35.3, 25–54), and the National Adult Reading Test (NART³²) (synesthetes: Experiment 1, mean NART scores 118, s.d. 3.2, and Experiment 2, 123.3, s.d. 6.2; controls 120, s.d. 3.6 and 118.3, s.d. 6.8. Ten synesthetes (1 left-handed) and 10 controls (1 left-handed) participated in Experiment 1. Three of these synesthetes and 3 new ones, plus 8 additional controls, took part in Experiment 2 (all right-handed). A separate group of 10 right-handed controls participated in Experiment 3. The research was approved by the Ethics Committee, Maudsley Hospital, London. Informed consent was obtained.

Experiment 1. Blocks (30-s) of single spoken words (half abstract, half concrete) alternated with blocks of single pure tones in an AB boxcar design, five of each type over 5 min (fMRI studies of abstract and concrete words reveal similar responses, except for additional right superior temporal gyrus activation to abstract words³³). One word/tone occurred every 3 s. Each block of 10 words was matched for frequency according to a database³⁴. The order of words and tones within and between blocks was randomized across subjects. Tone frequencies ranged randomly from 250 to 550 Hz (within human voice frequencies). Subjects listened passively to the stimuli, eyes closed. After the scanning session, synesthetes were asked to describe the color experienced in response to each word to derive word-color correspondences for Experiment 3.

Experiment 2. Two tasks, counterbalanced for order across subjects, were presented within a single session: the Experiment 1 task, above, and color perception. For the latter, 30-s blocks of colored and achromatic Mondrians alternated in an AB boxcar design, 5 of each type over 5 min. Ten Mondrians were presented in each 30-s block, each for 2.5 s, followed by a white, high-luminance screen (91.8 cd/m²) for 0.5 s, to avoid motion cues at transitions to spatially new patterns. The mean values for the colors (in the center) were green, 53 cd/m²; red, 28 cd/m²; blue, 4.85 cd/m²; yellow, 76.2 cd/m²; white, 91.8 cd/m². To compensate for smaller group size (6 versus 10 in Experiment 1), we adjusted the type I error rate in Experiment 2 by the inverse ratio (10/6) of the group sizes.

Experiment 3. Non-synesthetes learned eight word-color pairings based upon those described by the synesthetes. Words were chosen from the list used in Experiment 1 with the constraints that each triggered a different color and a maximum of one word-color correspondence from each synesthete. Subjects sat in front of a personal computer showing eight colors in a 2 × 4 grid. Clicking on a color caused a word to be presented through headphones and the computer screen to fill with the color. This color remained on the screen until another was chosen. To test learning, subjects heard single words, initiated by themselves, through headphones, in random order, and clicked on the color paired with that word. No feedback was given. Subjects had to be 100% correct five consecutive times. Further cycles of learning and testing were applied until this criterion was reached. For testing in the scanner, subjects listened with eyes closed to blocks (30 s) of single spoken words alternating with blocks of single pure tones, one per 3 s, for 5 min, as in Experiment 1. Each subject was scanned twice: (i) with instructions to 'predict' the color associated with the word, (ii) with instructions to 'imagine' it, in that order. For 'predict', subjects were required simply to think of the name of the color associated with the presented word. For 'imagine', they were required to visualize the color as it appeared on the computer screen. At the end of each 5-min scan, subjects reported the percentage of successful predictions/images. All reported 80–100% success. There was then a re-learning phase in the scanner. The words were presented followed immediately by the appropriate color, back-projected onto a translucent screen over the end of the scanner bore. A short re-test session followed, in which the words were presented one at a time, and subjects responded by naming the associated color. Subjects were required to be 100% correct. All subjects reached criterion on the first re-test session. Re-learning lasted approximately 2 min. Subjects were finally scanned twice more in the 'predict' and 'imagine conditions', as described above.

Image acquisition and analysis. Gradient-recalled echoplanar MRI data were acquired using a GE Signa 1.5-Tesla system (General Electric, Milwaukee, Wisconsin) retrofitted with advanced NMR hardware using a standard head coil. One hundred T2*-weighted images depicting BOLD contrast³⁵ were acquired at each of 14 noncontiguous near-axial planes (7 mm thick, 0.7 mm slice skip) parallel to the intercommissural (AC-PC) line; TE, 40 ms; TR, 3 s; flip angle, 90°; number of signal averages, 1. After estimation and correction of movement-related effects in the fMRI time series at each voxel³⁶, a linear regression model was used to estimate the amplitude of response to periodic stimulation. To account for locally variable hemodynamic delay, the periodic input function was separately convolved with two Poisson functions (with parameters $\lambda = 4$ s and 8 s). The variance accounted for by these two columns of the design matrix, divided by the residual variance, was estimated by least squares at each voxel^{37,38}. The null distribution of this test statistic was estimated, with few assumptions, by repeatedly, randomly resampling the observed time series in the wavelet domain and fitting an identical model to each resampled series after its transformation back to the time domain (see ref. 37 for more detailed description and validation of wavelet resampling in fMRI). Statistic maps representing the observed and resampled values of the test statistic at each voxel for each individual were registered in the standard space of Talairach and Tournoux³⁹ by an affine transformation to a template image⁴⁰. Generic brain activation maps, indicating voxels that were significantly activated on average over all individuals under each experimental condition, were then constructed by testing the median observed statistics against a null distribution ascertained from the permuted statistic maps (see ref. 40 for detailed description and validation). This is a nonparametric and robust random-effects analysis using the median rather than the mean as a measure of central location to mitigate the potential impact of outlying observations in small samples. We applied a preliminary probability threshold ($p = 0.05$) in this way to the observed median statistic maps and set to zero all voxels with values below threshold. This created a set of spatially connected suprathreshold voxel clusters. We tested each of these clusters against a null distribution ascertained experimentally, by prior analysis of a group of six images identically acquired while subjects were asked to lie quietly in the scanner. Analysis of these 'null' or resting, data showed directly that a maximum cluster size of 4 voxels or more had $p < 0.05$ under the null hypothesis⁴¹. This cluster-size threshold was therefore applied to the cluster maps generated from our experimental data sets to achieve a family-wise type 1 error $p = 0.05$, corrected for multiple comparisons. For between-group comparisons, an analysis of variance (ANOVA) model was fitted to the observed time series statistics at each voxel in standard space. The ANOVA model parameter coding group membership was then tested for significance at cluster level exactly as described above for within-group analysis.

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Competing interests statement

The authors declare that they have no competing financial interests.

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