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## Synaesthetic perception of colour and visual space in a blind subject: An fMRI case study

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### ABSTRACT

In spatial sequence synaesthesia (SSS) ordinal stimuli are perceived as arranged in peripersonal space. Using fMRI, we examined the neural bases of SSS and colour synaesthesia for spoken words in a late-blind synaesthete, JF. He reported days of the week and months of the year as both coloured and spatially ordered in peripersonal space; parts of the days and festivities of the year were spatially ordered but uncoloured. Words that denote time-units and triggered no concurrents were used in a control condition. Both conditions inducing SSS activated the occipito-parietal, infero-frontal and insular cortex. The colour area hOC4v was engaged when the synaesthetic experience included colour. These results confirm the continued recruitment of visual colour cortex in this late-blind synaesthetes. Synaesthesia also involved activation in inferior frontal cortex, which may be related to spatial memory and detection, and in the insula, which might contribute to audiovisual integration related to the processing of inducers and concurrents.

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### 1. Introduction

In synaesthetes, stimulation of one sensory or cognitive pathway provokes a spurious additional sensory experience (a concurrent) in a different sensory modality or submodality. Illusory colour sensations associated with viewing graphemes or hearing phonemes are the commonest forms of synaesthesia. Many synaesthetes, including some with coloured graphemes or coloured phonemes, experience *spatial sequence synaesthesia* (SSS) (Sagiv, Simner, Collins, Butterworth, & Ward, 2006). In SSS, one or more categories of ordinal stimuli, particularly numbers, days of the week or months of the year, when heard spoken or even imagined, are perceived visually, as if forming a two- or three-dimensional array of coloured or achromatic shapes, floating in peripersonal space (Eagleman, 2009; Galton, 1883; Hubbard, Arman, Ramachandran, & Boynton, 2005; Sagiv et al., 2006; Seron, Pesenti, Noel, Deloche, & Cornet, 1992). While a number of behavioural studies have provided evidence of the authenticity of SSS (Price & Mentzoni, 2008; Sagiv et al., 2006; Smilek, Callejas, Dixon, & Merikle, 2007), the functional neuroanatomy of SSS remains to be determined. Although SSS is a very common form of synaesthesia (Barnett et al., 2008; Niccolai, Jennes, Stoerig, & Van Leeuwen, 2012), it appears to be under-represented from a functional anatomical point of view. The present paper is the first study which aims at shedding light on the neural correlates of SSS for time-units, both coloured and uncoloured, in a man with late-onset blindness.

There were few reports of illusory visual concurrents evoked by touch or sound in blind people prior to a study by Steven and Blakemore (2004). They described six late-blind participants who retained synaesthetic colour experience after onset of

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blindness: four had been without any form of genuine colour vision for over 10 years. It is known that differences in the functional neuroanatomy of sighted and early-blind subjects reflect predominantly early recruitment of visual cortical areas for tactile (Sadato et al., 1996) and auditory stimulation (Roder, Stock, Bien, Neville, & Rosler, 2002; Weeks et al., 2000), and during verbal (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Burton, Snyder, Diamond, & Raichle, 2002), and memory processing (Raz, Amedi, & Zohary, 2005). However, in late-blind individuals, visual cortical areas seem to retain some aspects of their original specificity. For instance, tactile perception of motion and faces activates visual cortical areas previously involved in analysis of equivalent visual stimuli (Goyal, Hansen, & Blakemore, 2006). And in a late blind synaesthete (the subject of the present report), both striate and extrastriate visual areas appeared to be engaged in the synaesthetic perception of coloured and spatially located concurrents (Steven, Hansen, & Blakemore, 2006). Although it is recognised that blind people can orientate and navigate quite effectively (Jones, 1975), the processes and brain areas unpinning spatial processing in the blind remain to be determined. What is known is that posterior parietal areas are strongly activated during auditory localisation tasks in both sighted and congenitally blind subjects (Weeks et al., 2000).

On the basis of the known literature on the neural correlates of spatial processing, parietal cortex may play an important role also in SSS. In normal sighted non-synaesthetes, the parietal cortex appears to play a role in representing space and in binding objects to each other (Colby & Goldberg, 1999; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Robertson, 2003). Moreover, posterior parietal cortex, together with frontal cortex, has been shown to be functionally specialised for engaging and controlling spatial attention (Corbetta & Shulman, 2002). Further evidence for the anatomical substrate of spatial localisation comes from the clinical condition of Balint's syndrome, associated with bilateral occipito-parietal damage (Rizzo & Vecera, 2002): the interpretation of spatial information beyond one's own body and the capacity to attend to more than one spatial location are severely disrupted.

Results of Spalding and Zangwill (Spalding & Zangwill, 1950) suggest that the parietal cortex also plays a role in the spatial processing involved in SSS in sighted synaesthetes: they reported that occipital-parietal injury in a synaesthete caused the loss of SSS for numbers, weekdays, months and letters of the alphabet, in addition to severe dyscalculia. A recent fMRI study on SSS for numbers showed bilateral activation in the posterior intraparietal sulci during a number-order task (Tang, Ward, & Butterworth, 2008). Altogether, these data are consistent with the hypothesis that parietal areas support mental manipulation of visuospatial information.

We hypothesised that a non-numerical form of synaesthesia, namely SSS for time-units, would involve the posterior parietal cortex. We were fortunate to be able to investigate this in JF, one of the late-blind synaesthetic subjects studied by Steven and Blakemore (Steven & Blakemore, 2004). JF experiences visual spatial sequences, which are sometimes coloured, as concurrents when he listens (or thinks about) words for time-units. Although involvement of his parietal cortex in the processing of time-units was suggested in the fMRI study of Steven et al. (2006), those authors focused predominantly on JF's colour concurrents. In the present study we aimed to disentangle the substrates of two forms of synaesthesia, namely colour and spatial sequence synaesthesia. We created two experimental conditions in which either one or both concurrents were elicited, allowing us to assess separately the neural correlates of each form of synaesthesia, as well as a control condition in which no synaesthesia was triggered.

We expected areas in the posterior ventral cortex, known to be involved in normal colour processing, to be activated during synaesthetic conditions that evoked coloured concurrents, and parietal cortex to be activated during non-coloured spatial synaesthetic experience of non-numerical sequences. Given the evidence that semantic and syntactic aspects of processing are functionally distinct and involve different parts of the neural network underlying word processing (Caramazza & Hillis, 1991; Friederici, Opitz, & von Cramon, 2000; Shapiro et al., 2005), we controlled for these characteristics of the stimuli in the different conditions of our experiment. Finally, we took account of reports (Hubbard, Ranzini, Piazza, & Dehaene, 2009; Piazza, Pinel, & Dehaene, 2006) that SSS for numbers is more intensely triggered when stimuli or the particular task induce a strong notion of sequence. Specifically, Hubbard et al. (2009) showed that numerical-spatial interactions may be most strongly present in synaesthetes when both numerical and spatial information are explicitly task-relevant. We therefore required our subject to perform a task using the semantic and the spatial information present in his synaesthetic experiences.

## 2. Methods

### 2.1. Subjects

JF, a right-handed male engineer, 60 years of age at the time of testing, lost his sight completely at age 45 due to retinitis pigmentosa. His sight had been poor since early childhood, but he could distinguish the colours of lights until the age of about 40. He reported that for as long as he could remember he had experienced SSS for many types of spoken words representing categorical stimuli. JF now has coloured-Braille, i.e. touch-induced visual synaesthesia (Steven & Blakemore, 2004). However, he still perceives time-units and categories of orchestral instruments as coloured, rectangular shapes arranged in body-centered visual space. He has similar sequence-colour synaesthesia for pay-scales and military denominations, but in these cases the 'blobs' that he perceives are achromatic. Our study focused on his synaesthesia for time-units, in which days of the week and months of the year appear to JF as coloured, rectangular shapes, spatially ordered in peripersonal space. He likened this to a path of stepping stones in a garden, on which he would walk, starting from a reference point corresponding

to the current day. JF also reported SSS for words representing parts of the day (“morning”, “evening”, etc.) and for festivals of the year (such as “Easter” and “Christmas”). These also had a shape and the position of festivities followed the months in which they occurred. Unlike days and months, public holidays and parts of the day did not induce colours. Results of a test/re-test of consistency of verbal descriptions of perceived colour confirmed that JF’s synaesthetic experiences were stable over 18 months with a consistency score of 94.7%. Specifically, JF used the same colour names to describe the colours of all but one weekday and month in the test and retest session. The spatial arrangement of the items was represented on a grid and did not vary between test and retest. No information on intensity of synaesthesia for the different experimental stimuli was collected. Six sighted right-handed non-synaesthetes (4 men, 44.5 years old on average, SD = 9.8) also took part to the study and performed the same behavioural task as our synaesthete. Although consistency scores were not collected for controls, these subjects reported no association between time-units and colours/positions in space. Subjects gave informed consent prior to experimental sessions. The study was approved by the local ethics committee of the Heinrich-Heine-University of Düsseldorf, in accordance with the Declaration of Helsinki.

## 2.2. Procedure

In our event-related fMRI study, words spoken by a native English speaker were presented through scanner-compatible headphones. Three conditions were compared.

1. *Coloured SSS (S + C)*; days of the week and months of the year were played to JF, eliciting SSS in the form of distinct, spatially localised, coloured shapes.
2. *Non-coloured SSS (S)*; words describing parts of the day (“morning”, “afternoon”) and holidays of the year (“Christmas”, “Easter”) were presented, i.e. time-words that elicited SSS and the perception of shapes but not of colours.
3. *Non-synaesthetic control (Con)*; JF heard other time-unit words (“second”, “season”, “year”) that, for him, do not evoke synaesthetic sensations (see Table 1).

We organised the stimuli into trials of seven words of the same type. In order to enhance SSS, we introduced a detection task (Hubbard et al., 2009; Piazza et al., 2006). In all conditions, the words were presented either in the conventional, continuous serial order shown in Table 1 (e.g. ‘Monday’, ‘Tuesday’, ‘Wednesday’... or ‘Monday’, ‘Wednesday’, ‘Friday’...), or with one change in direction (‘Monday’, ‘Wednesday’, ‘Tuesday’), or with two such changes (‘Monday’, ‘Thursday’, ‘Wednesday’, ‘Tuesday’, ‘Friday’, ‘Saturday’). These switches were introduced to ‘move’ JF’s synaesthetic experiences forward and backward in his synaesthetic space. Stimulus duration was 0.56 s on average and the inter-stimulus interval was 2.5 s. Two and a half seconds after the last stimulus of each trial, a beep lasting 110 ms was played to prompt JF to indicate the number of ‘switches’ within the sequence, by pressing one of three response buttons with his right hand (0, 1, or 2 changes). Trials were randomized and interleaved with rest times of 10 s. All sequences were unique with respect to the combination of the

**Table 1**  
Time-units used in the three conditions.

Conditions	Coloured SSS (S + C): colour and spatial sequence synaesthesia	Non-coloured SSS (S): spatial sequence synaesthesia, no colour	Control (Con): no synaesthesia
	Monday	Morning	Picosecond
	Tuesday	Middy	Nanosecond
	Wednesday	Noon	Millisecond
	Thursday	Afternoon	Second
	Friday	Evening	Minute
	Saturday	Midnight	Hour
	Sunday	Night	Day
	January	New Year	Week
	February	Epiphany	Month
	March	Candlemas	Season
	April	Lent	Year
	May	Easter	Decade
	June	Pentecost	Century
	July	Advent	Millennium
	August	Christmas	Era
	September		Aeon
	October		
	November		
	December		
Word rareness	7.6	12.0	10.8

Time-unit words used in the three conditions in the standard order of presentation (without reversals). The coloured and non-coloured spatial sequence synaesthesia conditions included two groups of stimuli, which were not mixed in individual trials, whereas the control condition consisted of one larger group. At the bottom of the table, the mean rareness of the stimuli is reported for each condition. Rareness is defined as the number of occurrences of a specific word related to the article “the” (i.e. “the” has about 2<sup>7.6</sup> the number of occurrences a word in the coloured SSS condition).

number and position of switches, and each sequence was therefore used only once. Since days of the week and months of the year are overlearned sequences with a frequency of use in daily language significantly higher than that of the words in the S and Con conditions ( $F_{(2,47)} = 6.94$ ,  $p < 0.01$ ; <http://corpora.informatik.uni-leipzig.de/?dict=en>), all sequences belonging to each condition were practiced twice before the fMRI session to avoid large word-familiarity effects. The practice further aimed to assess whether JF understood the task and was able to perform it well. Since JF had no difficulty with the task, no further practice was required. Practice runs included the reversals and double-reversals, and JR had to respond after each run as in the scanner. Response devices inside the MR scanner (MR-scanner-compatible Lumitouch response box) were the keyboard for the practice session. Total runtime was ~22 min (974 MR images). Controls participants were given a list of the stimuli several days before the behavioural test and they practiced 5 trials randomly assigned from all conditions on a response box, to assess whether they understood the task.

### 2.3. Stimulus presentation

Presentation software (version 10.2, Neurobehavioral Systems Inc., [www.neurobs.com](http://www.neurobs.com)) was used to present the stimuli and to record the responses. Stimuli were played through MR compatible stereo headphones and intrusion from scanner noise was reduced by positioning extra padded cushions around the subject's head. The volume was adjusted so that the stimuli were clearly audible for the subject.

### 2.4. MRI acquisition

MR data were acquired with a 3.0 Tesla Siemens TrioTim MR scanner. A single shot gradient echo-planar imaging (EPI) sequence was used to acquire functional MR images (31 slices, TE = 35 ms, TR = 2280 ms, flip angle = 80°, 224 mm FOV, 64 × 64 matrix, 3.5 × 3.5 × 3.5 mm voxel size, 3.0 mm slice thickness, 0.5 mm slice gap). A high-resolution T1-weighted structural image was acquired (MPRAGE, TE = 2.96 ms, TR = 2300 ms, 256 mm FOV, 256 × 256 matrix, 1 mm<sup>3</sup> resolution).

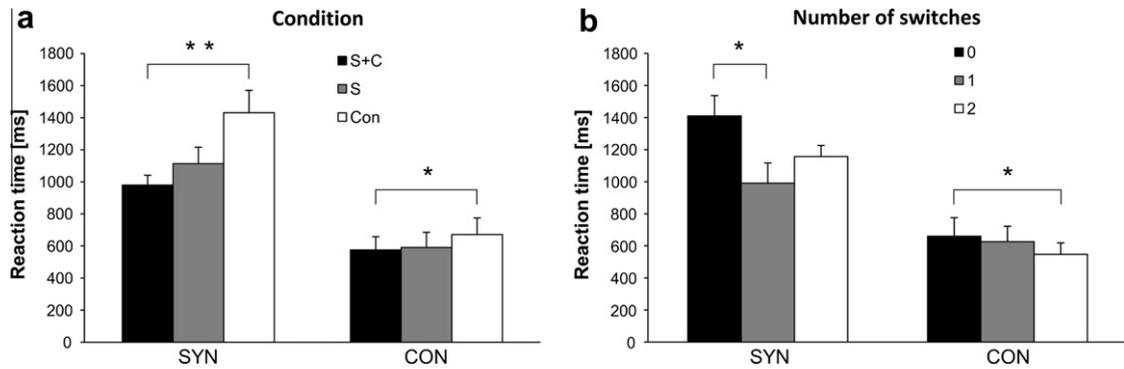
### 2.5. Data analysis

MR data were pre-processed and analysed with SPM8 software (Wellcome Department of Imaging Neuroscience, [www.filion.ucl.ac.uk/spm/software/spm8/](http://www.filion.ucl.ac.uk/spm/software/spm8/)) implemented in Matlab (Mathworks Inc., Natick, MA, USA). Prior to analysis, the first 5 volumes were discarded to avoid transient T1 effects. The remaining volumes were spatially realigned to the first image to correct for head movement between scans. After slice time correction, the EPI images were coregistered to the anatomical image and transformed into a standard stereotactic space corresponding to the MNI (Montreal Neurological Institute) atlas. During normalisation, the images were re-sampled to 2 × 2 × 2 mm resolution. Finally all images were spatially filtered using a 5 mm FWHM isotropic Gaussian filter. Statistical analyses were based on the General Linear Model (GLM) framework. The design matrix was constructed and the BOLD signal was modelled by the canonical hemodynamic response function (HRF). A high-pass filter (128 s cut-off) was used to remove low-frequency effects. Effects of interest were modelled by event onsets and included in the design matrix. The design matrix contained regressors for each of the three experimental conditions (S + C, S, Con) and for prompts, responses and rest periods. Although the present study included twelve trials per condition, the 7 events within each trial were analysed in an event-related design, thus enhancing the generalizability of the results. The six realignment parameters, obtained during pre-processing, were included in the model as covariates of no interest. Parameter estimates were obtained for each condition to generate relevant contrast images. Coordinates of peak activity are reported in MNI coordinates in the order (x, y, z) and may include multiple brain areas. The initial threshold was an uncorrected  $P < 0.001$  at the whole-brain level, with a cluster-level statistic of  $P_{FWECorr} < 0.05$ . The extent threshold was set to a minimum cluster size of 50 voxels. In addition, we examined the contrast (S + C, S, Con) > Rest as well as the individual conditions versus Rest. Corresponding brain regions and Brodmann areas were retrieved from the Münster T2T-Converter ([www.neuro03.uni-muenster.de/ger/t2tconv/conv3d.html](http://www.neuro03.uni-muenster.de/ger/t2tconv/conv3d.html)) and verified with the SPM8 Anatomy toolbox (Eickhoff et al., 2005).

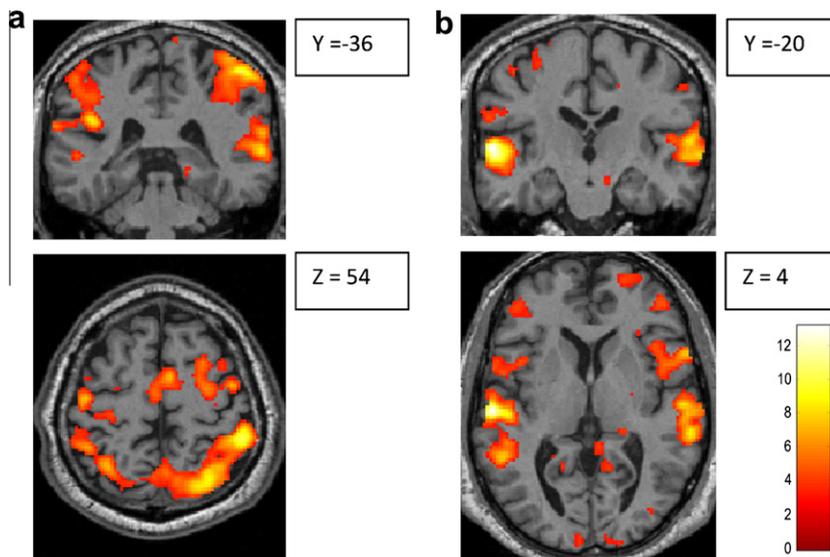
## 3. Results

### 3.1. Behavioural results

An ANOVA for reaction times with Group as between-subjects factor and Condition as within-subjects factor resulted in a significant interaction Condition × Group ( $F_{(2,10)} = 7.49$ ,  $p = 0.01$ ). A significant main effect of Condition ( $F_{(2,10)} = 18.23$ ,  $p < 0.001$ ) was found, but the effect of Group did not reach significance ( $F_{(1,5)} = 5.37$ ,  $p = 0.07$ ). Following pairwise comparisons with Tukey test showed a significant difference between the S + C and the Con condition both for JF ( $F_{(2,31)} = 4.60$ ,  $p = 0.01$ ) and for controls ( $F_{(2,31)} = 3.70$ ,  $p < 0.05$ ) (Fig. 1a). No difference between S and Con ( $p > 0.05$ ) and between S + C and S ( $p > 0.05$ ) emerged in either group, although JF showed a trend towards a difference between S and Con ( $p = 0.07$ ).



**Fig. 1.** (a) Average reaction time and standard error of the mean in the three conditions for the synaesthete JF (SYN) and six controls (CON). S + C = coloured spatial sequence synaesthesia condition; S = non-coloured SSS condition; Con = control condition. (b) Average reaction time and standard error of the mean in trials with no switch, one switch and two switches in direction. Trials were collapsed across conditions. \*\* $p = 0.01$ , \* $p < 0.05$ .



**Fig. 2.** Coronal (top) and axial (bottom) views (right hemisphere on the right) of the large parietal (a) and temporal (b) clusters of activation in the contrast Time-Words > Rest at coordinates (50, -36, 54) and (-58, -20, 4) respectively. For details see Table 2.

An ANOVA for accuracy with the same factors resulted in no interaction ( $F < 1$ ), no main effect of condition ( $F < 1$ ) or group ( $F < 1$ ).

An almost significant interaction between Number of changes and Group ( $F_{(2,10)} = 3.67$ ,  $p = 0.06$ ) together with an effect of Number of changes in trial direction emerged ( $F_{(2,10)} = 5.59$ ,  $p < 0.05$ ). Pairwise comparisons with Tukey test showed longer reaction time in trials with no changes than in those with one change in direction for JF ( $F_{(2,33)} = 4.14$ ,  $p < 0.05$ ) and longer reaction time in trials with no changes than in those with two changes for controls ( $F_{(2,31)} = 3.54$ ,  $p < 0.05$ ) (Fig. 1b).

### 3.2. fMRI results

To explore the activation elicited by Time-words, we contrasted the three conditions S + C, S, and Con with the Rest condition. This showed quite widespread activation (Fig. 2). In particular, the superior temporal gyrus was bilaterally active, together with the right inferior parietal cortex and the right superior and inferior frontal gyrus. Comparison of the two conditions producing synaesthesia with the control (S + C, S > Con) showed significant activation bilaterally in occipital cortex, right inferior parietal cortex, right inferior frontal cortex and the insula. The coordinates, laterality, and the extent of these activations are reported in Table 2.

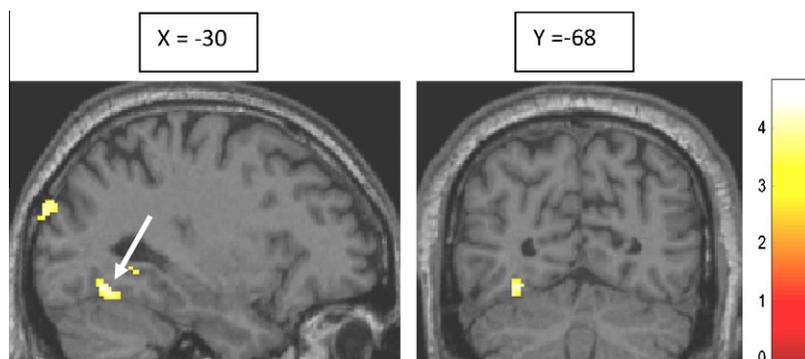
The contrast between the S + C condition and the Con condition was expected to show the effect of colour and spatial perception. A significant activation appeared at coordinates (-30, -68, -12) in the left hemisphere (Fig. 3), a region belonging to the cytoarchitectonic area hOC4v – the putative colour area, V4. This is very similar to the activation during

**Table 2**Anatomical regions, MNI coordinates for peak activations, cluster size, Brodmann areas, and *P*-values revealed by comparing condition as listed in column 1.

	Side	MNI coordinates			Cluster size (voxels)	BA	<i>P</i>
		<i>x</i>	<i>y</i>	<i>z</i>			
<i>S + C, S, Con &gt; Rest</i>							
SPL, IPC	R	50	−36	54	1428	7	<0.001
STG	L	−58	−20	4	397	22	<0.001
STG	R	58	−16	0	531	22	<0.001
MTG	L	−56	−48	6	100	21	<0.001
IFG	R	48	10	14	414	44	<0.001
SFG	R	28	−6	62	317	6	<0.001
<i>S + C, S &gt; Con</i>							
SOG, IPC	R	42	−86	26	236	19	<0.001
SOG	L	−26	−94	26	162	19	<0.001
IFG, IS	R	30	20	−20	226	47	<0.001
<i>S + C &gt; Con</i>							
IFG, MFG, IS	R	28	26	−12	192	47	<0.001
IPC	R	40	−88	26	66	19	<0.05 <sup>a</sup>
MOG, SOG	L	−28	−96	24	113	19	<0.01
MOG	R	38	−90	8	94	18	<0.02
hOC4v	L	−30	−68	−12	56	19	<0.05 <sup>a</sup>
<i>S &gt; Con</i>							
IPC, SOG	R	44	−82	30	100	19	<0.02
MOG, SOG	L	−26	−94	26	83	19	<0.05
IFG, IS, STG	R	30	20	−20	77	47	<0.04
<i>Con &gt; Rest</i>							
SPL	R	30	−62	54	568	7	<0.001
IPL	R	50	−38	54	349	2	<0.001
STG	R	60	−16	0	529	22	<0.001
STG	L	−60	−20	4	392	22	<0.001
IFG	R	48	10	14	497	44	<0.001
IFG	L	−44	10	28	148		<0.001
<i>S + C &gt; Rest</i>							
SPL	R	16	−64	60	642	7	<0.001
IPL	R	48	−38	56	176	1	<0.001
STG	L	−58	−20	4	167	22	<0.001
SFG	R	30	−6	62	116	6	<0.001

*S + C* = coloured spatial sequence synaesthesia condition, *S* = non-coloured spatial sequence synaesthesia condition, *Con* = control condition. BA = Brodmann Area; L = left hemisphere; R = right hemisphere. IPL = inferior parietal lobule; IPC = inferior parietal cortex; IPS = intraparietal sulcus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; PG = precentral gyrus IS = insula; SOG = superior occipital gyrus; MOG = middle occipital gyrus; OLcun = occipital lobe cuneus; IPC = inferior parietal cortex; SPL = superior parietal lobule; MTG = middle temporal gyrus; STG = superior temporal gyrus; hOC4v = visual colour area V4. *P* indicates FWE<sub>corr</sub> value at cluster level corrected for entire brain volume.

<sup>a</sup>  $P_{FDR_{corr}}$  value. Puncorr < 0.001 was used as initial threshold for all contrasts except those including Rest (*S + C, S, Con > Rest, Con > Rest* and *S + C > Rest*), which were thresholded with a  $P_{FWE_{corr}}$  < 0.01 because of the broad significant activations that these contrasts elicited.



**Fig. 3.** Sagittal (left) and coronal (right) views of activations in the visual colour area V4 (coordinates −30, −68, −12) in the *S + C > Con* contrast. For details see Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

coloured-time-word synaesthesia reported for the same subject by Steven et al. (2006) (coordinates −29, −67, −18). This contrast also revealed significant frontal activation ( $P_{FDR_{corr}} = 0.002$ ), which, according to the Anatomy Toolbox, included

the anterior insular cortex at coordinates (32, 20, –20). Additionally, we found significant activation at coordinates (40, –88, 26), a region having 40% probability of belonging to the inferior parietal cortex. The middle occipital gyrus was bilaterally activated.

For the  $S > \text{Con}$  contrast, which reveals the effects of spatial synaesthesia without colour, we expected, *a priori*, to find posterior parietal activation but none in V4. This expectation was fulfilled, with no activation in V4 but significant activation at coordinates (44, –82, 30), a region having a 80% probability of being inferior parietal cortex, somewhat rostral to the parietal activation in the  $S + C$  condition. The  $S > \text{Con}$  contrast also revealed significant activation in middle and superior occipital cortex, as well as right superior temporal, and inferior frontal gyrus; the last focus extended into the anterior insula. The contrast between coloured and non coloured spatial synaesthesia ( $S + C > S$ ), which was expected to result in V4 activation, did not show significant effects at the whole-brain level. The reverse contrast  $S > S + C$  showed significant bilateral activation of the superior temporal gyrus, possibly related to lower frequency of stimuli in the  $S$  condition compared to  $S + C$ . To further explore the activations of the control and colour synesthetic condition, we contrasted them to the rest period. The  $\text{Con} > \text{Rest}$  contrast showed significant activation in the right superior and inferior parietal lobule in addition to the superior temporal and the inferior frontal gyri. The  $S + C > \text{Rest}$  contrast also revealed right inferior and superior parietal activation together with left superior temporal gyrus and right superior frontal gyrus. A summary of the significantly activated areas is presented in Table 2.

## 4. Discussion

The present study reports on coloured and non-coloured spatial sequence synaesthesia for spoken time-words in a late-blind subject. First, we discuss the behavioural findings and then the fMRI results. Finally, neural commonalities between SSS and spatial imagery will be discussed in the light of findings from this and other studies.

### 4.1. Behavioural data

The average reaction time in the coloured spatial synaesthesia ( $S + C$ ) condition was significantly shorter in JF than in the no-synaesthesia ( $\text{Con}$ ) condition: the switches in direction within the sequences of synaesthetic stimuli were easier to detect than in the control sequences. A possible explanation for this is that the synaesthetic visualisation of items triggered in the  $S + C$  condition facilitated processing of the sequences for JF. The synaesthetic visual (colour and spatial), as well as auditory dimension of the stimuli might have resulted in inter-sensory facilitation and hence faster task performance compared to the  $\text{Con}$  condition. The trend towards significant difference in reaction time between  $S$  and  $\text{Con}$  suggests that the facilitation appeared to diminish when only the spatial but not the colour dimension of synaesthesia ( $S$ ) was present. Although there was no difference in task accuracy between  $S + C$  and  $\text{Con}$  conditions, we cannot exclude the possibility that the former condition involved less effort and therefore shorter reaction times.

Another possibility is that the detection of sequence reversals in the less familiar words of the  $\text{Con}$  condition was simply more demanding, and therefore slower. To test these possibilities, six non-synaesthetes were required to perform the same task. Indeed, controls showed longer reaction times in the  $\text{Con}$  compared to the  $S + C$  condition, thus suggesting that the difference in word frequency did affect reaction time also for JF.

JF took longer to respond on trials with no changes in direction compared to those with one change. This could well have been due to longer mental rehearsal of the sequences without reversals, to be confident of negative reports. Also control subjects were slower to respond on trials with no changes in direction compared to those with two changes. This result is in line with findings on serial search showing that reaction time are about twice as great for target absent than for target present (Treisman & Gelade, 1980).

### 4.2. fMRI data

#### 4.2.1. V4, occipital, and parietal cortex

The contrast of all three time-words conditions  $S + C$ ,  $S$ , and  $\text{Con}$  versus the  $\text{Rest}$  condition showed that language comprehension activated both left and right temporal areas (Fig. 2), thus replicating previous findings on congenitally blind individuals (Roder et al., 2002). These together with previous findings in sighted subjects (Creutzfeldt, Ojemann, & Lettich, 1989) account for the hypothesis of a bilaterally extended language related brain activity. Besides, we found activation of the right inferior parietal cortex. The activity in this region is likely to depend on the time-related stimuli that we used. Recent findings challenge the idea that the inferior parietal cortex is responsible solely for the visual spatial processing. Battelli, Pascual-Leone, and Cavanagh (2007) showed that the area within the inferior parietal lobe and including the right angular gyrus, the supramarginal gyrus and the posterior superior temporal sulcus plays a crucial role in tasks that require the analysis of time. The inferior parietal activation found in our study might therefore partly be related to the engagement of this so called “when” pathway together with the “where” pathway, as JF maps time onto space.

The combined spatial synaesthesia conditions  $S + C$  and  $S$  versus the  $\text{Con}$  condition evoked occipito-parietal, infero-frontal and insular activation. This result shows activation of extra-striate visual areas in our late-blind subject during presentation of synaesthesia-inducing auditory stimuli. The occipito-parietal activation corresponds well with the different synaesthetic

concurrents (position in peripersonal space, and, in the S + C condition, colour) elicited by days of the week, months and festivities of the year. BA 19 in the occipito-parietal cluster belongs to the dorsal stream, which is thought to encompass the “where” pathway and is associated with representation of object locations. As suggested by previous studies (Spalding & Zangwill, 1950; Steven et al., 2006), the occipito-parietal region is likely to be involved in SSS. Tang et al. (2008) investigated SSS for numbers and found more rostral parietal activation. This might depend on the magnitude property of numbers. Our control condition, which possibly included a quantity manipulation task due to the nature of the stimuli, activated a region in the right intraparietal sulcus which falls within the coordinates reported by Tang et al. (2008) (small volume correction, 2 mm sphere at MNI coordinates 42, -57, 40,  $P_{FWECorr} = 0.002$ ). Dehaene, Piazza, Pinel, and Cohen (2003) showed that the intraparietal sulcus is systematically activated whenever numbers are manipulated, independently of number notation, and with increasing activation as the task puts greater emphasis on quantity processing. The fact that we did not find activation of the intraparietal sulcus in the synaesthetic conditions possibly depended on the quantity manipulation task in the Con condition. The proposed analogy between the quantity system and the internal number line is supported by a recent study, which applied a quantity comparison task and showed that the size effect (faster comparison time for smaller than larger numbers, given a fixed intrapair distance) reflects a basic feature of the mental number line (Pinhas, Tzelgov, & Guata-Yaakobi, 2010). Indeed, the Con condition elicited activation in the right intraparietal sulcus (Fig. 4a). It is therefore possible that this condition activated brain regions involved in sequence-space processing, subtracting out possible intraparietal activation from the S + C and S conditions in the comparison with the Con condition. Consistently with this interpretation, the contrast S + C > Rest revealed parietal activity (Fig. 4b, Table 2). Besides, it is worth noting that activation of middle and superior occipital areas, as observed for the S + C, S vs Con contrast, has been found alongside V4 in colour processing tasks (Bartels & Zeki, 2000; Mullen, Dumoulin, McMahon, de Zubicaray, & Hess, 2007). It might therefore also contribute to the processing of synaesthetic colour.

In addition to the bilateral occipital (BA19) and the right inferior parietal cortex, the S + C > Con contrast showed activation of the left colour area V4. As hypothesised, V4 was not activated in the S condition, which elicited non-coloured synaesthesia. The activation of V4 replicates results from several fMRI studies on phoneme-colour synaesthesia (Gray et al., 2006; Nunn et al., 2002; Steven et al., 2006) and on grapheme-colour synaesthesia (Hubbard et al., 2005; Sperling, Prvulovic, Linden, Singer, & Stirn, 2006; Van Leeuwen, Petersson, & Hagoort, 2010). It should however be noted that some studies failed to show V4 activation during synaesthetic experience (Aleman, Rutten, Sitskoorn, Dautzenberg, & Ramsey, 2001; Paulesu et al., 1995; Weiss, Zilles, & Fink, 2005); this inconsistency remains to be explained. Also, we found activation at the coordinates which correspond to those reported by Steven et al. (2006) in a study on coloured-hearing synaesthesia in the same subject. All together, these results reinforce the hypothesis that brain colour areas are recruited in synaesthetes perceiving coloured concurrents and continue to be engaged in colour perception in a late-blind synaesthete.

Surprisingly, V4 activation was not evident when the spatial coloured synaesthesia (S + C) was directly compared with spatial non-coloured synaesthesia (S). It is possible that the processing of shape, which was involved both in the S + C and in the S condition, activated V4. As reported by Rouw, Scholte, and Colizoli (2011), shape processing as well as retention of shape information in visual working memory activates V4. Although in a different way, colour and shape processing may have activated V4 to the same extent, thus explaining the lack of significant V4 activation in the contrast S + C > S. The contrast of S vs. Con, however, did not activate V4 significantly, suggesting that the activation of V4 by shape alone is not strong enough to explain the effect that was found in V4 for the S + C vs. Con condition.

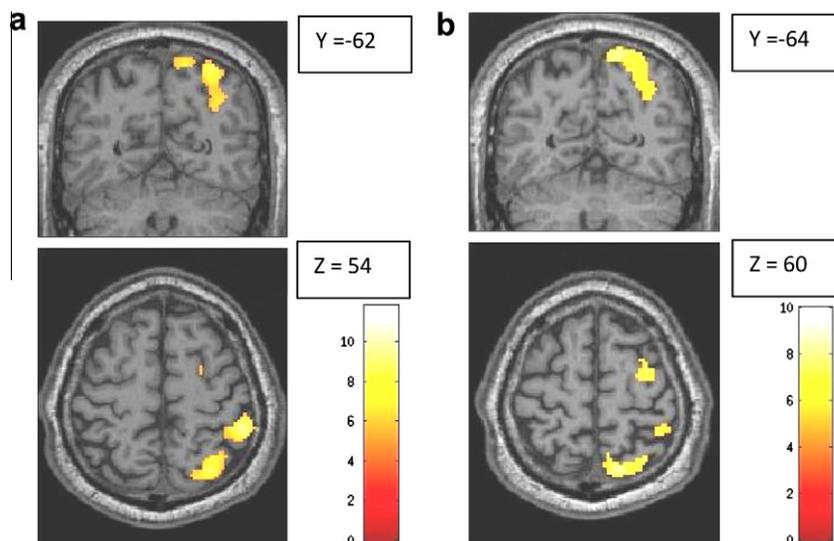


Fig. 4. Coronal (top) and axial (bottom) views of parietal activation in the contrast C > Rest (a) and S + C > Rest (b). For details see Table 2.

#### 4.2.2. Inferior frontal cortex

We found significant activation of the inferior frontal cortex both in the S + C > Con and S > Con contrast. This activation may be related to spatial memory processes: to identify the presence of a switch, information concerning the direction given by the last two heard items needed to be retained. As the items elicited SSS, the processing of visual spatial information was entangled in the memory processing. The right prefrontal cortex has been shown to be implicated in the maintenance of spatial information for short periods of time (Jonides et al., 1993) as well as in spatial retrieval (Moscovitch, Kapur, Kohler, & Houle, 1995). Specifically, Jonides et al. (1993) proposed that the neural activity recorded in prefrontal cortex is itself the internal representation of spatial location that is maintained during a retention interval. Indeed, involvement of the right prefrontal activation has been reported in non-synaesthetes building up and keeping the mental number line active (Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005) and in synaesthetes engaged in ordinal numerical judgments (Tang et al., 2008). All together these findings suggest a role of the right prefrontal cortex in storing and recalling the spatial information processed in SSS as required by the task.

In the previous study on JF (Steven et al., 2006), no frontal activation emerged, possibly because the one-back matching task did not engage spatial memory processing as strongly as the task in the present study. It is worth noting that the right inferior frontal activation has been observed in previous fMRI studies on synaesthesia (Aleman et al., 2001; Paulesu et al., 1995), in which the task consisted of passive listening to words and did not require visual spatial working memory. Paulesu et al. (1995) interpreted the right inferior frontal activation as due to the attentional demand of hearing words compared to tones. However, the same area was activated in our study, which included word stimuli in all conditions; in fact, the words used in the S + C condition are more common and therefore less demanding than those in the Con condition. Besides, right inferior frontal activation was seen in a study on synaesthesia for visually presented letters (Sperling et al., 2006). The frontal activation is likely to play a modulatory role on other brain regions. A number of studies suggested frontoparietal interaction related to working memory (Chafee & Goldman-Rakic, 2000; Gruber & von Cramon, 2001) and, more specifically, to spatial working memory (Curtis, 2006; Diwadkar, Carpenter, & Just, 2000; Ricciardi et al., 2006). Interestingly, rTMS of the right IFG suppresses the Spatial-Numerical Association of Response Codes (SNARC) effect (Rusconi, Bueti, Walsh, & Butterworth, 2009), which consist in the association of small numbers with the left side and large number with the right side of space in a mental number line. Given the high interconnection between prefrontal and parietal cortices, cooperation between these two areas is very probable: such a loop is likely not only to create and maintain internal representation, but also to integrate and transform information for problem solving activities such as determining sequence relationships (Acuna, Eliassen, Donoghue, & Sanes, 2002). Also, according to Mellet et al. (1996), the occipitoparietal-frontal network for spatial processing is not bound to the modality under which information is delivered: this may explain the finding of occipitoparietal-frontal network activation in studies applying stimuli through different sensory modalities.

#### 4.2.3. Insular cortex

Both the S + C and the S conditions compared to Con triggered activation in the insula, thus replicating findings from previous imaging studies on phoneme/grapheme-colour synaesthesia (Aleman et al., 2001; Nunn et al., 2002; Sperling et al., 2006) and supporting the hypothesised role of the insula as an ideal neuroanatomical locus for synaesthesia (Ramachandran & Hubbard, 2001). Due to its connectivity with diverse auditory, somatosensory, olfactory, limbic and para-limbic structures (Banati, Goerres, Tjoa, Aggleton, & Grasby, 2000; Hadjikhani & Roland, 1998), the insula is an important cross-modal area, where the cross-modal effects of synaesthesia could be mediated. Specifically, this structure supports the detection of visual-auditory synchrony (Calvert, 2001) and is involved in audio-visual integration of conceptually related objects (Naghavi, Eriksson, Larsson, & Nyberg, 2007). We suggest that the simultaneous perception of acoustic inducers and visual concurrents may lead to the activation of the insula, where different types of sensory information are combined. The abundance of evidence for the insula activation in different forms of synaesthesia suggests that this structure may be crucially required by the synaesthetic process.

The insula's high connectivity with a number of different structures opens, nevertheless, the way to other interpretations of our findings. The insula appears to be part of a specific mental navigation network encoding spatial information in an ego-centric frame of reference (Ghaem et al., 1997). Indeed, the task used in the present study required JF to move across the time-units in his synaesthetic peripersonal space: this process might be responsible for the anterior insula activation. Although the control condition involved a sequence as well, it did not invoke any moving in the peripersonal space, which could explain higher insula activity in the S + C and S conditions.

#### 4.2.4. Spatial sequence synaesthesia and visuo-spatial imagery

Results of the present study suggest that the spatial geometry of SSS is related to occipitoparietal areas engaged by spatial imagery in blind (Vanlierde, De Volder, Wanet-Defalque, & Veraart, 2003) and sighted non-synaesthetes (Mellet et al., 1996). Whether visuo-spatial imagery and SSS share neural correlates is an open issue. Published evidence suggests that parieto-occipital as well as frontal cortex plays a role in spatial imagery (Ghaem et al., 1997; Levine, Warach, & Farah, 1985; Mellet, Tzourio, Denis, & Mazoyer, 1995). Superior occipital, inferior parietal and inferior frontal cortices have been shown to be involved in the processing of nonperceptual spatial information during a mental construction task (Mellet et al., 1996), whereas the mental production of figural nonspatial properties of evoked objects did not elicit occipito-parietal activation (Mellet, Tzourio, Denis, & Mazoyer, 1998). Trojano et al. (2000) found convergence between spatial imagery and visual perception within the posterior parietal lobes in non synaesthetes. In particular, orienting attention to the extra-personal space

and to internal representations has been shown to activate a largely overlapping network constituted by the parietal, frontal, and occipital areas; the overlap occurred in brain areas noted to be engaged in visual spatial orienting tasks (Nobre et al., 2004). Rich and Mattingley (2002) proposed a model for grapheme- and phoneme-colour synaesthesia, according to which synaesthetic colours can result from activity at one of two stages: either colour categorisation/recognition (most closely related to colour perception) or object colour knowledge/imagery (a type of vivid colour imagery). Our results together with findings from the literature suggest that this model, specifically the activation of the imagery stage, might apply to SSS.

## 5. General conclusions

The present study demonstrates continued recruitment of visual colour cortex in a late-blind synaesthete as well as engagement of occipitoparietal areas into the spatial geometry of SSS. Studies of sighted non-synaesthetes and SSS synaesthetes performing the same task are needed to understand whether and how this network differs from that activated in these groups.

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