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Brain areas involved in synaesthesia: A review

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Despite a recent upsurge of research, much remains unknown about the neurobiological mechanisms underlying synaesthesia. By integrating results obtained so far in Magnetic Resonance Imaging (MRI) studies, this contribution sheds light on the role of particular brain regions in synaesthetic experiences. First, in accordance with its sensory nature, it seems that the sensory brain areas corresponding to the type of synaesthetic experience are activated. Synaesthetic colour experiences can activate colour regions in occipito-temporal cortex, but this is not necessarily restricted to V4. Furthermore, sensory and motor brain regions have been obtained that extend beyond the particular type of synaesthesia studied. Second, differences in experimental setup, number and type of synaesthetes tested, and method to delineate regions of interest may help explain inconsistent results obtained in the BOLD-MRI (Blood Oxygen Level Dependent functional MRI) studies. Third, an overview of obtained results shows that a network of brain areas rather than a single brain region underlies synaesthesia. Six brain regions of overlapping results emerge, these regions are in sensory and motor regions as well as 'higher level' regions in parietal and frontal lobe. We propose that these regions are related to three different cognitive processes inherently part of synaesthesia; the sensory processes, the (attentional) 'binding' processes, and cognitive control processes. Finally, we discuss how these functional and structural brain properties might relate to the development of synaesthesia. In particular, we believe this relationship is better understood by separating the question what underlies the presence of synaesthesia ('trait') from what determines particular synaesthetic associations ('type').

> 'If someone scratches a blackboard with his or her nails, I taste iron. The intro of "Time" by Pink Floyd is golden yellow and blue. Poems have a colour if they are cited, and sometimes when I read them'.

This is an excerpt of a synaesthete's report participating in our research. Synaesthesia is a condition in which a particular sensation ('inducer') evokes another specific sensation not commonly associated with it ('concurrent'). Well-known and common examples of synaesthesia are colours evoked by letters or words, and numbers or time units (e.g., days of the week) that occupy specific locations in space (e.g., Jarick *et al.*, 2009; Price & Mentzoni, 2008; Seymour, 1980; Smilek, Callejas, Dixon, & Merikle, 2007). Quite different types of synaesthesia have also been reported. For example, synaesthetic taste

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can be elicited by words (e.g., 'part' tastes like chicken noodle soup; Ward, Simner, & Auyeung, 2005). Animate qualities such as personality and gender can be attributed to linguistic units such as letters, numbers, and days (Simner & Holenstein, 2007). Or certain visual information, such as flashes or motion, causes the perception of sound (Saenz & Koch, 2008).

The field of synaesthesia research has changed over the years from a relatively small group of researchers targeting a largely unknown phenomenon to a well-accepted research topic that receives an increasing interest in different fields of cognitive, neurological, and developmental aspects of human functioning. A major influence on this change in perspective is work showing that synaesthesia is a 'real' phenomenon (e.g., Baron-Cohen, Wyke, & Binnie, 1987; Baron-Cohen, Harrison, Goldstein, & Wyke, 1993; Cytowic, 1995; Cytowic & Wood, 1982; Dixon, Smilek, Cudahy, & Merikle, 2000; Mattingley, Rich, Yelland, & Bradshaw, 2001; Palmeri *et al.*, 2002; Ramachandran & Hubbard, 2001a, b; Smilek, Dixon, Cudahy, & Merikle, 2001). Synaesthetes report a consistent and reliable within-subject experience that is not 'made up' and is not evoked by drug use or mental disease and seems to be present from early childhood.

This phenomenon can, therefore, now be studied and viewed as a natural variation in healthy human cognition. Furthermore, the field has taken advantage of new techniques to examine how certain brain properties relate to synaesthesia. Previous papers have provided excellent reviews aimed in particular at cognitive processes and behavioural experiments, as well as developing explanatory models for synaesthesia (e.g., Grossenbacher & Lovelace, 2001; Hubbard, Brang, Ramachandran, 2011, in this issue; Hubbard & Ramachandran, 2005; Mattingley, 2009; Rich & Mattingley, 2002). As we will discuss below, one interesting recent development is that an increasing number of studies measure structural as well as functional brain properties in synaesthetes. This review aims to compile what these studies have taught us so far about the neurobiological basis of synaesthesia. The purpose of this review is to discuss functional and structural localization of synaesthesia rather than timing of network activity; thus, in pursuit of brevity, we focus on MRI-based and not on electrophysiology studies. In particular, four questions are addressed: First, as colour is the most common and most studied synaesthetic concurrent, what have we learned about activation of colour areas during synaesthesia? Is a particular colour area activated during synaesthesia, and is activation limited to that particular area? Second, studies examining the role of V4 in synaesthetic colour experiences do not seem completely consistent. What might explain these inconsistent results? Third, we look at the whole brain rather than specific (colour processing) regions. Which locations in the brain seem particularly relevant in the neurobiological mechanisms involved in synaesthesia? We discuss both activation patterns and structural differences in the brains of synaesthetes versus non-synaesthetes. Fourth, differences between synaesthetes and non-synaesthetes are found in both structure and functioning of the brain, and this raises the question, what is the role of these differences in the development of synaesthesia. We present a framework to shed light on this issue by separating current findings on what underlies the presence of synaesthesia ('trait') from what determines particular synaesthetic associations ('type').

Part I: The synaesthetic brain

One important way in which synaesthesia differs from those simple 'associations' between concepts that are found in the general population (such as between 'grass' and 'green'), is that standard associations are only made at a conceptual or semantic level. In

contrast, the synaesthetic associations also contain a modality-specific or sensory feature. Indeed, perceptual studies (synaesthesia aiding in a crowding task, Hubbard, Arman, Ramachandran, & Boynton, 2005; synaesthetic colour-opponency, Nikolić, Lichti, & Singer, 2007; synaesthetic photisms influencing visual perceptions, Smilek *et al.*, 2001) have shown the perceptual or percept-like nature of synaesthetic experiences. This raises the intriguing question of what is the relationship between synaesthetic experiences and the corresponding sensory-specific cortices. Theoretical accounts have proposed that activation of perceptual or sensory areas can take place by 'cross-activation' through increased local connectivity or by 'disinhibited feedback' from higher-level cortical areas. The first model stresses the role of structural brain differences (see Hubbard *et al.*, 2011), possibly due to genetic predisposition, and a fast cross-over of activation from inducer to concurrent (e.g., Ramachandran & Hubbard, 2001b). The second model stresses the role of functional brain differences only, and dis-inhibition between brain areas (e.g., from a multi-sensory nexus as superior temporal cortex to sensory areas; Grossenbacher & Lovelace, 2001) or within a brain area (Cohen Kadosh & Henik, 2007).

The great majority of neuro-imaging work on synaesthesia examined types of synaesthesia, in which colour experiences are evoked by hearing or seeing linguistic stimuli. There seems to be confusion in the literature on the terms used ('colored-hearing' and 'grapheme-color').[1] Most studies unfortunately did not report whether participants were selectively sensitive to an auditory or a visual presentation modality or both. Similarly, a synaesthete with coloured words might or might not have coloured letters (and vice versa). It is, therefore, difficult to know the specific characteristics of the synaesthetes in these studies, and we chose to describe the different studies based on characteristics of the study instead. While 'grapheme-color' synaesthesia is often tested by visual presentation of letters and 'colored-hearing' synaesthesia is often tested by auditory presentation of words, a more general term is 'linguistic-color' synaesthesia (Barnett *et al.*, 2008), (but see Novich, Cheng, & Eagleman, 2011, showing that these synaesthetes might in fact belong to the category of 'sequence-color'). In 'linguistic-color' synaesthetes, a meaningful symbol (e.g., the letter 'A', or the word 'table') evokes an additional experience of a particular colour (e.g., bright red). Understanding this type of synaesthesia is fundamental, as the majority of synaesthetic inducers are linguistic and the majority of synaesthetic concurrents are colour (Barnett *et al.*, 2008; Rich, Bradshaw, & Mattingley, 2005; Simner *et al.*, 2006). With colour as the synaesthetic concurrent in these studies, it follows naturally that a key question (e.g., Hubbard *et al.*, 2005; Nunn *et al.*, 2002; Paulesu *et al.*, 1995; Rich *et al.*, 2006) is to what degree this synaesthetic colour experience evokes the same (brain) mechanisms as a 'normal' colour experience, that is, a colour experience that is evoked by a corresponding colour stimulus.

Neurobiological basis of colour processing

V4 is generally regarded as the specialized area processing colour. This is mostly based on the work of Semir Zeki (Zeki, 1990; Zeki *et al.*, 1991). Zeki however writes: 'While we refer to human V4 and V5 as the colour and motion centres, respectively, we do not wish to imply that the processing of colour or motion is necessarily their only function, or that these are the only areas involved with those sub-modalities of vision.

[1] *We thank an anonymous reviewer for pointing out and clarifying this issue.*

We state only that colour and motion are among their chief functions' (Zeki *et al.*, 1991). Indeed, human V4 is also involved with the processing of shape (David, Hayden, & Gallant, 2006), deployment of attention (Luck, Chelazzi, Hillyard, & Desimone, 1997), and retention of shape information in visual working memory (Sligte, Scholte, & Lamme, 2009). Conversely, V4 is not the only area involved in normal colour vision (e.g., Hadjikhani, Liu, Dale, Cavanagh, & Tootell, 1998). While this brain region is certainly important, colour vision is in fact supported by a network of brain areas (Barrett *et al.*, 2001; Beauchamp, Haxby, Jennings, & DeYoe, 1999; Heywood & Kentridge, 2003; Wandell, Dumoulin, & Brewer, 2006). Different groups used BOLD-MRI to show that in humans, V1 can be the most responsive area to react to the difference between colour signals and luminance signals (Engel, Zhang, & Wandell, 1997; Kleinschmidt, Lee, Requardt, & Frahm, 1996). Beyond V3, area V4 has been linked with 'higher-level' perceptual aspects such as colour constancy (Heywood & Kentridge, 2003). Perceptual colour aspects in turn evoke at least partially different activations from (object) colour knowledge (Chao & Martin, 1999; Zeki & Marini, 1998). Furthermore, which particular 'color' brain area is activated is influenced by attentional modulation (Beauchamp *et al.*, 1999). Moreover, not only V4 seems involved in perceptual colour. Brewer, Liu, Wade, and Wandell, (2005) found, besides V4, additional areas that also respond stronger to colour changes than luminance changes, namely VO1 and VO2. Interestingly, it is possible to decode which colours were presented to subjects on the basis of V1, V2, V3, hV4, and VO1 (VO2 was not analyzed) but not based on more parietal areas such as LO1, LO2, V3A/B, or MT+ (Brouwer & Heeger, 2009).

As we will subsequently show, different choices are made in synaesthesia research in delineating the 'color area' as a region of interest (ROI), which has implications for the functional properties and locations of the obtained colour regions. Another implication for synaesthesia research is that different cognitive demands (e.g., increased attentional demand) between baseline and experimental conditions will likely affect brain activation in colour regions regardless of the presence or absence of the synaesthetic colour. As we will see below, this broader perspective on colour processing areas in the brain aids understanding of some of the contradicting results found on the role of V4 during synaesthetic colour experience.

Activation of V4

In an eminent study, Nunn *et al.*, (2002) measured brain activation in 13 synaesthetes, while they listened to words that elicit a synaesthetic colour. This result was compared with brain regions activated by coloured abstract patterns ('Mondrians') in control subjects. The only significant overlap was found in the left fusiform gyrus, at co-ordinates similar to those of V4. Hubbard *et al.*, (2005) found increased activation in V4 in response to seeing greyscale graphemes that evoke synaesthetic colour. While studies such as these show that synaesthetic colour experience is related to V4 activation, literature does not present a completely consistent image. For example, Aleman, Rutten, Sitskoorn, Dautzenberg, & Ramsey, (2001) and Paulesu *et al.*, (1995) did not find activation in V4 during auditory presentation of letters numbers. One explanation for not finding V4 activation is lack of power of that particular study. For example, the use of PET (Positron Emission Tomography) in the study by Paulesu *et al.*, (1995) and the fact that Aleman and colleagues studied only one synaesthete could explain the absence of V4 activation.

While these are certainly important factors, they do not explain all null findings. Rich *et al.*, (2006) and Weiss, Zilles, and Fink, (2005) examined a similar number

of synaesthetes (7 and 9, respectively) as Hubbard *et al.* (2005) (6 synaesthetes) but did not obtain increased activation in V4. Remarkably, Rich *et al.* (2006) did find that *mental imagery* of colour activated right V4 in both synaesthetes and non-synaesthetes. Synaesthetic colour, in contrast, activated the left medial lingual gyrus. As we will discuss in the next section, whole-brain studies report activation in response to (naming) synaesthetic colour in the left posterior ventro-lateral region of temporal cortex (Gray *et al.*, 2006), in middle temporal and fusiform gyrus (Rouw & Scholte, 2007), in right fusiform and inferior occipital gyrus (Laeng *et al.*, 2011), and in retro-splenial and extrastriate cortex (Weiss, Shah, Toni, Zilles, & Fink, 2001). Taken together, synaesthetic colour activation is found related to visual cortex, but this is not restricted to V4. As is reported in 'real' colour processing (e.g., Beauchamp *et al.*, 1999; Schluppeck & Engel, 2002), synaesthetic colour has been found to activate a broader range of areas in ventral occipito-temporal cortex.

Another explanation for finding inconsistent results is the heterogeneity in the experiments and analyses used. As can be seen in Table 1, several characteristics of the studies vary, such as how colour ROIs were delineated, the experimental manipulation (tasks) used, and the number and types of synaesthetes. The current number of studies is not sufficient to reveal how each of these characteristics influences results. One interesting pattern does however catch the eye. Counter to expectations, relatively many of the studies using auditory stimuli find activation in colour-selective regions. A similar pattern emerges when looking at whole-brain studies (Table 2), where occipital activations are found in studies using auditory presentation. This could be related to the type of synaesthesia tested. Another explanation relates to a different experimental set-up. In the 'colored-hearing' studies, the experimental condition of listening to words is contrasted with a baseline condition of listening to a pure tone. In contrast, several grapheme-colour studies have a visual task in both experimental and baseline conditions. Thus, the baseline condition might employ brain regions responding to colour, as they are expected to respond to other visual information as well. The additional effect of synaesthetic colour activation is not necessarily easiest to obtain in a visual-to-visual contrast.

The third factor that influences results are individual differences between the subjects. The relatively small number of subjects in most studies increases the influence of individual differences. Note that the location of 'synaesthetic color' activation is subject to both variations in brain structure and to variations in structure–functioning relationships (Brett, Johnsrude, & Owen, 2002). Both Steven, Hansen, and Blakemore, (2006) and Nunn *et al.*, (2002) find V4 activation during synaesthetic colour but point at possible different function-to-structure mappings in synaesthetes or synaesthetic processes as compared with 'normal' colour perception (but see Mattingley, 2009). Individual differences between synaesthetes have also been found to influence synaesthetic colour activation. Sperling, Prvulovic, Linden, Singer, and Stirn, (2006) studied brain activation during linguistic-colour synaesthetic experiences and found that two synaesthetes showed bilateral V4 activation while the other two synaesthetes did not. Similarly, Hubbard *et al.*, (2005) found that individual differences in V4 activation correlated with behavioural effects. As synaesthetes are a heterogeneous group (Dixon, Smilek, & Merikle, 2004; Rouw & Scholte, 2010; Sperling *et al.*, 2006), results are likely influenced by the selection of the synaesthetes tested.

In Table 1, we summarize those studies with specific conclusions about the question whether V4 is activated during synaesthetic colour experience. These studies examine developmental synaesthetes in whom (auditory or visual) presentation of words, letters,

Table 1. V4 activation (in green) during synaesthetic colour experience. Studies measuring brain activation (with BOLD-MRI and PET), during linguistic-colour synaesthesia, that draw a conclusion about V4 activation in response to synaesthetic colour. Indicated are number of synaesthete (Syn) and non-synaesthete control (Con) subjects, modality of presentation of stimuli during fMRI task (Auditory or Visual), the contrast (C) used to measure brain activation and the fMRI task (T) presented during measurement (C/T means that these two are the same). The second column presents the analysis method. For each study, three conclusions are presented (Yes, No, or Not Available): V4 activation during synaesthetic colour experience; V1 activation during synaesthetic colour experience; V4 activation to 'real' colour in synaesthetes.

First author, year	ROI or whole-brain	V4 Syn Colour	V1 Syn Colour	V4 physical Colour
Hubbard 2005				
6 Syn, 6 Con, VIS	ROI*	Yes	No	N.A.
C: greyscale graphemes and non-linguistic symbols				
T: stimuli printed italic or normal?				
*Retinotopic mapping, V1, V2, V3, V4, and grapheme				
Nunn 2002				
13 Syn, 28 Con, AUD	Whole-brain	Yes*	No	Yes**
C/T: passive listening to words vs. pure tone		Left		
*V4 based on coordinates colour activation controls, E1				
** Synaesthete right, non-synaesthete bilaterally				
Sperling, 2006				
4 Syn, VIS	ROI*	Yes	No	Yes
C: letters do (not) induce Syn. colour	V4/V8, V1, VP	2/4 subjects,		Bilateral
T: no information on task provided		Bilateral		
*Combination of retinotopic and functional mapping, also whole-brain analysis performed				
Steven 2006				
1 late-blind Syn, 1 late-blind, and 1 sighted Con, AUD	Whole-brain	Yes	Yes	N.A.
C: time-word vs. control word		Left	Left	
T: one-back matching				
van Leeuwen 2010				
21 Syn, 19 Con, VIS	ROI	Yes	N.A.	Yes
C: graphemes do (not) induce Syn. colour		Right		Bilateral
T: passive viewing (Exp. 1)				
*VOI: contrast of black vs. coloured non-inducing graphemes				
Aleman 2001*				
1 Syn, AUD	ROI	N.A.	Yes	N.A.
C/T: passive listening words vs. pure tone verbal fluency vs. pure tone	Anatomical; V1			
Tasks taken together	Whole-brain	No	No	N.A.
*No coordinates of activation provided				

Table 1. *(Continued)*

First author, year	ROI or whole-brain	V4 Syn Colour	V1 Syn Colour	V4 physical Colour
Gray 2006				
15 Syn, AUD	Whole-brain	No*	N.A.	Yes
C/T: passive listening words vs. pure tone, Exp1				Right**
*Activation more laterally in left post. ventro-lateral temp. cortex.				
**But synaesthetes with alien colour effect bilaterally				
Paulesu 1995 (PET)				
6 Syn, 6 Con, AUD	Whole-brain	No	No	N.A.
C/T: perceive words passively vs. tone				
Rich 2006				
7 Syn, 7 Con, VIS	ROI*	No**	N.A.	Yes
C: greyscale letters vs. rectangles				Left
T: 4 letters/symbols, indicate which disappears				
*Colour-selective regions in ventral occipital cortex				
**Activation in lingual gyrus				
Rouw 2007**				
18 Syn, 18 Con, VIS	Whole-brain	No*	No	N.A.
C: greyscale graphemes that do or do not induce Syn. colour				
T: grapheme presented italic or normal?				
*Activation in fusiform gyrus.				
**Same conclusions in Rouw and Scholte, (2010) (partially the same subjects)				
Weiss 2001				
1 chromatic–lexical Syn, VIS	Whole-brain*	No**	No	Yes
C: Names that do or do not induce Syn. colour				Bilaterally
T: indicate synaesthesia				
*Compare with coordinates Zeki *et al.*, (1991)				
**Activation in secondary extra-striate visual areas				
Weiss 2005				
9 Syn, VIS	ROI*	No	N.A.	No
C: letters that do or do not induce Syn. colour		Trend left		
T: indicate synaesthesia	Whole-brain	No		Yes
*Coloured letters activate area at putative. position of colour area				

or names evoke synaesthetic colour. We have also included information, if available, whether V1 is activated during synaesthetic colour experience (insufficient information is available on activation in other visual areas to include them in the table), and whether V4 was activated in response to normal colours in the synaesthetes. The summary shows

Table 2. Brain areas activated during linguistic-colour synaesthesia, as measured in whole-brain (BOLD-MRI or PET) neuroimaging studies. Presented are Brodmann area (if provided), left (L) or right (R) hemisphere activation, the label we provided (Jülich histological/Harvard-Oxford cortical structural atlas), coordinates (if necessary converted to MNI), t or z score of the effect, modality (visual or auditory) of the presented stimuli, contrast used (S = Synaesthete, C = Control). Below references and threshold of these studies. For tasks see Table 1. We include only activations and not deactivations in response to synaesthetic experience. This is not because we believe it is less meaningful, but because only a few studies report deactivation, which makes it difficult to compare between studies.

BA		Area	x	y	z			Stim	Subjects	Ref
Occipital										
n/a	L	Cuneal C	−3	−75	30	3.75	t	VIS	42 S > 19 C	5
19	R	Lat. occ. C, inf. div	46	−70	−14	5.05	t	VIS	2 S	1
19	L	Lat. occ. C, inf. div	−50	−72	−12	5.12	t	VIS	2 S	1
19	L	Lat. occ. C, inf. div	−33	−69	6	-	-	AUD	10 S	2
n/a	R	Lat. occ. C, inf. div*	48	−68	−16	3.5	Z	VIS	18 S > 18 C	4
n/a	L	Lat. occ. C, inf. div	−48	−76	0	3.0	Z	VIS	1 S	8
n/a	R	Lat. occ. C, inf. div	53	−72	−16	4.0	Z	VIS	1 S	8
19	L	Lat. occ. C, sup. div	−32	−78	12	-	-	AUD	10 S	2
19/7	L	Lat. occ. C, sup. div	−16	−82	31	2.9	Z	AUD	6 S > 6 C	3
n/a	L	Lat. occ. C, sup. div	−30	−72	28	3.85	t	VIS	42 S > 19 C	5
19	L	Lingual G.	−22	−44	−13	-	-	AUD	10 S	2
19	L	Lingual G.	−22	−44	−13	-	-	AUD	10 S	2
19	L	Occ. fusif. G.	−33	−67	−19	-	-	AUD	10 S	2
19	L	Occ. fusif. G.	−33	−67	−19	-	-	AUD	10 S	2
19	L	Occ. fusif. G.	−30	−66	−20	-	-	AUD	1 blind S	7
19	L	Occ. fusif. G.	−42	−66	−14	-	-	AUD	1 blind S	7
19	R	Temp. occ. fusif. G.	46	−60	−18	5.30	t	VIS	2 S	1
19	R	Temp. occ. fusif. G.	46	−60	−18	5.30	t	VIS	2 S	1
23	L	V1	−16	−62	6	-	-	AUD	10 S	2
18	L	V2	−26	−98	8	-	-	AUD	1 blind S	7
18	R	V2	24	−98	8	-	-	AUD	1 blind S	7
17	L	V3	−14	−93	−4	-	-	AUD	1 blind S	7
19	L	V4	−36	−82	−18	5.95	t	VIS	2 S	1
Temporal										
22/39	L	Middle temp. G., temporo-occ. part	−51	−47	9	-	-	AUD	10 S	2
n/a	R	Inf. temp. G., temporo-occ. part	57	−47	−15	3.8	Z	VIS	18 S > 18 C	4
20/37	L	Inf. temp. G., post. div	−55	−42	−22	2.4	Z	AUD	6 S > 6 C	3
n/a	L	Middle temp. G., post. div	−57	−15	−20	3.85	t	VIS	S nr 1	6
n/a	R	Middle temp. G., post. div	64	−22	−13	3.16	t	VIS	S nr 2	6
n/a	R	Middle temp. G., post. div	64	−10	−26	2.55	t	VIS	S nr 3	6
42	L	Primary auditory C. (TE 1)	−57	−20	9	-	-	AUD	10 S	2

Table 2. *(Continued)*

BA		Area	x	y	z			Stim	Subjects	Ref
22/42	L	Primary auditory C. (TE 1)	−48	−25	5	-	-	AUD	10 S	2
22	R	Primary auditory C. (TE 1)	55	−11	4	3.1	Z	AUD	6 S > 6 C	3
21/22	R	Sup. temp. G., post. div	53	−18	0	-	-	AUD	10 S	2
Parietal										
40	R	Inf. par. L.	50	−44	54	2.66	t	VIS	2 S	1
40	R	Inf. par. L.	50	−44	40	4.35	t	VIS	2 S	1
39/40	L	Inf. par. L.	−40	−62	35	-	-	AUD	10 S	2
	L	Inf. par. L.	−40	−70	30	-		AUD	1 blind S	7
7	R	Ant. intra-par. S.	36	−66	44	4.45	t	VIS	2 S	1
7	L	Intra-par. S.	−26	−76	30	4.51	t	VIS	2 S	1
-	L	Intra-par. S.	−36	−50	44	4.8	t	VIS	9 S	9
23/31	L	Precuneus C.	−19	−57	13	-	-	AUD	10 S	2
31	L	Precuneus C.	−6	−64	25	-	-	AUD	10 S	2
n/a	L	Precuneus C.	−2	−59	30	3.9	Z	VIS	1 S	8
40	L	Prim. somatosensory C.	−27	−31	56	-	-	AUD	10 S	2
7	L	Sup. par. L.	−36	−62	40	5.22	t	VIS	2 S	1
7	R	Sup. par. L.	30	−72	56	4.29	t	VIS	2 S	1
19/7	L	Sup. par. L.	−30	−66	40	3.0	Z	AUD	6 S > 6 C	3
19/7	R	Sup. par. L.	26	−68	40	3.0	Z	AUD	6 S > 6 C	3
7	L	Sup. par. L.	−8	−56	64	-		AUD	1 blind S	7
7	R	Sup. par. L.	10	−60	64	-		AUD	1 blind S	7
n/a	L	Sup. par. L.	−24	−70	52	4.5	t	VIS	9 S	9
7	L	Sup. par. S.	−28	−68	54	6.75	t	VIS	2 S	1
Frontal										
n/a	L	BA44/Centr. opercular C.	−41	8	11	4.21	t	VIS	S nr 1	6
44	R	BA44/Inf. front. G.	44	14	28	3.60	t	VIS	2 S	1
48	L	BA44/Inf. front. G.	−60	10	2	2.48	t	VIS	2 S	1
n/a	L	BA44/Inf. front. G.	−44	19	9	3.09	t	VIS	S nr 2	6
n/a	L	BA44/Broca's area	−48	10	5	2.29	t	VIS	S nr 1	6
n/a	R	BA44/Broca's area	53	15	−2	3.11	t	VIS	S nr 1	6
n/a	L	BA44/Broca's area	−51	16	1	2.29	t	VIS	S nr 2	6
n/a	R	BA44/Broca's area	53	15	3	2.77	t	VIS	S nr 2	6
47	L	Front. operculum C.	−46	16	−6	2.93	t	VIS	2 S	1
46	R	Front. pole (BA 9**)	38	40	24	2.89	t	VIS	2 S	1
46	R	Front. pole (BA 9**)	36	46	12	3.36	t	VIS	2 S	1
46/10	R	Front. pole (BA 9**)	30	51	11	2.9	Z	AUD	6 S > 6 C	3
n/a	L	Front. pole (BA 9**)	−32	48	23	6.36	t	VIS	S nr 1	6
n/a	R	Front. pole (BA 9**)	30	49	23	2.97	t	VIS	S nr 1	6
n/a	R	Front. pole (BA 9**)	42	40	22	1.68	t	VIS	S nr 2	6
n/a	R	Front. pole (BA 9**)	30	42	23	2.07	t	VIS	S nr 3	6

Table 2. *(Continued)*

BA		Area	x	y	z			Stim	Subjects	Ref
45	R	Middle front. G.	46	28	30	3.57	t	VIS	2 S	1
n/a	L	Middle front. G.	−44	25	28	3.58	Z	VIS	18 S > 18 C	4
10	R	Paracingulate G.	7	44	−5	-	-	AUD	10 S	2
44	L	Precentral G.	−40	4	26	3.40	t	VIS	2 S	1
6	R	Precentral G.	46	2	30	3.40	t	VIS	2 S	1
6/44	L	Precentral G.	−45	0	35	-	-	AUD	10 S	2
44/9	R	Precentral G.	36	7	31	3.1	Z	AUD	6 S > 6 C	3
n/a	L	Precentral G.	−40	5	27	6	t	Vis	42 S > 19 C	5
n/a	L	Precentral G.	−46	2	29	5.0	t	VIS	9 S	9
6	L	Premotor C.	−56	6	40	4.31	t	VIS	2 S	1
8	R	Sup. front. G.	22	25	54	-	-	AUD	10 S	2
Subcort./Cerebellum***										
-	L	Cerebellum	−42	−70	−24	5.57	t	VIS	2 S	1
-	L	Cerebellum	−4	−82	−28	5.52	t	VIS	2 S	1
-	R	Cerebellum	43	−69	−24	3.98	Z	VIS	18 S > 18 C	4
-	R	Insula	33	−6	4	-	-	AUD	10 S	2
-	R	Insular C.	40	8	0	3.5	Z	AUD	6 S > 6 C	3
-	R	Insular C.	44	7	0	2.78	t	VIS	S nr 1	6
-	R	Insular C.	39	3	5	2.51	t	VIS	S nr 2	6
-	L	Pallidum	−12	2	0	2.02	t	VIS	2 S	1
-	R	Thalamus	2	−4	2	2.38	t	VIS	2 S	1
-	R	Thalamus	2	−22	10	2.33	t	VIS	2 S	1

*The Harvard-Oxford employs this label for quite a large brain area.
**In these atlases, BA9 is not included. Inspecting these coordinates in an MNI brain with use of a Brodmann atlas indicated BA9.
***These structures were labelled with Harvard-Oxford Subcortical structural atlas or the MNI structural atlas.
1 Laeng *et al.*, 2009 ($p < .05$, 30 voxels).
2 Nunn *et al.*, 2002 (exp1) (voxel-wise $p < 0.0005$).
3 Paulesu *et al.*, 1995 ($p < .01$).
4 Rouw & Scholte, 2007 ($z > 2.3$, $p = .05$).
5 Rouw & Scholte, 2010 ($z > 2.3$, $p = .05$).
6 Sperling *et al.*, 2006 ($p < .05$).
7 Steven *et al.*, 2006 ($z > 2.3$, $p < .01$).
8 Weiss *et al.*, 2001 ($p = .001$).
9 Weiss *et al.*, 2005 ($t = 4.52$, $p < .05$).

how differences between the studies influence results. In sum, five of the 13 studies report V4 activation related to the synaesthetic colour, and four more studies report activation in response to synaesthetic colour in other parts of ventral occipito-temporal cortex (Rich *et al.*, 2006; Rouw & Scholte, 2007; Weiss *et al.*, 2001; Weiss *et al.*, 2005). Only two out of nine studies found increased V1 activation related to synaesthetic colour experience. Possibly, increased activation in V1 due to synaesthesia was obscured in other studies by activation during both baseline and experimental conditions. It is also possible that normally striate cortex is not activated sufficiently during synaesthetic colour experiences.

The first question addressed here is whether synaesthetic colour experiences activate 'normal' colour regions. It is reasonable to conclude that activity in colour areas can be obtained in response to synaesthetic colour experiences. However, activation is not limited to V4, and results are not consistent due to differences in experimental set-up. Three recommendations can be made to improve sensitivity to synaesthetic colour activation. The first is using cortical mapping, which both improves the signal-to-noise ratio and can be used to average regions over subjects. One study that used retinotopic mapping did indeed obtain a positive relationship between V4 activation and synaesthetic colour experiences (Hubbard *et al.*, 2005). The second is using an experimental set-up that takes into account that brain activation in response to general colour processing is not limited to one particular (V4) location, and that 'color areas' are likely to respond to other cognitive functions as well. The third is testing larger groups of synaesthetes, and select synaesthetes based on characteristics of their synaesthesia (e.g., strong perceptual sensations).

Activation in the whole brain

After addressing the question whether synaesthetic colour activates V4, and what might explain the inconsistent results obtained, we now turn to the question, which brain regions seem related to synaesthesia. An increase of brain activation obtained in a ROI analysis does not necessarily mean that this increase is the strongest or most prominent in the whole brain. For example, Aleman *et al.*, (2001) found increased V1 activation in a ROI analysis but did not obtain increased activation in any visual area in the whole brain analysis of that same data. Whole brain analyses are particularly informative about which of all the possible (and perhaps unexpected) brain areas show the strongest and most consistent activation during synaesthesia. These exploratory analyses are important to understanding the mechanisms involved in synaesthesia, considering how little is known about its neurobiology.

We compiled the whole-brain studies that measured (with fMRI or PET) brain activation in response to synaesthetic colour and displayed these coordinates in an MNI brain. In these studies, the specific task used, number and type of linguistic-colour synaesthetes examined, and presentation of stimulus material differs (see Table 2). We choose the contrasts that seem to most closely measure the mere presence of synaesthetic experience (e.g., greyscale graphemes rather than contrasting congruent with incongruently coloured graphemes). If available, we chose contrasts that include an interaction with group (synaesthete versus control). Only studies reporting coordinates are included (if needed converted from Talairach to MNI). To increase comparability, all coordinates provided in the studies are labelled with the Jülich histological atlas, and, if this did not provide a clear label, with Harvard-Oxford cortical structural atlas. As the study of Sperling *et al.*, (2006) presents three synaesthetes separately, these nine studies provided 11 data points in total.

On first inspection, these studies show activity at different locations. This could be due to the differences in experimental and statistical approach. Six brain locations, however, emerge where studies (minimally three of the nine) converge in reported locations, despite these differences. The rather low number of studies allows only for qualitative comment rather than strong statistical conclusions. Still, we believe it is warranted to discuss the areas of convergence because they reveal a pattern, which provides insight on what has so far been found in neuroimaging studies.

The first region is bilateral activation in occipito-temporal cortex. This is an expansion rather than replications of the studies in Table 1, as they partially include the same

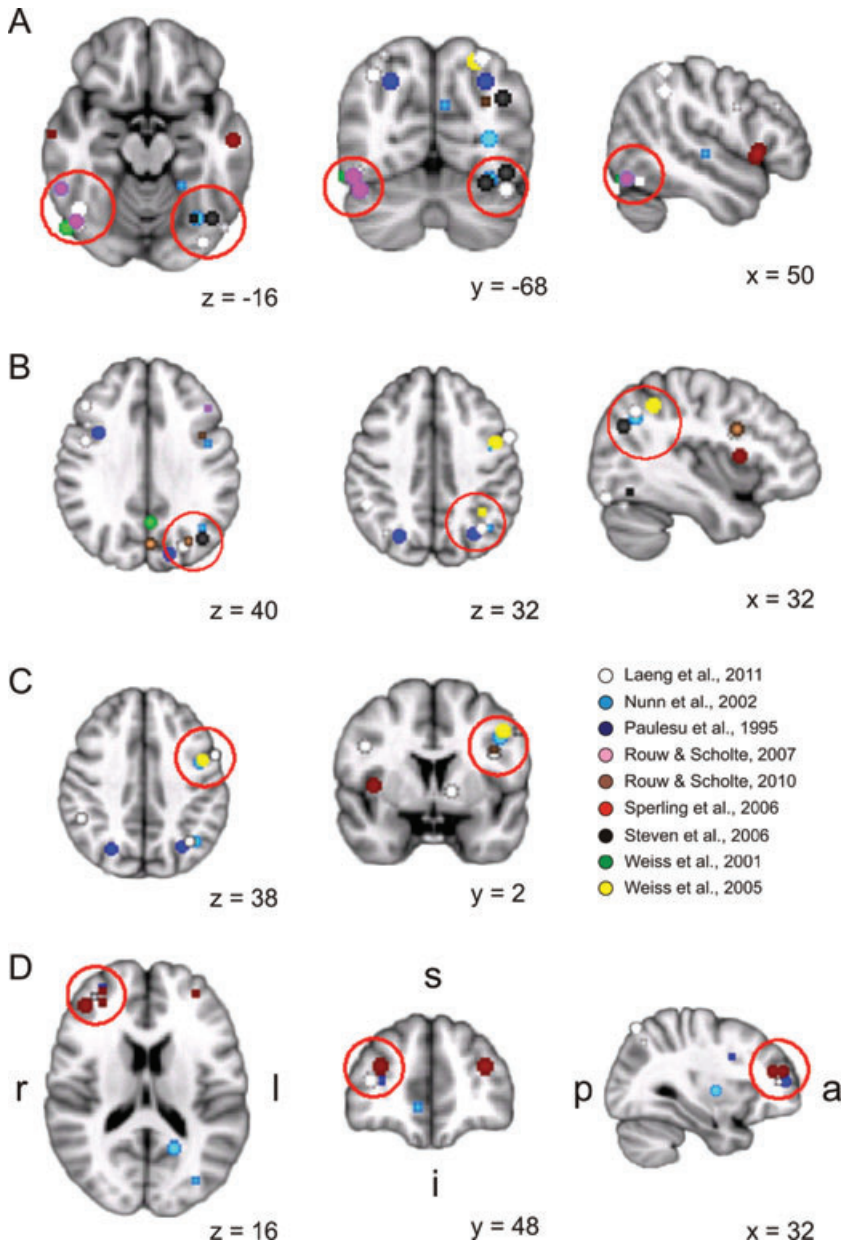

Figure 1. Brain areas activated during linguistic-colour synaesthesia, as measured in whole-brain (BOLD-MRI or PET) studies. Coordinates of obtained activation in nine different studies are depicted in an MNI brain. For tasks and methods of the studies see Table 1 and 2.

studies. The current analysis shows that activation is found in visual cortex, beyond striate cortex. And that these findings are strong and consistent enough to appear in whole-brain analyses (left: Laeng *et al.* 2011; Nunn *et al.*, 2002; Steven *et al.*, 2006; right: Laeng *et al.*, 2011; Rouw & Scholte, 2007; Weiss *et al.*, 2001). As can be viewed in Figure 1A, the obtained location of increased activation is not restricted to coordinates

of V4 only. As we discussed in the previous section, this can be due to differences in measurement methods, but also seems to support a more widespread network of ventral occipito-temporal areas involved in synaesthetic colour perception.

The role of visual areas in synaesthetic colour experiences becomes increasingly clear. One future direction of research is to develop methods that are more sensitive. Laeng *et al.* (2011) presented synaesthetes with coloured letters and manipulated colour distance between the typeface colour of the letter and of the synaesthetic colour it evoked. This is an elegant manner to measure a more (methodologically) sensitive manipulation of the subjective experience itself by manipulating the nature of the combined (synaesthetic and typeface colour) experiences rather than merely contrasting presence versus absence of synaesthetic colour experience (studies presented in Table 1). The study from Laeng and colleagues showed that increased distance in colour space led to greater recruitment of neural units of V4/V8. This shows that the simultaneous conscious experience of more than one colour is supported by simultaneous activation of the colour areas. Overall, these results show that some of the brain areas in occipito-temporal cortex that are activated by real colour are also activated by synaesthetic colour. (Although in colour brain areas, a synaesthetic colour prime does not suppress the BOLD response for subsequently presented real colours, van Leeuwen, Petersson, & Hagoort, 2010). The involvement of corresponding sensory-specific cortex might explain the perceptual or percept-like nature of the synaesthetic experience (Hubbard *et al.*, 2005; Nikolić *et al.*, 2007; Palmeri *et al.*, 2002; Smilek *et al.*, 2001).

Brain areas specifically tuned to processing graphemes or colour, are not sufficient to explain the activation patterns during linguistic-colour synaesthesia. The most eye-catching in our analyses are clusters of activation obtained in parietal cortex, almost exclusively located in posterior parietal cortex. The posterior parietal cortex consists of the superior parietal lobule and the inferior parietal lobule. Whole-brain studies report increased activation in both left (Laeng *et al.*, 2011; Weiss *et al.*, 2005) and right (Laeng *et al.*, 2011; Paulesu *et al.*, 1995; Weiss *et al.*, 2005) superior parietal lobule in response to synaesthetic colour experiences. The most compelling area of common activation across studies was the inferior parietal lobule. With the exception of Laeng *et al.* (2011) (and possibly Elias, Saucier, Hardie, & Sarty, 2003, but the use of different labels complicates comparison with this study), these studies report activation in the left hemisphere only (Nunn *et al.*, 2002; Rouw & Scholte, 2010; Steven *et al.*, 2006, Weiss *et al.*, 2005). Inspection of the coordinates of the obtained clusters showed that some clusters are located more anterior and superior (Laeng *et al.* 2011, Nunn *et al.*, 2002, Weiss *et al.*, 2005) and others more posterior and inferior (Laeng *et al.*, 2011; Rouw & Scholte, 2010; Steven *et al.*, 2006), see Figure 1B. All locations of activation in inferior parietal lobule, however, are best summarized as either near the intraparietal sulcus or in the angular gyrus. The significance of this region was verified in two TMS studies, showing a decreased effect of synaesthetic colour in a behavioural task (Esterman, Verstynen, Ivry, & Robertson, 2006; Muggleton, Tsakanikos, Walsh, & Ward, 2007). It is not yet clear why the TMS studies found only reliable effects on synaesthesia after TMS on right parieto-occipital region, while the neuroimaging studies find mostly left inferior parietal activation.

The parietal lobule has gained increasing attention in the field of synaesthesia research. Its known role in (attention-based) visual feature binding (Donner *et al.*, 2002; Shafritz, Gore, & Marois, 2002) makes this an important candidate region for binding or 'hyperbinding' the inducer to the concurrent sensations (Esterman *et al.*, 2006; Hubbard, 2007; Robertson, 2003; Weiss & Fink, 2009). In sum, brain regions in inferior and superior

posterior parietal lobules seem important components of the network of brain regions involved in synaesthesia, possibly related to the 'binding' that is an inherent part of synaesthesia.

The fourth region is bilateral insula (Nunn *et al.*, 2002; Paulesu *et al.*, 1995; Sperling *et al.*, 2006) and operculum. Insula activation could be related to the conversion process of a particular external stimulus to a different internal stimulus (Paulesu *et al.*, 1995). Activation in this region might also be related to the emotional quality that seems to often accompany synaesthetic experiences, as synaesthetes often report that a certain 'feel' belongs to a synaesthetic experience. If this explanation is correct, increased insula activation can be obtained in different types of syanesthesia.

Five studies found activation in left precentral gyrus (Laeng *et al.* 2011; Paulesu *et al.*, 1995; Nunn *et al.*, 2002; Rouw & Scholte, 2010; Weiss *et al.*, 2005), while three found activation in right precentral gyrus (Laeng *et al.*, 2011; Paulesu *et al.*, 1995; Rouw & Scholte, 2010) (Figure 1C). As it is not directly clear how motor (preparatory) responses could be different between baseline and experimental task in these studies, it might relate to the synaesthetic experience. The extended activation in brain regions involved in sensing of and acting in the outside world (visual cortex, activation in and near insula, and precentral activation) suggests a larger network of brain areas is involved in synaesthesia. It possibly also reflects additional aspects of the synaesthetic experience (Eagleman & Goodale, 2009).

The frontal lobe has so far received relatively little attention in synaesthesia research, even though most whole-brain studies (seven out of nine) report activation at some location in frontal cortex during the synaesthetic experience (Table 2). Three studies (Laeng *et al.*, 2011; Paulesu *et al.*, 1995; Sperling *et al.*, 2006, the latter study found activation bilaterally) from the nine studies found activations very adjacently located (Figure 1D) in right dorsolateral prefrontal cortex. While this is a small number of studies, activation of this region might reflect an important aspect of synaesthesia, namely increased cognitive control processes (Duncan & Owen, 2000). As the conflict between internally and externally generated sensations is an inherent part of synaesthesia, certain locations in the synaesthetic brain network are expected to be related to cognitive control. Weiss *et al.*, (2005) found that conflict between physically evoked and synaesthetically perceived colours of letters increased activation in right fusiform gyrus and left dorsolateral prefrontal cortex. This conflict might also relate to activation in parietal cortex. Cohen Kadosh, Cohen Kadosh, & Henik, (2007) presented a task (slightly different from those used in the studies presented in Table 1) that showed that a congruency effect modulated activity in the intraparietal sulcus and in the angular gyrus in the left parietal lobe, as well as the P300 amplitude.

Unfortunately, only a few studies have so far examined brain activation in other types of synaesthesia. These studies do, however, present two similar inferences. The first is activation in sensory brain areas corresponding to the particular synaesthetic experience. An acquired sound-touch synaesthete showed increased activation in secondary somatosensory cortex during synaesthesia (Beauchamp & Ro, 2008). Similarly, the synaesthetic experience of touch, evoked by seeing another person being touched, showed activation patterns that were interpreted as the brain's mirror system (somatosensory cortex, left premotor cortex and anterior insula cortex bilaterally; Blakemore, Bristow, Bird, Frith, & Ward, 2005). A patient that reported that certain odours increased his neuropathic pain (Villemure, Wassimi, Bennett, Shir, & Bushnell, 2006), showed increased activation during odour-evoked pain in both pain related areas (including the thalamus, amygdala, insular and anterior cingulate cortex) as well as

trends in primary somatosensory cortex in the hand/arm area, which is where the man felt the neuropathic pain. Second, in these studies several brain areas rather than only particular sensory activations were measured. As in linguistic-colour synaesthesia, a network of brain areas rather than isolated sensory-specific activation is found related to synaesthesia (see Rouw, 2011).

A common type of synaesthesia, next to coloured letters or words, is number-form synaesthesia, where sequences of numbers are experienced on a mental line. Tang, Ward, and Butterworth, (2009) showed that when demands of the tasks are spatially similar to their number-form representation, the synaesthetes showed increased activation in bilateral precentral gyri, left insula, and several parietal regions including the left superior parietal lobule and the bilateral posterior intraparietal sulcus (IPS). The authors related the bilateral posterior IPS to the ordinal representations that are essential for number-forms. Finding the same activated locations in number-form synaesthesia as in linguistic-colour synaesthesia can be due to a similarity in the type of synaesthesia (both in number-form and in linguistic-colour synaesthesia, numbers will induce visual/spatial representations). It can also reflect that these brain areas are related to synaesthesia in general rather than to a specific type of synaesthesia. As in other types of synaesthesia, Tang *et al.* (2009) found more widespread activation than only in corresponding sensory areas, including activation in frontal, temporal, and cingulate gyri. Eagleman, (2009) proposes instead a role of temporal cortex in spatial sequence synaesthesia, based on increased cross-talk between areas involved in over-learned sequences (in the middle temporal gyrus) and an area implicated in visual object representation (in inferior temporal lobe).

So far, we discussed six regions that have been found to be related to synaesthetic experiences. The current review also shows how certain regions, proposed to play a crucial role in synaesthesia, have *not* been obtained. Acquired synaesthesia studies (Beauchamp & Ro, 2008; Ro *et al.*, 2007) have suggested a relationship between synaesthesia and the thalamus. In these studies, a thalamic lesion resulted in acquired synaesthesia. This was explained as a positive outcome of the neural plasticity induced by the stroke. No relationship could be established between synaesthesia and the thalamus in the current review. Thalamus (in)activation is seldom reported in neuroimaging studies. Perhaps the thalamus is not always carefully analysed in these studies. Alternatively, inherently different neurobiological mechanisms underlie developmental and acquired synaesthesia. Another prediction that has not received support is the proposed role of the superior temporal cortex. This poly-sensory brain area has been proposed to mediate synaesthesia via feedback connections to uni-sensory cortical areas (Grossenbacher & Lovelace, 2001). The summary (Table 2) shows that a relationship between synaesthetic experiences and this particular brain area is not supported by current findings.

All findings discussed so far were obtained by measuring brain activity during synaesthesia with BOLD-MRI or PET. We now turn to the question what is the status of research on the *structural* properties of brains of synaesthetes as compared with non-synaesthetes.

Synaesthetes have a structurally different brain

Since 2007, three studies have appeared exploring the anatomical differences between synaesthetes and controls in terms of white matter tract coherency as measured with fractional anisotropy (FA) (Hänggi, Beeli, Oechslin, & Jäncke, 2008; Jäncke, Beeli, Eulig, & Hänggi, 2009; Rouw & Scholte, 2007; see Table 3A), and four studies have appeared

Table 3A. Structural brain differences in white matter properties of developmental synaesthetes and non-synaesthetes. In columns: hemisphere (left or right), location (derived from the Jülich histological atlas (Eickhoff *et al.*, 2007) or the Harvard-Oxford atlas, the coordinates, the t value and extent in mm^3 of the effect, method of analyses is Fractional Analysis (FA) either, number of synaesthetes (S) and controls (C) or musicians (music.) contrasted, and type of synaesthesia reported by the authors (IT = interval-taste and tone-colour; GC = grapheme-colour).

White matter Area		x	y	z	max t	mm^3	Contrast	Type	Ref
Occipital cortex									
L	Lateral occ. C., superior division	−25	−83	32	5	1493	1S > 1I music.	IT	1
R	Lateral occ. C., superior division	27	−78	28	5.3	1420	1S > 1I music.	IT	1
Temporal cortex									
R	Middle temp. G., temporo-occ. part	66	−44	9	3.7	97	1S > 1I music.	IT	1
L	Primary auditory cortex TE1	−42	−32	13	5.6	855	1S > 1I music.	IT	1
R	Primary auditory cortex TE1	41	−17	7	3.5	225	1S > 1I music.	IT	1
R	Temp. occ. fusiform G.	36	−40	−21	4.8	67	18S > 18C	GC	3
Parietal cortex									
L	Sup. par. lobule	−17	−61	55	4.8	44	18S > 18C	GC	3
Frontal cortex									
R	Sup. front. G./premotor C.	20	1	63	3.6	109	1S > 1I music.	IT	1
Sub-cort. areas and cerebellum									
L	Brainstem	−9	−33	−14	-	70	14S > 14 C	GC	2
L	Cerebellum, uvula of vermis	−2	−65	−34	4.87	2443	1S > 1I music.	IT	1
Cortico-cort. fibers									
L	Callosal body	−12	−40	11	-	34	14S > 14 C	GC	2
L	Cortico-spinal tract	−20	−25	55	3.7	53	18S > 18C	GC	3
R	Cortico-spinal tract	21	−21	57	4.4	100	18S > 18C	GC	3
L	Inf. fronto-occ. fasciculus	−25	20	14	-	49	14S > 14 C	GC	2
L	Optic radiation	−35	−52	−4	-	51	14S > 14 C	GC	2

1 Hänggi *et al.*, 2008.
2 Jäncke *et al.*, 2009.
3 Rouw & Scholte, 2007.
4 Rouw & Scholte, 2010.
5 Weiss & Fink, 2009.

exploring these differences in terms of grey matter (Hänggi *et al.*, 2008; Jäncke *et al.*, 2009; Rouw & Scholte, 2010; Weiss & Fink, 2009; see Table 3B). An overview of the areas in which differences were found are given in Table 3. To facilitate the comparison between these studies in this table, the names of brain areas are derived from the Jülich histological atlas (Eickhoff *et al.*, 2007), and if this did not provide a clear or strong interpretation, from the Harvard-Oxford atlas, based on the coordinates provided in these studies.

Even though the number of publications into the anatomical differences between synaesthetes and controls are limited, we believe that a picture emerges from these studies that converge with the findings from the functional studies. First, the data support the theory of cross-activation between these two (inducer and concurrent) areas, mediated by structural (connectivity) differences (Ramachandran & Hubbard, 2001b). Rouw & Scholte, (2007) found increased connectivity (increased FA values) near the fusiform gyrus in the neighbourhood of area V4. This has been partially replicated by Jäncke *et al.*, 2009, in right fusiform gyrus, at a threshold of $p = .05$. Furthermore, two of the studies showed that synaesthetes have increased grey matter in area V4 (Hänggi *et al.*, 2008; Weiss & Fink, 2009). Interestingly, a case in which either a tone or a tone interval induces synaesthesia Hänggi *et al.*, (2008) found increased connectivity (as measured in increased FA values) as well as increased white and grey matter volume in the primary auditory cortex. Structural differences in grey and white matter were also found in the concurrent (gustatory and visual regions) brain areas. Perhaps in less common types of synaesthesia, more distant rather than local cross-activation must be present (Hänggi *et al.*, 2008). Second, in all three studies dealing with linguistic-colour synaesthesia, the superior parietal lobe is larger in synaesthetes than controls. Third, synaesthesia seems to coincide with an increase in the grey matter density of sensory areas, even if they are not necessarily related to the synaesthetic modality. Hänggi *et al.*, (2008) and Jäncke *et al.*, (2009) found increased grey matter in V1 and V2, even though the Hänggi study examined interval-taste and tone-colour synaesthesia. Jäncke *et al.*, (2009) found increased grey matter in the secondary somatosensory cortex, while this study examined grapheme-colour synaesthesia. Perhaps these synaesthetes had another type of synaesthesia as well, since different types of synaesthesia are likely to co-occur (Simner *et al.*, 2006). It does, however, seem unlikely that the researchers did not find or report these additional, visual, types of synaesthesia as a possible explanation to their findings. Another possibility is that this increased grey matter in sensory cortex is related to individual differences. Rouw & Scholte, (2010) found increased grey matter in V1, auditory, and somatosensory cortex specifically in projector as compared with associated synaesthetes.

Finally, as can be seen in Table 3, it appears that structural differences between synaesthetes and controls can be found in different brain areas, both in terms of white and grey matter. This shows that synaesthesia coincides with large-scale anatomical differences throughout the brain and not only in the regions involved in the processing of the crossing experiences. As we will discuss later, these widespread differences indicate that different brain properties might be related to having the 'trait' synaesthesia as well as to the particular 'type' of synaesthesia.

Another implication of these anatomical differences is that it should be taken into account in interpreting functional differences. Anatomical between-group differences can result in a difference in BOLD-MRI activation between these groups. For instance, if V4 is in general larger in synaesthetes than in controls, BOLD-MRI activation will appear larger in the synaesthetes than the controls because of different underlying alignment.

Table 3B. Structural grey matter differences in developmental synaesthetes versus non-synaesthetes. In columns: hemisphere (left or right), location (derived from the Jülich histological atlas (Eickhoff *et al.*, 2007 or the Harvard-Oxford atlas), coordinates provided in these studies, the t, p and extent in mm^3 of the obtained effect, method (cortical volume, surface areas or cortical thickness), and subjects contrasted (Synaesthetes, Controls, Musicians, Projectors, Associators). We do not report white matter volume as it was measured in only one study (Hänggi *et al.*, 2008).

	Grey Matter Area	x	y	z	Max *t*/ *p*-value	mm^3	Method	Contrast	Syn	Ref
Primary sensory areas										
L	Intracalc. C., (V1)	−19	−61	8	2.42	2008	Cort. vol.	16Proj > 26Ass	GC	4
R	Intracalc. C. (V1)	5	−76	9	.0018	99.4	Cort. sur. area	24 S > 24 C	GC	2
R	Intracalc. C. (V1)	3	−69	8	.003	74.8	Cort. vol.*	24 S > 24 C	GC	2
R	Lingual G. (V1)	24	−51	−2	.0002	149	Cort. thickn.	24 S > 24 C	GC	2
L	Occ. pole, V2	−20	−97	10	3.55	234	Cort. vol.	1S >17 music.	IT	1
R	Occ. pole, V3	26	−91	−7	3.41	238	Cort. vol.	1S >17 music.	IT	1
R	Primary auditory C., TE1	40	−19	13	3.22	4664	Cort. vol.	16Proj > 42C	GC	4
R	Primary auditory C., TE1	40	−19	14	3.01	3776	Cort. vol.	16Proj > 26Ass	GC	4
R	Primary somatosens. C.	61	−10	40	.0039	27.8	Cort. thickn.	24 S > 24 C	GC	2
L	Secondary somatosens. C.	−35	−14	20	.0047	25.9	Cort. sur. area	24 S > 24 C	GC	2
R	Secondary somatosens. C.	46	−14	22	.0042	51.1	Cort. thickn.	24 S > 24 C	GC	2
Occipital cortex										
R	Lateral occ. C., inf. division	30	−86	7	.0021	39.7	Cort. sur. area	24 S > 24 C	GC	2
L	Lingual G.	−18	−46	−5	.0031	36.1	Cort. vol.*	24 S > 24 C	GC	2
R	V4	34	−69	−11	2.94	-	Cort. Vol., ROI	18S > 18C	GC	5
R	V4	51	−78	−7	4.02	604	Cort. vol.	1S > 17 music.	IT	1
L	V5	−37	−72	15	6.73	2510	Cort. vol.	1S > 17 music.	IT	1
Temporal cortex										
R	Inf. temp. G., post. div	45	−34	−21	3.87	74	Cort. vol.	1S > 17 music.	IT	1
L	Middle temp. G., post. div	−63	−39	−9	3.51	127	Cort. vol.	1S > 17 music.	IT	1
R	Middle temp. G., post. div	68	−15	−19	.0031	69.8	Cort. thickn.	24 S > 24 C	GC	2
L	Sup. temp. G.	−45	−20	−8	3.91	-	Cort. Vol., ROI	18S > 18C	GC	5
L	Temp. fusiform G.-post div.	−39	−38	−25	.0013	63.8	Cort. sur. area	24 S > 24 C	GC	2
R	Temp. occ. fusif. C.,	29	−50	−14	.0006	420	Cort. thickn.	24 S > 24 C	GC	2
R	Temp fusiform G., post div.	34	−34	−25	.0005	183	Cort. vol.*	24 S > 24 C	GC	2

Table 3B. *(Continued)*

Grey Matter Area	x	y	z	Max *t*/ *p*-value	mm^3	Method	Contrast	Syn	Ref
Parietal cortex									
L Anterior intra-parietal sulcus	−24	−64	47	3.84	-	Cort. Vol., ROI	18S > 18C	GC	5
L Inf. par. L.	−47	−61	33	2.96	2624	Cort. vol.	26Ass > 16Proj	GC	4
R Inf. par. L.	40	−57	46	3.56	5720	Cort. vol.	26Ass > 16Proj	GC	4
R Inf. par. L.	45	−79	21	.0042	72.5	Cort. thickn.	24 S > 24 C	GC	2
L Post. cingulate G.	−9	−48	19	.0052	12	Cort. vol.*	24 S > 24 C	GC	2
L Sup. par. L.	11	−58	61	3.5	2944	Cort. vol.	42S > 42C	GC	4
R Sup. par. L.	5	−67	53	3.5	3632	Cort. vol.	16Proj > 26Ass	GC	4
R Sup. par. L.	4	−59	27	.0046	39.1	Cort. sur. area	24 S > 24 C	GC	2
R Sup. par. L.	5	−67	53	3.5	3632	Cort. vol.	16Proj > 26Ass	GC	4
L Sup. par. L.	11	−58	61	3.5	2944	Cort. vol.	42S > 42C	GC	4
Frontal cortex									
L Ant. cingulate G.	-6	20	29	.0006	89	Cort. sur. area	24 S > 24 C	GC	2
R Front. orbital C.	10	25	−25	.0023	25.6	Cort. thickn.	24 S > 24 C	GC	2
R Inf. division of insula	40	−11	−13	.0027	26.4	Cort. sur. area	24 S > 24 C	GC	2
L Middle \ sup front. G.	−27	43	29	2.94	8240	Cort. vol.	16Proj > 26Ass	GC	4
L Orbito-front. C.	−23	12	−23	.0013	112	Cort. thickn.	24 S > 24 C	GC	2
R Orbito-front. C.	25	54	14	.0049	74.4	Cort. sur. area	24 S > 24 C	GC	2
L Precentral G.	−53	−3	38	3.39	3440	Cort. vol.	16Proj > 26Ass	GC	4
R Primary motor C.	48	−6	41	.0008	108	Cort. thickn.	24 S > 24 C	GC	2
L Sub-callosal C.	−10	26	−14	3.42	313	Cort. vol.	1S > 17 music.	IT	1
R Sup. front. G.	23	25	50	4.2	9632	Cort. vol.	16Proj > 26Ass	GC	4
R Sub-callosal cortex	9	26	−22	.0035	20.8	Cort. vol.*	24 S > 24 C	GC	2
Sub-cort. areas and cerebellum									
Cerebellum (middle)	9	−76	−28	4.51	22512	Cort. vol.	26Ass > 16Proj	GC	4
R Cornu ammonis of the hippocampus	28	−11	−19	3.19	3496	Cort. vol.	26Ass > 16Proj	GC	4
L Cornu ammonis of the hippocampus	−28	−21	−15	4.12	8560	Cort. vol.	26Ass > 16Proj	GC	4
R Nucleus accumbens	9	20	−7	3.59	254	Cort. vol.	1S > 17 music.	IT	1
R Sub-iculum of the hippocampus	12	−30	−4	2.74	3080	Cort. vol.	26Ass > 16Proj	GC	4
L Thalamus (temp. or occ.)	−19	−34	9	4.07	519	Cort. vol.	1S > 17 music.	IT	1
L Thalamus (temp.**)	−1	−15	14	3.55	222	Cort. vol.	1S > 17 music.	IT	1
L Thalamus (unclear projection)	−2	−4	−3	4.26	649	Cort. vol.	1S > 17 music.	IT	1
R Thalamus (posterior parietal.**)	16	−28	11	3.69	314	Cort. vol.	1S > 17 music.	IT	1

*Only Jäncke *et al.*, 2009 measured separately cortical volume, surface area, and thickness.
**Projection area (from Oxford Thalamic Connectivity Probability Atlas).
1 Hänggi *et al.*, 2008.
2 Jäncke *et al.*, 2009.
3 Rouw & Scholte, 2007.
4 Rouw & Scholte, 2010.
5 Weiss & Fink, 2009.

Together these studies imply that there are structural differences in synaesthetes throughout the brain. Structural differences are obtained in sensory brain regions that correspond with both inducer and concurrent information. A similar conclusion can be drawn here as in the previous section on functional (activation) data. The facts that structural differences are not restricted to sensory areas, and that differences are obtained in sensory regions that do not correspond with the particular synaesthetic experience, suggest that structural differences are not restricted to the type of synaesthesia. Therefore, these anatomical differences might also be interpreted to suggest that there is a general disposition to develop synaesthesia, irrelevant of the type. This concurs with the findings on the genetic basis of synaesthesia.

Conclusion

The current review shows that V4 is an important, but not sufficient, component of the brain areas related to synaesthetic colour experience. Instead, an extended network of areas seems involved in both linguistic-colour and other types of synaesthesia. We propose that this network supports three different cognitive functions that are inherently part of synaesthesia. The first are sensory processes. Current literature indicates that the synaesthetic experience activates corresponding sensory areas. That is, synaesthetic experiences activate those brain areas that are normally involved in a 'normal' sensation evoked by an external stimulus. A relationship with sensory brain areas that do not correspond with the particular synaesthetic associations studied might reflect the richness of the synaesthetic experience (insula activation reflecting the emotional quality of a synaesthetic concurrent). Furthermore, structural brain differences in different sensory regions might reflect that within a synaesthete, a predisposition is present to several, not one particular, type of synaesthesia. The second class of cognitive function is related to integrating (inducer with concurrent) information, such as processes involved in (attentional) feature binding. The parietal lobe holds the most important candidates for this function. We propose that a third class of processes involved in synaesthesia is cognitive control processes. The simultaneous presence of different, possibly conflicting, sensations is inherently part of synaesthesia. This 'synaesthetic conflict' has so far been found to be related to frontal cortex (in particular right dorsolateral prefrontal cortex) and parietal cortex. Finally, the question of whether there *are* structural brain differences between synaesthetes and non-synaesthetes has now been answered affirmative. What still needs to be determined, however, is the role of these structural and functional brain differences in the development of synaesthesia.

Part II: The development of the synaesthetic brain

Genetic differences

Synaesthesia tends to run in families. This was observed by Galton, (1883) and confirmed in modern studies, which show that at least 40% of synaesthetes have a first-degree relative with synaesthesia (Barnett *et al.*, 2008; Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996). Currently, multiple linkage studies are being conducted that search for poly-morphisms related to synaesthesia. Recently, the results from the first genome-wide linkage study of synaesthesia were published (Asher *et al.*, 2009), based on 43 multiplex families. Synaesthetes were selected based on their report of 'auditory-visual' synaesthesia. This most likely does not constitute a completely homogeneous subject group, since it is not further specified which particular material (sounds, spoken language, written language, single phonemes, and graphemes) evokes colour for each of these subjects. Results indicate that synaesthesia in this subject group is related to

multiple, but not unique, gene loci (2q24, 5q33, 6p12, 12p12). No evidence was found for a relationship with the X-chromosome. This is relevant because it has been hypothesized that an involvement of genes on the X-chromosome might drive a predominance of synaesthesia in females (Baron-Cohen *et al.*, 1996; Ward & Simner, 2005). Interestingly, the highest loading marker in this study (D2S142) contains TBR1, a gene involved in the regulation of reelin (Bulfone *et al.*, 1995), which plays a vital role in the development of the cerebral cortex. Knockout studies targeting this gene have shown that a de-regulation of reelin leads to abnormalities in the laminal organization of the brain (Hevner *et al.*, 2001) and influences the path-finding of axons (Hevner, Miyashita-Lin, & Rubenstein, 2002). Taken together, these studies suggest that the genetic basis of synaesthesia will be found, at least in part, in genes that influence the development of connectivity in the brain. The synaesthetic genotype is a predisposition, rather than a defined predetermination. One particularly striking discovery is a case of monozygotic twins where one has synaesthesia while the other has not developed it (Smilek *et al.*, 2002).

Clearly, the starting point in understanding developmental synaesthesia is the genetic predisposition. Both genetic association studies and studies examining familial traits suggest that synaesthetes exhibit particular differences compared to non-synaesthetes from birth (Asher *et al.*, 2009; Barnett *et al.*, 2008). Intermediating between the genetic predisposition and the extraordinary sensations characteristic to synaesthesia are most likely neurobiological settings, in particular structural brain properties. Bargary and Mitchell, (2008) explicate how mutations in genes directly controlling cortical connectivity can lead to synaesthesia. They explain how differences in axonal guidance, border formation, or pruning, can create direct, feed-forward connections between adjacent areas that can drive the synaesthetic experience. This is an important contribution in understanding synaesthesia, showing how a genetic mutation could lead to differences in white matter pathways (see Marks, 1975; Ramachandran & Hubbard, 2001b; Spector & Maurer, 2009). Other theories on synaesthesia stress a difference in brain functioning instead (Cohen Kadosh & Walsh, 2008; Grossenbacher & Lovelace, 2001). This is by itself not contradictory, as differences in brain structure can be expected to lead to differences in brain functioning, and vice versa (see below). While in the past the question was raised whether structural differences are present between synaesthetic and non-synaesthetic brains, this question has in recent years been answered (Hänggi *et al.*, 2008; Jäncke *et al.*, 2009; Rouw & Scholte, 2007; 2010; Weiss & Fink, 2009). What remains to be answered, is the exact level at which cross-activation occurs, the role of the different brain areas involved, the role of the structural brain differences, and the role of learning in synaesthesia.

Developing synaesthesia: Trait versus types

Familial studies on synaesthesia reveal that having synaesthesia, rather than having particular types of synaesthetic associations, runs in families (Barnett *et al.*, 2008; Rich *et al.*, 2005). Thus, your synaesthetically coloured letters are a hint that you can probably find synaesthetes in your family, but it gives no information whether their 'A's will also be blue, or even that their synaesthesia is expressed as coloured letters. This is in line with the genetic association study, which related synaesthesia to multiple genes, which are expected to relate to general effects rather than effects limited to a particular brain location. In line with this hypothesis, we found functional and structural effects not only in those brain areas related to the specific inducer or concurrent, but also in other sensory areas. Similarly, parietal and frontal mechanisms that we speculate are involved in the 'binding' and control mechanisms in synaesthesia are, proposedly, an inherent part of the general synaesthetic trait, not of a particular type.

Thus, if (genetically based) differences in brain properties shape a general 'synaesthetic constitution', this constitution is not specialized to a certain type of synaesthesia. In particular, increased connectivity resulting from a genetic predisposition likely has a widespread rather than localized effect in the brain. This explains why having a certain type of synaesthesia increases the chance of having other types of synaesthesia as well (Sagiv, Simner, Collins, Butterworth, & Ward, 2006). In addition, if a subject has several types of synaesthesia, this does not imply similar properties of these associations (Ward *et al.*, 2005). The effect of the 'constitution' possibly extends beyond synaesthesia. Burrack, Knoch, and Brugger, (2006) found a high prevalence within synaesthetes of 'mitempfindung', where tactile stimulation of one part of the body simultaneously produces a sensation at a different location. These authors note how erratic neural connectivity might underlie both phenomena.

In the development of language (Halliday, 1975), a predisposition is present in the child to learn to speak a language, but it is the environment determining which particular language a child will learn. Similarly, a child may be born with a predisposition to develop synaesthesia, but will not be born with a red 'A'. These highly specific cross-associations are somehow created or picked up in early childhood (e.g., Rich *et al.*, 2005). Simner, Harrold, Creed, Monro, and Foulkes, (2009) show how the synaesthetic associations are shaped during development, with more associations present in 7.5-year-old than in 6.5-year-old. In special cases, the source of a particular association has been retrieved, such as finding the refrigerator magnets that shaped a particular synaesthetes' letter-colour associations (Witthoft & Winawer, 2006). More general influences of experience on particular synaesthetic associations have also been found. Grapheme-colour synaesthetes show biases to certain associations over others (e.g., higher frequency graphemes are found related to higher frequency colour names, Simner & Ward, 2007; Simner *et al.*, 2005; or more saturated synaesthetic colours, Beeli, Esslen, & Jäncke, 2007; or luminance of synaesthetic colour, Smilek, Carriere, Dixon, & Merikle, 2007). Importantly, when non-synaesthetes are asked to devise letter-colour associations, the same trends (though not necessarily as strong) are found as in synaesthetes (Marks, 1975; Rich *et al.*, 2005; Simner *et al.*, 2005; 2007). Synaesthetes share with non-synaesthetes the same environment, and therefore, the same environmental influences on specific types of associations over others. This does not relate to having, or not having, the synaesthetic trait. We propose that this notion of how environment influences synaesthetic associations extends to culture; in the current account, the number of adults with synaesthesia is expected to be culture-independent, but we hypothesize that the exposure to a certain type of material in a culture (e.g., the ubiquity of language or music in early childhood) predicts, which particular types of synaesthesia develop.

Thus, we see that there are two aspects of synaesthesia, with two different answers to the question 'how does synaesthesia develop'. The first question is what underlies *having* synaesthesia in general. Research has shown a genetic predisposition to synaesthesia, which is proposed to bias general characteristics of brain structure and functioning. These characteristics are idiosyncratic to synaesthetes. One example is a genetic predisposition to develop differences in white matter pathways. The second question is what underlies having a *particular type* of synaesthetic association. The specific associations that develop are highly dependent on environment. These biases can also be found in non-synaesthetes as they are under strong influence of the environment.

Inducers versus concurrents

We will now turn to the question what determines which particular material is inducer and which is concurrent. Synaesthetic associations are often (but not always, Cohen

Kadosh *et al.*, 2007) directional. The study from Simner *et al.*, (2009) showed the developmental pattern of learning synaesthetic associations during childhood. As we have argued above, we believe that particular associations are shaped in interaction with the environment. Rather than a lack of functional specialization (Cohen Kadosh, Henik, & Walsh, 2009), we believe that this interaction leads to additional, highly specialized, cross-connections between inducer and concurrents. We propose that a child with a predisposition for synaesthesia will tend to map newly learned material, onto an already present, earlier learned category. This can explain why colour is the most common concurrent but rare as an inducer (Barnett *et al.*, 2008), as it is one of the earliest categories learned. Colour categories can be used when learning linguistic material, as pre-linguistic infants have been found to already perceive colour categorically (Bornstein, Kessen, & Weiskopf, 1976; Franklin & Davies, 2004). While there are exceptions (such as pain or taste as concurrent), in many types of synaesthesia, the order in which material is learned seems to influence inducer–concurrent relationships. A child is likely to be exposed to taste categories before learning musical tone intervals (Beeli *et al.* 2005), to taste before words (Ward & Simner, 2005), and to animate-like qualities such as personality or gender before learning linguistic material (Simner & Holenstein, 2007). In terms of biological factors, Bargary and Mitchell, (2008) note how early- versus late-maturing brain areas bias the maintenance of certain cross-activation over others. For example, the brain is ready to store colour information before it is ready to store more complex linguistic information. In line with the interactive account, the biological and environmental settings are two sides of the same coin. Functional and structural brain properties are influenced by a child's learning experiences. Conversely, a child will tend to show interest to particular material at a moment the brain is ready to 'receive' (process) that type of information.

An important assumption of this interactive account of shaping synaesthetic types is that the relationship from gene to structural brain properties to behaviour, also has a reverse direction: from behaviour back to (structural) brain differences. Recent studies have indeed related expertise or experience in particular skills to differences measured in white and grey matter properties. The measured skills are quite diverse: driving a taxi in London, playing an instrument, playing the game Baduk (aka Go), meditating, or practicing mathematics (Aydin *et al.*, 2007; Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Habib & Besson, 2009; Han *et al.*, 2009; Johansen-Berg *et al.*, 2007; Lazar *et al.*, 2005; Lee *et al.*, 2010; Maguire *et al.*, 2000; Tuch *et al.*, 2005). As in synaesthesia research, these studies are cohort studies, and therefore, contrasting groups necessarily precludes conclusions on causality. Some studies have, however, obtained longitudinal measurements that allow conclusions about the direction of the effect. Draganski *et al.*, (2004) examined brain structure with MRI voxel-based morphometry during the training of a visuo-spatial skill (juggling). The jugglers showed expansion of grey matter in related brain areas. Furthermore, this expansion was decreased after 3 months in which juggling was not practised. A similar effect of experience-dependent structural changes was found in white matter (underlying the intraparietal sulcus) following training of juggling over several weeks (Scholz, Klein, Behrens, & Johansen-Berg, 2009). A recent study showed training-induced plasticity of white matter in a purely cognitive skill without motoric component, namely working memory (Takeuchi *et al.* 2010).

These studies show that repeated experiences or behaviour can in turn affect brain properties. In principle, it is possible that in synaesthesia (as in training a 'normal' skill), the particular synaesthetic associations become 'hardwired' in the brain. One hypothesis is that particular synaesthetic associations, while they develop, also affect particular brain areas (i.e., corresponding sensory regions). As argued before, effects obtained in brain

imaging studies support the idea of both general effect of synaesthesia and specifically localized effects based on the particular type of synaesthetic associations. In short, this view would suggest that the synaesthetic predisposition (Asher *et al.*, 2009; Barnett *et al.*, 2008) enables making synaesthetic associations, through general brain properties (e.g., a bias to increased white matter connectivity, Bargary & Mitchell, 2008; Hänggi *et al.*, 2008; Jäncke *et al.*, 2009; Ramachandran & Hubbard, 2001a; Rouw & Scholte, 2007; Spector & Maurer, 2009). Particular synaesthetic associations develop in interaction with the environment (Beeli *et al.*, 2007; Rich *et al.*, 2005; Simner & Ward, 2007; Simner *et al.*, 2005; Smilek *et al.*, 2007; Witthoft & Winawer, 2006). These synaesthetic associations are 'hardwired' in the brain through changes in structural and functional brain properties. The structural brain differences that arise through both the 'trait' and the 'type' of synaesthesia (Hänggi *et al.*, 2008; Jäncke *et al.*, 2009; Rouw & Scholte, 2007; 2010; Weiss & Fink, 2009) in turn support the highly persistent, automatic (in the sense that it takes little effort), and consistent associations in adulthood (Baron Cohen *et al.*, 1987; Baron-Cohen *et al.*, 1993; Cytowic & Wood, 1982; Dixon *et al.*, 2000; Mattingley *et al.*, 2001).

The role of brain properties in synaesthesia raises the interesting question whether the genetic predisposition is just a 'stepping stone' to create synaesthetic experiences, or if it is a prerequisite. A study by Meier & Rothen, (2009) has shown that synaesthete-like behaviour can be obtained in non-synaesthetes after training. The study from Scholz *et al.*, (2009) shows that training a certain skill may become 'hard-wired' as changed properties of white matter tracts. The question whether learned synaesthetes can become 'real' synaesthetes, both in terms of the perceptual nature of synaesthesia and in terms of their brain structure and functioning, is an interesting topic for future research.

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