

Demographic Characteristics and Neural Mechanisms of Synaesthesia

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Zusammenfassung

Bei Synästhesie löst die Stimulation einer sensorischen Bahn eine zusätzliche sensorische Empfindung in einer anderen Modalität oder sub-Modalität aus. Daten über demographische Merkmale der Synästheten und verschiedene Aspekte der synästhetischen Empfindungen wurden von 63 Synästheten gesammelt und mit den Ergebnissen früherer Erhebungen behandelt. Folgenden Fragestellungen wurden adressiert: Prävalenz der verschiedenen Formen der Synästhesie, Spezifität der für die Modulation der Synästhesie verantwortlichen Stimulus-Komponenten, Auswirkungen der hohen Prävalenz cross-modaler Synästhesie und Variabilität des Zustands im Laufe der Zeit.

Um zu verstehen, welche Rolle perzeptuelle und semantische Prozesse in Synästhesie spielen, wurde mit Hilfe der Elektroenzephalographie (EEG) der zeitliche Ablauf der Graphem-Farbe Synästhesie untersucht, in der Grapheme Farbwahrnehmungen auslösen. EEG und Verhaltensmessungen wurden während einer *cued-congruency* Aufgabe von Synästheten und Nicht-Synästheten erhoben. Die Letzteren wurden auf Graphem-Farbe Assoziationen trainiert. Eine invertierte *priming* Aufgabe wurde verwendet, um implizite bidirektionale Synästhesie zu untersuchen. Die Ergebnisse zeigten eine längere Reaktionszeit und stärkere N400 und N300 Komponenten für inkongruente als für kongruente Assoziationen in beiden Gruppen. Während bei Nicht-Synästheten weitgehend kognitive Prozesse auftraten, zeigten Synästheten kongruenzbezogene und schnellere perzeptuelle Aktivierung als

die Kontrollprobanden. Implizite bidirektionale Synästhesie äußerte sich in frühe und späte kognitive Prozesse.

Ereignis-bezogene funktionelle Kernspintomographie (fMRI) wurde verwendet, um die neuronalen Grundlagen der Synästhesie zu untersuchen und mögliche gemeinsame neuronale Mechanismen zwischen diesem Zustand und der Vorstellung festzustellen. Räumliche Sequenz Synästhesie (SSS), bei der ordinale Reize von Probanden räumlich angeordnet wahrgenommen werden, wurde bei einem blinden Synästhete untersucht. Die zusätzliche synästhetische Farbwahrnehmung, die der Studie-Teilnehmer für einige Reize beschreibt, bot die Gelegenheit, zwei verschiedene experimentelle Bedingung und eine Kontrollbedingung zu vergleichen: farbige SSS, nicht-farbigen SSS, und nicht synästhetische Kontrollbedingung. SSS-hervorrufende Reize aktivierten die okzipito-parietale, inferior frontale und den insularen Cortex. Der visuelle Farbbereich hOC4v wurde aktiviert, wenn die synästhetische Empfindung Farbe beinhaltete, was auf die ständige Verwendung der visuellen Cortex bei einem spät-erblindeten Synästhete hinwies. Die okzipito-parietale Aktivierung legt nahe, dass die Wahrnehmung der räumlichen Geometrie in SSS Gehirnareale betrifft die auch zur räumlichen Vorstellung sowohl bei Blinden als auch bei sehenden Nicht-Synästheten verwendet werden.

Abstract

In synaesthetes, stimulation of one sensory pathway provokes an additional sensory experience in a different modality or sub-modality. Data concerning the demographic characteristics of synaesthetes and various aspects of the synaesthetic experience were gathered from 63 synaesthetes and compared with results of previous surveys. The following issues were addressed: prevalence of the different forms of synaesthesia, specificity of stimulus components responsible for modulating synaesthesia, implications of the high prevalence of cross-modal synaesthesia and variability of the condition over time.

To understand the role that perceptual and semantic processes play in synaesthesia, I investigated by means of electroencephalography (EEG) the time-course of grapheme-colour synaesthesia, a form in which graphemes elicit the perception of colours. EEG and behavioural measurements were collected during a cued-congruency task applied to synaesthetes and non-synaesthetes who were trained on grapheme-colour associations. An inverted priming task was used to investigate implicit bidirectional synaesthesia. Results showed longer reaction time and more negative N400 and N300 components for incongruent than for congruent trials in both groups. While non-synaesthetes largely engaged cognitive processes, synaesthetes showed congruency-related and faster perceptual activation than controls. Implicit bidirectional synaesthesia relied both on early- and late-stage cognitive processes.

Event-related functional magnetic resonance imaging (fMRI) was used to shed light on the neural basis of synaesthesia and on possible shared neural mechanisms between this condition and imagery. Spatial sequence synaesthesia (SSS), which involves the perception of ordinal stimuli as arranged in peripersonal space, was investigated in a blind synaesthete. The additional synaesthetic colour perception that the subject reported for some of the stimuli, provided the opportunity to compare two different experimental and one control condition: coloured SSS, non-coloured SSS, and non-synaesthetic control. Stimuli eliciting SSS activated the occipito-parietal, infero-frontal and insular cortex. The visual colour area hOC4v was engaged when the synaesthetic experience included colour, thus indicating the continued recruitment of visual colour cortex in a late-blind synaesthete. The occipito-parietal activation suggests that the perception of spatial geometry in SSS is related to areas that are also engaged in spatial imagery in the blind as well as in sighted non-synaesthetes.

Introduction

General Introduction

It may appear obvious that the perception of a flower involves different types of sensory information such as the flower's smell, colour, shape and texture. It is however less obvious how the information from different sensory modalities as well as from different pathways within the same modality (e.g., colour-shape) is integrated. What is known is that different sensory as well as sub-sensory features of an object are processed in distinct cortical regions of the brain. It remains to be determined how the representations of different features are bound together to form a coherent percept (the binding problem).

The anatomical base of multisensory integration has been identified in associative brain regions, whose neurons respond to stimulation of more than one modality. However, there is also evidence for the fact that brain regions belonging to one sensory modality may respond to stimulation of a different modality. For instance, Amedi et al. (2001) showed that neurons of the visual cortex may also respond to somatosensory stimuli. In individuals with synaesthesia, stimulation of one sensory or cognitive stream (the inducer) leads to an associated experience (the concurrent) in a second unstimulated stream (Hubbard, 2007). The varied manifestations of synaesthesia, based on a number of possible cross-modal associations between inducer and concurrent, indicate that different multisensory and sub-sensory interactions are involved in this neural condition. Understanding the neural

mechanisms of synaesthesia may therefore contribute to the determination of neural binding processes in normal cognition.

Developmental synaesthesia typically arises spontaneously in early childhood, is induced involuntarily, and appears quite stable over time. The perception of the concurrent is vivid and personally important, and synaesthetes are normally surprised to discover that other people do not share their experiences. It is a possibility that the synaesthetes' awareness of their additional perceptions has been influenced by the wave of interest in synaesthesia. At the beginning of its history (1812) synaesthesia was an unknown and rare medical pathology. Now it is a widely investigated neurological phenomenon that is expected to contribute to the understanding of normal cognitive functioning. Research on synaesthesia dramatically advanced in the 1980s, when this non-pathological neurological condition started to be characterized by means of demographic investigations and systematic perceptual testing. While the results from surveys partially disagree on the prevalence of synaesthesia and its different forms in the population (see Study 1 for a review), the empirical investigations provide evidence for the perceptual reality of this neural condition.

Empirical demonstrations of synaesthesia

To prove the perceptual reality of synaesthesia and to rule out the possibility that inducer-concurrent associations of synaesthetes are a product of exceptional memory skills, a number of perceptual tests have been conducted. Smilek et al. (2001) showed

that the photisms in grapheme-colour synaesthesia could influence the perception of digits by modulating the colour congruence between the photism and the background on which the digit had to be identified and localized. While the synaesthete's performance decreased when the concurrent colour associated with the digit was congruent with the colour of the background, non-synaesthetes performed equally on congruent and incongruent trials. These results were therefore interpreted in favour of a perceptual difference between groups. Results from visual search tasks corroborate the idea that the synaesthetic experiences are really perceived. When asked to identify a target (a white "2") among a number of distractors (a set of white "S"), the synaesthete's colours were salient enough to shorten her reaction time compared to 7 non-synaesthetes (Palmeri et al., 2002). Also, synaesthetes showed higher accuracy than controls in an analogous visual search task, in which they had to discriminate a geometric shape defined by a group of graphemes (for example, black 'H's) embedded in a random array of distractors such as black 'P's and 'F's of the same size (Ramachandran and Hubbard, 2001a). Although these results were interpreted in the sense that colour concurrents can lead to a pop-out effect, synaesthetes were more efficient than controls only when the focus of attention was allocated on the grapheme, thus questioning the idea that the colour concurrents are automatically perceived (Laeng et al., 2004; Edquist et al., 2006).

Concomitantly, involuntary processing of the concurrent was demonstrated by means of a modified version of the Stroop test (Stroop, 1935) adapted to synaesthesia.

In this test, synaesthetes are typically presented a grapheme that is either of the same (congruent) or a different (incongruent) colour from the photism and they are asked to name the veridical colour. A number of studies applying this and other variants of the Stroop task (Wollen and Ruggiero, 1983; Mills et al., 1999; Dixon et al., 2000; Mattingley et al., 2001; Palmeri et al., 2002; Smilek et al., 2002; Nikolic et al., 2007) show that when the synaesthetic colour is congruent with the veridical one, processing the colour of the grapheme is facilitated, thus demonstrating that suppression of synaesthetic colours is difficult. Importantly, interference of synaesthetic colours in Stroop-like tasks vanishes when triggering stimuli are not available for conscious report (Mattingley et al., 2001), thus suggesting that only when attention has been focused on the target is the Stroop test effective. The Stroop effect occurs also in non-synaesthetes who are trained on associations between colour labels and alphabetic or shape stimuli (MacLeod and Dunbar, 1988; Meier and Rothen, 2009). Therefore, it has been argued that the Stroop effect shown by synaesthetes could be attributed solely to semantic associations between alphanumeric stimuli and colours rather than to the interference of perceptually experienced photisms (Smilek et al., 2002).

Indeed, the engagement of semantic processes in synaesthesia was shown by Ramachandran and Hubbard (2001b) by using an ambiguous symbol which could be seen as an "H" or an "A" depending on the word in which it was placed. Synaesthetes reported to experience different colours for the same symbol depending on the semantic context. In another experiment, which applied Navon-type local-

global stimuli that were comprised of letters, synaesthetes reported that the perceived colour changed depending on whether the local or the global form was attended (Ramachandran and Hubbard, 2001b). These results show that the emergence of synaesthetic experiences depends on top-down mechanisms and follows the allocation of selective attention. Moreover, the demonstration that synaesthetic Stroop interference can arise from the mere concept of a number, rather than from the processing of its visual or auditory form (Dixon et al., 2000), further supports the idea that semantic processes are engaged in synaesthesia.

Overall, these findings show that behavioural measurements alone are unable to detect at which level of the cognitive processing the synaesthetic experience arises. With the aim of shedding light on the time-course of synaesthesia and identifying the perceptual and conceptual processing involved in this condition, high temporal-resolution methods such as electroencephalography (EEG) have been applied.

Electrophysiological correlates of synaesthesia

The few EEG studies on synaesthesia have focussed on common forms of synaesthesia like grapheme-, phoneme-, and sound-colour synaesthesia. Schiltz et al. (1999) investigated grapheme-colour synaesthesia and showed more positive responses over frontal and prefrontal regions in synaesthetes as compared to non-synaesthetes at a relatively late point in time (200–600 ms); this effect was found both for target and non target stimuli in an oddball task. The authors proposed that the frontal positivity was related to cortical inhibition. This depended on an effort of the

nervous system to keep the synaesthetic perceptions to a minimum since these interfere with normal perception and lead to sensory conflicts. A more recent EEG study on grapheme-colour synaesthesia applied the synaesthetic Stroop task and showed more negative N1, more positive P2 and less negative N4 components in synaesthetes in response to contextually congruent graphemes as compared to incongruent ones (Brang et al., 2008). These results indicate that in synaesthetes the interaction between the colour expectation and the colour concurrent emerges at a very early stage of processing and affects late EEG components as well. The authors broadened these findings in a recent study, in which event related potentials (ERPs) of synaesthetes were compared with those of non-synaesthetes, who were trained to memorize specific grapheme-colour associations (Brang et al., 2011). This time, while both groups showed congruency effects at 400 ms, early congruency effects at 170 ms were manifest only in synaesthetes. This indicated group differences at a perceptual level of processing.

In their study on phoneme-colour synaesthesia, Beeli et al. (2008) showed that differences between synaesthetes and non-synaesthetes emerged over inferior posterior temporal sites at 122 ms after the onset of an auditory presented word or letter. Specifically, synaesthetes showed longer latencies and lower amplitudes of the auditory evoked potentials N1 and P2 than controls. In line with these results, Goller et al. (2009) reported smaller N1 in sound-colour synaesthetes compared to controls.

In a study of Barnett et al. (2008b), simple visual stimuli that do not elicit synaesthetic colour experiences and that bias both magnocellular and parvocellular responses

were presented to linguistic-colour synaesthetes and controls. Synaesthetes showed a significantly enhanced C1 (negative peak at 90 ms) and P1 component in response to stimuli with high spatial frequency and high contrast respectively. No group difference emerged for the N1 and P1 component. The absence of colour experiences in response to any of these simple stimuli accounted for fundamental group differences in early visual sensory processing being responsible for the effects observed. In particular, synaesthetes have been suggested to show decreased responsiveness in magnocellular system and concomitant increased responsiveness in parvocellular system.

In conclusion, findings from EEG studies are consistent in showing different sensory-perceptual processes in synaesthetes compared to non-synaesthetes and suggest that different neural mechanisms are at work in these two populations. The specification of possible structural and/or functional differences has been addressed in neural models of synaesthesia, which are discussed in the following section.

Neurocognitive models of synaesthesia

Two main neurocognitive models have been suggested to explain the occurrence of synaesthesia. One of them, the cross-activation theory, postulates that synaesthesia arises when the pruning of synapses is not completed between some brain areas (Maurer and Maurer, 1988; Ramachandran and Hubbard, 2001a). According to this theory, all humans experience synaesthesia early in life, and pruning of cross-modal connections results in a loss of these synaesthetic experiences. In children from the

time they are young infants until they are around 3 years old, spoken language elicits activity over the auditory as much as over the visual cortex (Neville, 1995). Enhanced activity in the somatosensory cortex following tactile stimulation accompanied by the sound of a white noise has been reported in human newborns (Wolff et al., 1974). Animal studies are also in line with these findings: they show transient connections between visual, auditory, tactile, and motor cortices in kittens (Dehay et al., 1988) and between the auditory cortex and the visual area V4 in infant monkey (Kennedy et al., 1997). Hubbard (2007) proposes a decreased pruning of these prenatal pathways in synaesthetes so that connections between the number grapheme area and V4 would persist into adulthood, leading to the experience of colour when viewing numbers or letters. Because synaesthesia tends to run in families (Baron-Cohen et al., 1996; Rich et al., 2005; Barnett et al., 2008b) and appears to have a genetic basis (Asher et al., 2009; Tomson et al., 2011), it is possible that the hypothesized decreased pruning in synaesthetes depends on a genetic factor. Indeed, pruning of projections from auditory to visual regions appears to be independent from visual experience (Innocenti et al., 1988). The synaesthetic intra-modal or intermodal associations would therefore be related to anomalous or additional connectivity between brain areas that subserve the relevant sensory modalities (Fig. 1a). Moreover, the adjacency of these regions per se would not play a fundamental role, as synaesthesia may arise through an overactivation of parietal binding mechanisms in concert with connectivity between brain regions (the two-stage model; Hubbard, 2007) (Fig. 1b).

The second main theory attempting to explain the neurological background of synaesthesia is the disinhibited feedback theory, which postulates that synaesthesia results from disinhibited feedback in existing neural pathways (Grossenbacher and Lovelace, 2001) (Fig. 1d). According to this theory, neural activity associated with the processing of an inducer would eventually converge with activity associated with stimulation from bimodal or multimodal domains, 'leaking' back to unimodal regions. The absence or attenuation of inhibitory mechanisms in synaesthetes would result in the co-activation of otherwise independent perceptual pathways. In the case of grapheme-colour synaesthesia, disinhibited feedback from a "multisensory nexus" might be responsible for the colour perception. The disinhibited-feedback theory, differently from the cross-activation theory, posits no abnormal neural connections and proposes instead that synaesthesia is entirely mediated by paths that exist in normal adult human brains. The induction of synaesthetic experiences in non-synaesthetes by means of hallucinogenic drugs and sensory deprivation (Armel and Ramachandran, 1999) has been taken as a sign that synaesthesia relies on normally existing adult networks. However, the large perceptual differences (e.g., in complexity) between drug-induced and developmental synaesthesia argue against this hypothesis (Hubbard, 2007).

A hybrid theory, the reentrant model of synaesthesia, combines some aspects of the cross-activation and the disinhibited feedback theory. It proposes that aberrant neural activity from anterior inferior temporal regions dependent on meaning processing feeds back to representations in posterior inferior temporal regions

engaged in form processing and V4, thus leading to the experience of synaesthetic colours (Smilek et al., 2001) (Fig. 1d). This model of synaesthesia is similar to that of Grossenbacher and Lovelace (2001) as it also proposes abnormal feedback from higher-level to lower-level areas. The reentrant model is also similar to the cross-activation model as it postulates a cross-activation between the posterior inferior temporal regions and V4. However, compared to the disinhibited feedback theory, the reentrant model furthermore localizes the high-level multimodal nexus in the anterior inferior temporal gyrus and specifies that the abnormal feedback travels along connections back to V4. Differently from the cross-activation model, the reentrant model does not postulate structural differences in synaesthetes as compared to non-synaesthetes, and proposes that the activation of the grapheme's meaning is critical in the elicitation of synaesthesia. The relationship between the colour concurrent and the semantic context of a grapheme is a proof of evidence in favour of this model. However, as argued by Hubbard and Ramachandran (2005), the presence of behavioral top-down modulations cannot distinguish between the local cross-activation and the re-entrant model of synaesthesia, because neither model has been specified with sufficient precision.

Finally, the model of Rich and Mattingley (2002) proposes various stages of grapheme and colour encoding. According to this model, grapheme processing includes analysis of the grapheme's basic features, identification of the symbol and then access to a stored representation of alphanumeric characters. Colour processing instead involves wavelength discrimination, colour categorization, colour semantic,

colour imagery and access to colour names. According to this theory, synaesthesia occurs by spreading activation from one of two alternative modules (feature analysis or symbol recognition) to one of two stages of colour processing (either colour categorization or object colour knowledge/imagery) (Fig. 1c).

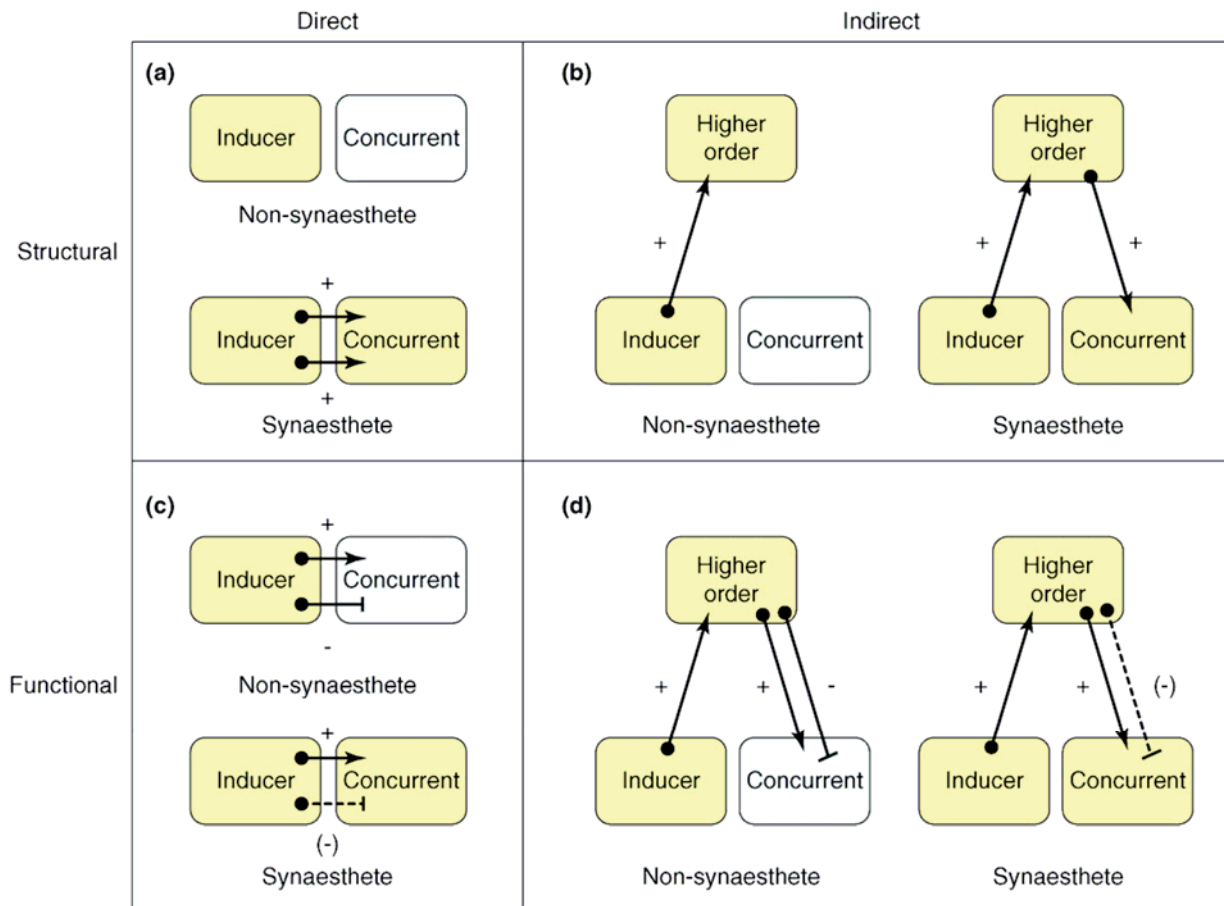


Fig. 1. Models of synaesthesia. Models differ in the proposed route of cross-activation (direct or indirect) between the inducer area and the concurrent area and the proposed underlying difference in synaesthetes (structural or functional). Yellow areas are active (starting with the inducer area) and blue areas are inactive. Excitatory connections are shown as arrows and inhibitory connections as blunt ended. Dashed lines represent structurally present but functionally ineffective connections. Reprinted from Trends in Neurosciences, 31(7), Gary Bargary and Kevin J. Mitchell (2008), with permission from Elsevier.

Although it is a possibility that different neurocognitive models apply to different forms of synaesthesia or even of synaesthetes subtype (van Leeuwen, 2011), the evidence for a genetic transmission of synaesthesia and the presence of different forms of synaesthesia occurring within the same family account for a unique

neurophysiologic mechanism. Up to now, there is some evidence for the cross-activation theory, as shown by investigations on the structural and functional anatomical characteristics of synaesthesia.

Structural and functional anatomical correlates of synaesthesia

The hypothesis of local anatomical cortical differences between grapheme-colour synaesthetes and non-synaesthetes in the vicinity of the V4 complex is supported from a morphometric analysis showing increased cortical thickness, cortical volume and cortical surface area in the right and left fusiform gyrus, as well as in the lingual gyrus and the calcarine cortex (Jaencke et al., 2009). As the authors correctly observe, the altered brain anatomy in grapheme-colour synaesthetes might be the anatomical basis for this particular form of synaesthesia, but also a possible consequence of the life-long experience of grapheme-colour synaesthesia.

A few studies tested possible different brain connectivity between synaesthetes and non-synaesthetes, as proposed by the cross-activation theory. Increased structural connectivity in grapheme-colours synaesthetes as compared to matched controls was found in the left superior parietal cortex and bilaterally in the superior frontal cortex (Rouw and Scholte, 2007). Increased gray matter volume in the right fusiform gyurs and in the left intraparietal cortex was shown by Weiss and Fink (2009). These results appear to support the two-stage model of grapheme-colour synaesthesia, which implies cross-activation at the level of the fusiform gyrus and hyperbinding at the level of the parietal cortex. However, some inconsistent findings also emerged:

Jaenke et al. (2009) found increased brain connectivity in the left inferior frontal cortex in synaesthetes and no group difference in the fusiform gyri. Haenggi et al. (2011) found higher connectivity in synaesthetes compared to non synaesthetes at a whole brain level, but no group difference emerged when the analysis was restricted to the fusiform gyrus and the intraparietal sulcus.

Results from functional magnetic resonance imaging (fMRI) studies show activation of the visual colour area V4 both in grapheme-colour and in coloured-hearing synaesthesia (Paulesu et al., 1995; Nunn et al., 2002; Gray et al., 2006; Steven et al., 2006; van Leeuwen et al., 2010). The finding of co-activation of grapheme and colour brain areas (Hubbard et al., 2005) as well as of fusiform gyrus and parietal cortex (van Leeuwen et al., 2010) in grapheme-colour synaesthetes provides support for the two-stage cross-activation theory. Synaesthesia-related activation of the intraparietal sulcus emerged in some studies (Weiss et al., 2005; Tang et al., 2008). Moreover, the disruption of grapheme-colour integration in synaesthetes by means of repetitive transcranial magnetic stimulation on the right posterior parietal lobe (Esterman et al., 2006) confirms the engagement of the parietal cortex in synaesthesia as hypothesized in the two-stage model. However, other areas also appear to play a role in synaesthesia: right inferior frontal activation was found in synaesthetes in response to visually presented letters (Sperling et al., 2006) and to words presented in the auditory modality (Paulesu et al., 1995; Aleman et al., 2001). Beeli et al. (2008) applied low resolution brain electromagnetic tomography (LORETA) and showed stronger activation in phoneme-colour synaesthetes in left posterior inferior temporal and in

orbitofrontal brain regions in addition to the fusiform gyrus, as compared to controls. Activation of posterior inferior temporal brain region concomitantly to V4 was also found in a magnetoencephalographic study on grapheme-colour synaesthesia (Brang et al., 2010).

The simultaneous activation of these brain regions was interpreted as a direct communication between these areas. This argues against the cortical disinhibited feedback model of grapheme-colour synaesthesia, which predicts activation of V4 only after substantial processing has occurred.

All together, these studies provide evidence for the engagement of colour brain areas during photism perception in synaesthesia and point to a role of inferior temporal and parietal cortex in the binding between inducer and concurrent. The frontal activation reported in some studies hints to an engagement of cognitive control processes to solve the perceptual conflict resulting from synaesthesia.

Evidence for a continuum between synaesthesia and normal cognition

One interesting issue concerning synaesthesia is whether this fascinating neural condition relies on the same neurocognitive mechanisms of normal cognition. It is known that audiovisual connectivity is present in the normal population (Calvert et al., 2001a). More than half of visually responsive neurons also respond to auditory and/or somatosensory stimuli (Macaluso, 2006). Animal studies show projections from auditory to visual central and peripheral regions (Falchier et al., 2002; Rockland and Ojima, 2003) as well as somatosensory input to auditory association cortex

(Schroeder et al., 2001). It could be therefore possible that synaesthetes and non-synaesthetes share some cross-modal neural paths.

Some behavioural findings agree with this hypothesis. Ward et al. (2006) investigated the way in which synaesthetes and non-synaesthetes associate tone properties (e.g., tone-pitch) with visual properties of a stimulus (e.g., colour luminance). Results showed an identical trend in both groups to associate low pitch with dark colours and high pitch with light colours. Trends in cross-modal associations in non-synaesthetes have been consistently reported in adults (Marks 1975; Walker and Smith, 1984; Melara, 1989) and children (Mondloch and Maurer, 2004).

Moreover, the relationship between synaesthesia and imagery further accounts for common neural paths subtending synaesthesia and normal cognition. Results from self-report scales and behavioural testing point to more vivid imagery (Barnett and Newell, 2008) and stronger imagery skills (Spiller and Jansari, 2008) in synaesthetes compared to controls. Up to now, results from functional anatomical investigations are inconsistent with the behavioural findings and do not find overlapping pathways when comparing colour imagery with grapheme-colour synaesthesia (Rich et al., 2006; Steven et al., 2006). Although these results might be explained by some differences between synaesthesia and imagery (e.g., consistency and level of elaboration), the hypothesis of common neural processes subtending synaesthesia and imagery remains to be tested on other forms of synaesthesia.

Finally, differences in photism perception among synaesthetes bear out the continuum between synaesthesia and normal functioning. Depending on whether the photism is perceived in the external space or “in the mind’s eye”, synaesthetes have been defined as projectors or associators respectively (Dixon et al., 2004). The description that associators make of their synaesthetic perception appears remarkably similar to how a non-synaesthete would describe the experience of visual mental imagery (Barnett and Newell, 2008). Besides, some individuals report colour-grapheme associations like synaesthetes, even if they do not see a concurrent colour and show less consistency over time (Steven et al., 2004; van Leeuwen et al., 2011). These findings account for the existence of an implicit form of synaesthesia. In a hypothetical continuum between synaesthesia and normal cognition, associators might thus find a place in a position closer to implicit synaesthetes as compared to projectors. As proposed by Proulx and Stoerig (2006), only at the end of this hypothetical continuum is the concurrent sensation explicitly phenomenal.

Study 1

Modality and Variability of Synaesthetic Experience

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Abstract

In synaesthesia, stimulation of one sensory or cognitive pathway leads to additional, involuntary experiences in a second sensory or cognitive pathway. We here review previous surveys on this neurologically-based phenomenon and report the results of 63 synaesthetes who completed our Internet and paper questionnaire on synaesthesia. In addition to asking for personal data and information on the participant's synaesthesia, the questionnaire focused on the components of the inducer that elicit and/or modulate synaesthesia. Results show that synaesthesia was most often developmental (92%) and of the grapheme-color type (86%). Sixty-two percent of the participants perceived time-related words in a spatial configuration. Music-color synaesthesia was common (41%), and synaesthesia for natural and artificial sounds (33%) was higher than in previous estimates. Eighty-one percent of participants experienced more than one form of synaesthesia. Multimodal synaesthesia, where inducer and concurrent belong to two different sensory modalities, occurred in 92% of the subjects. Overall, auditory stimuli were most often reported as inducers, and visual concurrents were most common. Modulations of the synaesthetic experiences such as changes of the concurrent color, expansion within the same or to a different sensory modality, or reduction of the number of inducers over time were reported by 17% of participants. This challenges the presumed consistency of synaesthesia and the adequacy of the test-retest consistency score still most commonly used to assess the veracity of reported synaesthesia. Implications of

the high prevalence of cross-modal synaesthesia and the variability of synaesthesia are discussed.

Key words: synaesthesia; survey; variability; modality.

Introduction

A “feminine and old narrow-minded ‘6’” has nothing in common with a “strong and dynamic ‘9’” (participant 7). While few non-synaesthetes associate numbers with personality, individuals with grapheme-personification synaesthesia would not be surprised by such attributions. Synaesthesia is a neurologically-based phenomenon in which a stimulus in one sensory modality triggers an additional experience in another. In effective inventory of diagnostic criteria, Price and Mentzoni (2008) summarized the following hallmarks of developmental synaesthesia: it tends to arise spontaneously in early childhood, it is induced involuntarily, it is vivid and personally important, and its precise details vary idiosyncratically, even if its broader nature often has some similarity across synaesthetes. Besides, synaesthesia appears quite stable over time and synaesthetes are typically surprised to discover that other people do not share their experiences.

A number of surveys conducted to explore this fascinating condition made important contributions to the study of synaesthesia, although consensus has not been reached for every aspect. Studies vary widely in the prevalence estimates that range from 1 in 4 to 1 in 100.000 (for a summary see Simner et al., 2006a), and often disagree on which form of synaesthesia is the most common. While grapheme-color synaesthesia

is the most frequent type according to some (Baron-Cohen et al., 1996; Rich et al., 2005), other authors report similarly high prevalence rates for number forms (Sagiv et al., 2006) or spatially arranged time units (Simner et al., 2006a; Barnett et al. 2008a). There are some factors which may be responsible for inconsistent prevalence rates. First, the different studies are based on different, sometimes small, sample sizes (for a summary, see Table I), and apply different inclusion criteria. For example, Baron-Cohen et al. (1996) excluded participants who only reported day-color synaesthesia, while Simner et al. (2006a) excluded reports of letters and numbers having spatial orientations, gender and personality traits. In contrast, Sagiv et al. (2006) purposely focused on number-form synaesthesia. Second, the recent wave of interest in synaesthesia shapes its taxonomy (Emrich et al., 2002) and increases synaesthetes' awareness of their additional perceptions; both factors may further contribute to the variance of prevalence rates. Third, studies vary in their recruitment procedures (Table I). While earlier studies recruited participants through advertisements in local newspapers (Baron-Cohen et al., 1996; Rich et al., 2005) or from university communities and museum visitors (Simner et al., 2006a), more recent surveys have used a university website (Sagiv et al., 2006) or both internet and newspaper advertisements (Barnett et al., 2008a). All together, these factors may impact the estimated prevalence rate of synaesthesia and its subtypes.

Compared to more traditional sources, internet surveys on synaesthesia have several advantages. First, due both to the simplicity of internet searches and the fact that synaesthetes are normally interested in their particular condition, as evidenced by

the abundance of internet forums, blogs and associations of synaesthetes, they allow for the collection of a large amount of responses in a relatively short time. The recent proliferation of internet-based synaesthesia questionnaires and publication of data based on large samples of synaesthetes (Tomson et al., 2011) support the notion that Internet is a valuable instrument to collect information on this population: for example, see the questionnaire of Waterloo University (<http://www.bu.edu/dbin/synesthesia>), the UK Synaesthesia Association (<http://www.uksynaesthesia.com/questionnaire.htm>), and the Synaesthesia Battery by Eagleman et al. (2007). Second, participants can comfortably respond at home at a time of their choosing, and do not need to contact or visit a research centre, a time-consuming procedure that may be discouraging. Third, people may find it easier to respond openly to internet than paper questionnaires or interviewers, because of the internet's relative anonymity. Although anonymity might have a drawback in terms of honesty, it is relevant for sensitive topics including drug use or medical conditions, but also to synaesthesia as such. Several synaesthetes report that they have been ridiculed for their experiences, and thus tend to keep them to themselves (Ramachandran and Hubbard, 2001b; Emrich et al., 2002; Price and Mentzoni, 2008). However, it is worth noting that Internet research also has some shortcomings. For example, the easiness of internet data reports might affect the depth of the data collection. Participants might be less careful in their completion of the questionnaire via Internet compared to a laboratory setting as they may feel that they are not supervised. In addition, this sampling method can make prevalence difficult to

estimate: to track and estimate the number of visitors to our website, we used an Internet statistical instrument (<http://www.google.com/analytics>) in the present study.

We here report data collected by means of an internet questionnaire uploaded at Düsseldorf University as well as a paper questionnaire completed by synaesthetes who were recruited through a an advertisement on a synaesthesia-related website. Our questionnaires aimed at characterizing the synaesthetic associations and specifically the components of the inducers that elicit and/or modulate synaesthesia. Studies on grapheme-color synaesthesia have already shown that a variety of stimulus parameters affect the induced synaesthetic experiences (“concurrents”). Systematic relationships between the colors generated by words and those generated by graphemes within the word have been reported (Ward et al., 2005). Simner et al. (2006b) proposed a process of competition between constituent graphemes, in which stressed graphemes and word-initial graphemes are disproportionately weighted. Asking whether homophones (sun/son) or words with similar initial phonemes but different initial letters (fish/photograph) would evoke concurrents reflecting semantics, phonemes or graphemes, Baron-Cohen et al. (1993) found that in their nine synaesthetes it was the initial letter that determined the word color. A marked impact of first or dominant phonemes/graphemes on the concurrent color has been described in other studies (Baron-Cohen et al., 1993; Rich et al., 2005). Moreover, the font has been suggested to influence the intensity of coloring (e.g., saturation; Witthoft and Winawer, 2006). While these studies focused on the influence of a

word's visual characteristics on the synaesthetic percept, others suggest that phonemes may determine the concurrent colors (Galton, 1883; Harrison and Baron-Cohen, 1995; Paulesu et al., 1995; Aleman et al., 2001). Moreover, case studies show that the concept or categorization of a stimulus can trigger synaesthesia (Myles et al., 2003; Dixon et al., 2006). We here aim to shed more light on the triggers of the forms of synaesthesia that are present in our sample by inspecting the inducers' features and modality, and identifying components that are responsible for giving rise to and modulating concurrent experiences.

We also aim to explore two further issues that have not been extensively addressed in previous surveys. The first addresses the prevalence of cross-modal versus intramodal synaesthesia, the second the variability of synaesthesia over time. Considering forms of synaesthesia different from grapheme-color (GC¹) synaesthesia, it appears that the prevalence of cross-modal synaesthesia ranges between 23% (Barnett et al., 2008a) and 54% (Baron-Cohen et al., 1996) of the participants. However, since the percentage of participants with synaesthesia for spoken words, letters and/or digits has not been specified, an exact estimation of the occurrence of cross-modal synaesthesia is not possible. With regard to the variability of the synaesthetic experiences, the use of a retest to verify synaesthesia indicates that its stability over time is generally taken to be an important hallmark. However, contrary evidence comes from Rich et al. (2005), who reported that the intensity of synaesthesia can decrease with age, and from Hubbard et al. (2006) who describe a GC-synaesthete whose color experiences changed with the contrast of a digit, a

finding that was confirmed by Eagleman et al. (2007) in one of twelve GC-synaesthetes. Moreover, an analysis of the subjective locus of synaesthetic colors conducted by Edquist et al. (2006) suggested both that the reliability of self-reports of synaesthetes may be questionable and that the subjective experiences of synaesthesia are highly variable. We therefore explicitly asked participants to describe any variations they experienced in their synaesthesia in the period of time preceding the compilation of the questionnaire.

Methods

A German and a translated Dutch version of our questionnaire were used. The German version appeared on the Internet, the Dutch one was presented in a paper version. The internet questionnaire appeared in the Institute's section of the Düsseldorf Heinrich Heine University Website from March till August 2007. The paper questionnaire was completed by synaesthetes recruited through an advertisement on a synaesthesia-related website from June until December 2007. Following a brief introduction to synaesthesia, participants were asked to describe their form/s of synaesthesia in a free text field. Both the German and the Dutch questionnaire included multiple-choice and open questions (see supplementary material). The first part of the questionnaire focused on characteristics of the respondents' synaesthesia, their family members, spoken languages, medical history, active or passive forms of artistic occupation as well as hobbies. As the internet survey's advantageous anonymity would suffer if subjects were to enter

identification, we did not require respondents to enter their names or contact addresses. Although using a data code for each participant is a valuable alternative, this method was not applied in the present survey. The second part was divided into sections pertaining to different forms of synaesthesia. Here, a total of 159 stimuli including words, letters, numbers (both in form of word and digit), punctuation marks, time-related words, color names and non-words were presented. In addition, subjects could provide their own examples of inducers and concurrents. To describe concurrents, they could choose from 276 coded colors (RGB system) in the internet questionnaire and report details in writing in both internet and paper questionnaire. Thirty questionnaires were completed on-line and 33 questionnaires were returned by mail. Twenty-seven subjects from the Dutch sample took part to a surprise re-test on 20 graphemes 8–45 months (mean 28 months) after the initial study, yielding to an average consistency score of 91,2%. Because no marked difference emerged between the German and the Dutch questionnaire, data were collapsed for analysis.

Results

A total of 63 subjects completed our questionnaire. Responses to multiple-choice questions were ordered by item and the resulting frequencies were analyzed. For the sake of clarity, results are presented in subsections. Following a description of the participants' demographic characteristics, the prevalence and features of the different forms of synaesthesia in the sample are reported. We then address the characteristics

of the concurrents as well as the changes that affect both inducers and concurrents over time.

Demographic Characteristics of Participants

Considering that the number of visitors at our university website was about 1,500 during the same period, the prevalence rate would amount to 2%. However, the participants may have found the website when searching the internet for new information on synaesthesia, rather than accessing it for other reasons. In this not improbable case, the number of respondents would be unrelated to the number of visitors. No prevalence estimate is possible from the Dutch sample.

The sample's sex ratio was female biased (3.5 : 1 females/males). Fifty-seven percent of participants reported no academic degree. The remaining subjects were graduated or had a doctoral degree. While the age of the Dutch participants was on average 29 years (SD=10), age records for the German subjects were not available. However, it seems unlikely that the German sample consisted mainly of students, since 42% of these subjects reported that they discovered themselves to be synaesthetes after the age of 25 (Fig. 1), an uncommon age for the majority of university students. One person failed to report gender and educational data. For all but one participant the native language was either German or Dutch. Except for 3 cases, all participants indicated that they spoke a second language fluently or pretty well, and 57% spoke a third language although not fluently. The second and the third language were based on Roman script except in 4 cases where Cyrillic script was used. Eighty-five percent

of subjects with synaesthesia for words experienced it also in the foreign language(s). This included the 4 respondents who had learned to read Cyrillic script. Most subjects reported experiencing synaesthesia on a daily basis (81%) and having had synaesthesia all their lives (90%). The remaining subjects reported the first synaesthetic experience to occur at a specific age: two subjects at the age of 6/7, one at the age of 12 and one at the age of 25; one person failed to respond to this item. Ninety-two percent of the participants learned that they were synaesthetes after reaching the age of 14 and 81% rated their synaesthesia in the medium to strong range of intensity (between 5 and 10 in a 0-10 point scale).

Thirty-five percent of subjects reported having at least one first-degree relative with synaesthesia and as many subjects did not know or did not answer. In the majority of the cases, the participant's and the relative's synaesthesia were of the same type and in half of the cases the mentioned first-degree relative was the mother. Only one participant reported that a second-degree relative experienced a form of synaesthesia similar to his, and one synaesthete with multiple twins reported that the siblings did not experience synaesthesia.

Nine percent of the subjects and two of the 21 family members reported to be synaesthetes had an artistic profession. Questions regarding creative or artistic inclinations revealed that most respondents were artistically active (68%) and/or enjoyed visual art (62%). Interest in reading, photography and/or languages was frequently reported. Seventy-eight percent of subjects judged synaesthesia to be an advantage in creative jobs as well as in memorizing, learning or calculating. Whereas

the rate of reported benefits in learning was related to the presence of GC synaesthesia ($p = 0.001$, Fisher's exact test), the strength of synaesthesia (categorized as intensity $>$ or < 5) did not appear to play a role in advantages in learning ($p = 0.10$, Fisher's exact test). Consistent with data on the reported advantages of having synaesthesia, participants frequently described themselves as skilled at painting, learning, speaking foreign languages and memorizing things; 19% reported having a photographic memory. Relatively poor abilities were reported in mathematics and in tasks requiring sustained concentration, spatial imagination and spatial perception.

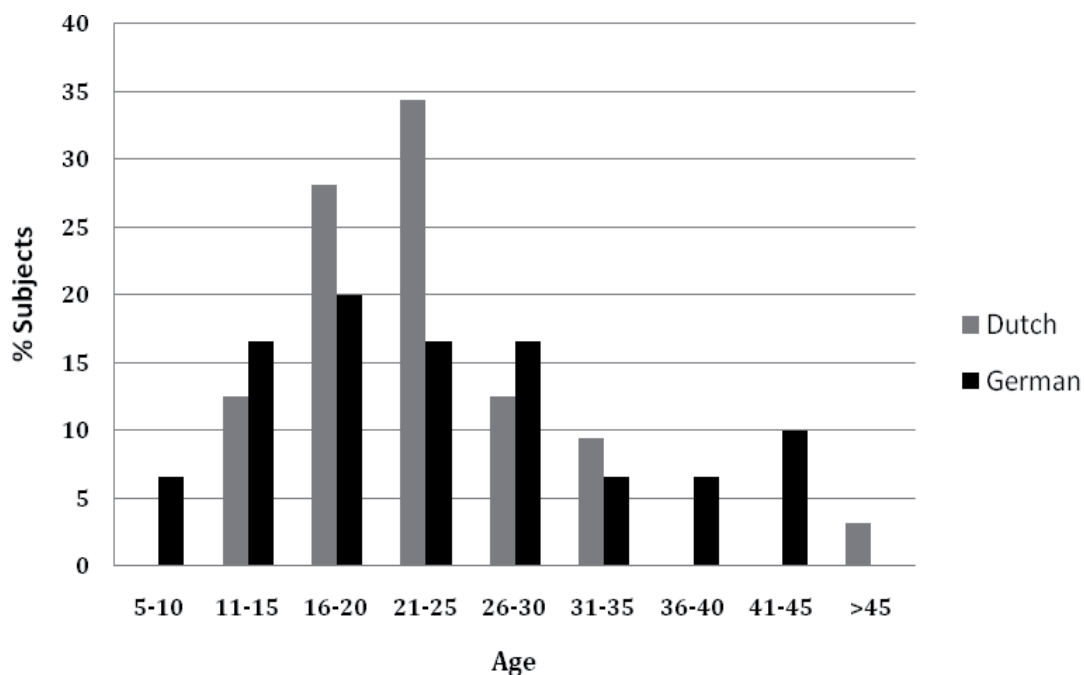


Fig. 1. Age at which participants belonging to the German ($N=31$) and the Dutch sample ($N=32$) learned they were synaesthetes.

Responses to a multiple-choice question indicated that 60% of participants assumed that synaesthesia has a genetic basis. Although 71% of participants could not think of

anything in their past that may have brought on synaesthesia, others suggested that their suffering from headache, depression or epilepsy influenced the development of synaesthesia. In six cases synaesthesia was reported to be initiated by some stimuli like the first children colored dictionary, a musical clock, or a TV-guide with colored weekdays. In one case, the color coding for numbers in electronics was mentioned as the origin of his synaesthesia: this subject received his first set of resistors with color-bands related to numbers for his sixth birthday.

The prevalence of migraine in the sample, which consisted in the large majority of women, was comparable to that found in the female German and Dutch population (30% vs. 32.5%; Stovner et al., 2006). Seventeen percent of participants reported depression. This self-reported rate is not significantly different from the depression prevalence rate in primary care in Germany (12%; Wittchen and Pittrow, 2002) ($\chi^2 = 1.31$; $p = 0.25$). Seven subjects reported occasional use of drugs (e.g. LSD, Cannabis).

Types of Synaesthesia

The most common form of synaesthesia among our participants was grapheme-color (GC) synaesthesia, with synaesthesia for digits being more frequent (86%) than synaesthesia for letters (79%) and words (81%) (Fig. 2). Only two persons reported personality and gender as concurrents for digits. Synaesthesia for time units was the second most frequently reported type (62%), followed by synaesthesia for music (41%) and for natural or artificial noises (33%). Synaesthesia for pain (14%), for smell (11%), and for emotions (11%) followed suit. Synaesthesia for touch and punctuation

marks were rarer still (8%), but more common than synaesthesia for textures/colors, people, temperature and abstract concepts.

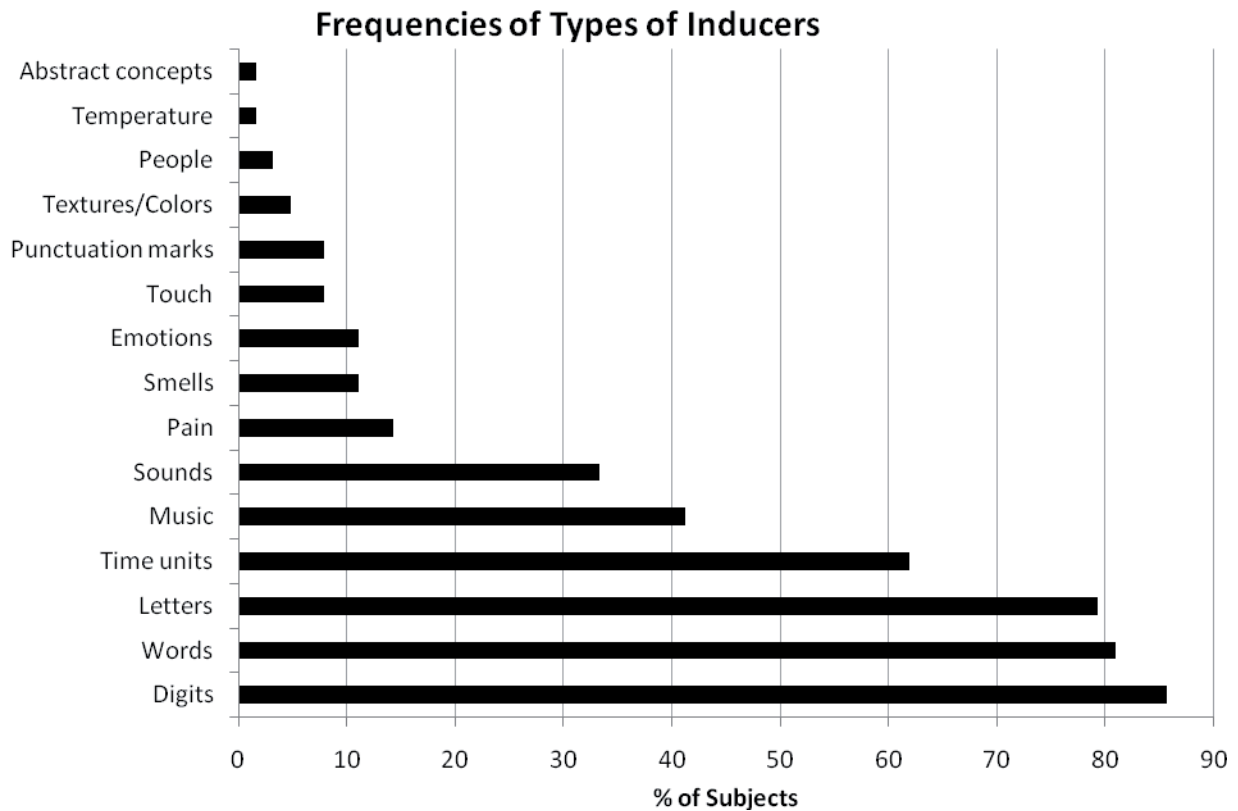


Fig. 2. Frequency rates for different forms of synaesthesia in the sample (N=63) grouped by type of inducer. Synaesthesia for digits was the most prevalent form: specifically, digits elicited colors in 86% of the subjects; time units triggered spatial configurations in 62%. Music elicited concurrents in 41% and sounds in 33%. Synaesthesia for pain, smell, emotion, touch, punctuation marks, textures/colors and people was rare, and synaesthesia for temperature and abstract concepts each occurred in one case only.

Ninety percent of our participants were self-reported associators who claimed that synaesthesia occurred in their „mind’s eye“. The remaining subjects described themselves as projectors who perceived the concurrents in the outside world, in the vicinity of the inducer, or on their own body (Dixon et al., 2004). Eighty-one percent of participants had multiple synaesthesias. Nineteen percent of the subjects reported synaesthesia from a single type of inducer, 32% responded to two, and the remaining

49% listed three to six types. The prevalence of the types of synaesthesia grouped for number of inducer is showed in Fig.3.

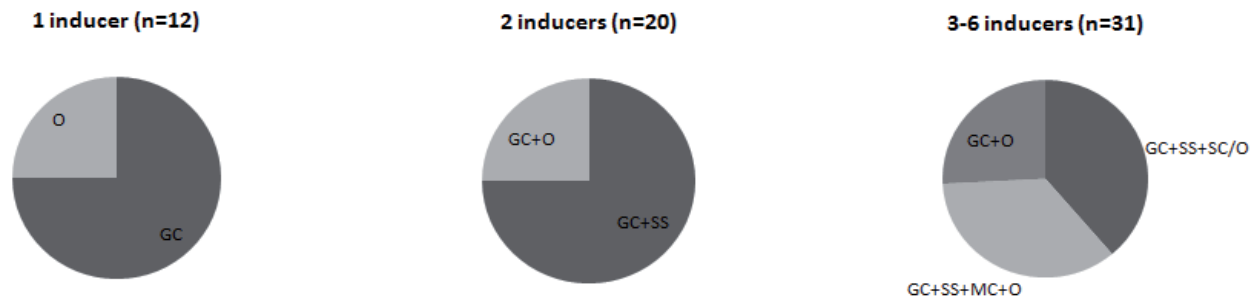


Fig. 3. Prevalence of combinations of synaesthesia types in the sample grouped by number of inducers. GC = grapheme-color synaesthesia; SS = sequence-space synaesthesia; MC = music-color synaesthesia; SC = sound-color synaesthesia; O = other forms of synaesthesia.

Grapheme-color synaesthesia: Sixty-five percent of subjects reported synaesthesia for letters, words, and digits. As shown in Figure 4, the synaesthetic perception for participants with GC synaesthesia depended on the modality in which the inducer was presented. Only heard (i.e. auditory presented) stimuli elicited synaesthesia in up to 18% of cases with grapheme-color synaesthesia. All other subjects either needed to read the inducers (up to 22%) or responded to both formats (up to 76%). While 59% experienced color concurrents for heard and read words, 18% reported it for read-only and 22% for heard-only words. Subtle differences in these proportions occurred for graphemes/phonemes, words, and digits. Words more often than either letters or numbers elicited synaesthetic experiences in either heard or read format but not both. The words' concurrents were influenced by their first letter and their

strongest vowel in 29% and 26% of the subjects with lexical synaesthesia respectively. In another 33% of cases, the concurrent reflected a combination of the synaesthetic colors elicited from each composing letter. In only 6% of cases did the words' meaning affect the synaesthetic perception. Hearing or reading color words (e.g., „red“) elicited a color concurrent in 89% of the subjects and in most cases the concurrent was reported to be congruent to the one indicated by the word. This data agrees with the concurrent color trends subjects reported for the color names from the word list. Seventy-four percent of participants with synaesthesia for words and letters also perceived colored concurrents for the non-words in the list, indicating that a meaningless series of graphemes or phonemes often suffices to elicit synaesthesia, and implying that synaesthesia was linked to early, pre-semantic stages of word processing.

Analogously, color concurrents of multi-digits (e.g., 1324) were in most cases determined by a combination of the constituents' colors (68%) or by the first digit's (13%). Variation in hue or lightness elicited by variations in font (e.g., italic, hand writing) and font size were reported by 16% of the participants.

Synaesthesia for Spoken Language, Music and Sounds: Forty percent of the subjects had synaesthesia for at least two of the three categories phonemes, heard music and sounds. Seventy-five percent of these subjects also responded to the written format. Approximately 90% of GC synaesthetes reported colors in response to spoken letters, digits, or words. Forty percent of the subjects with synaesthesia for spoken words

reported that voice pitch and/or features such as accent and prosody influenced the synaesthetic color. Differently, volume and speed of talking played a role only for a few individuals. Whereas the speakers' emotional inflection could affect the concurrent color, only two participants reported that their own mood altered the colors.

Forty-one percent of our subjects had synaesthesia for music. Heard music stimuli did elicit a concurrent in many more cases than visual music stimuli ($p = 0.01$, Fisher's exact test) (Fig.4). Seventy-five percent of the participants with synaesthesia for music perceived colors exclusively when listening to notes being played. Synaesthesia triggered by listening to musical stimuli showed that tone pitch and type of instrument affected the concurrent's color in 40% and 26% of subjects, respectively. Thirty-three percent of participants reported color concurrents for artificial environmental sounds (e.g., the doorbell sounds yellow) or animate and inanimate natural sounds: 'yellow bird song' and 'turquoise sounds made by leaves in the wind' exemplify these associations. One subject experienced pain or goose-flesh when hearing particular sounds (e.g., "kri"). In our sample, the stimulation of the auditory modality induced synaesthetic experiences as frequently as the stimulation of the visual modality.

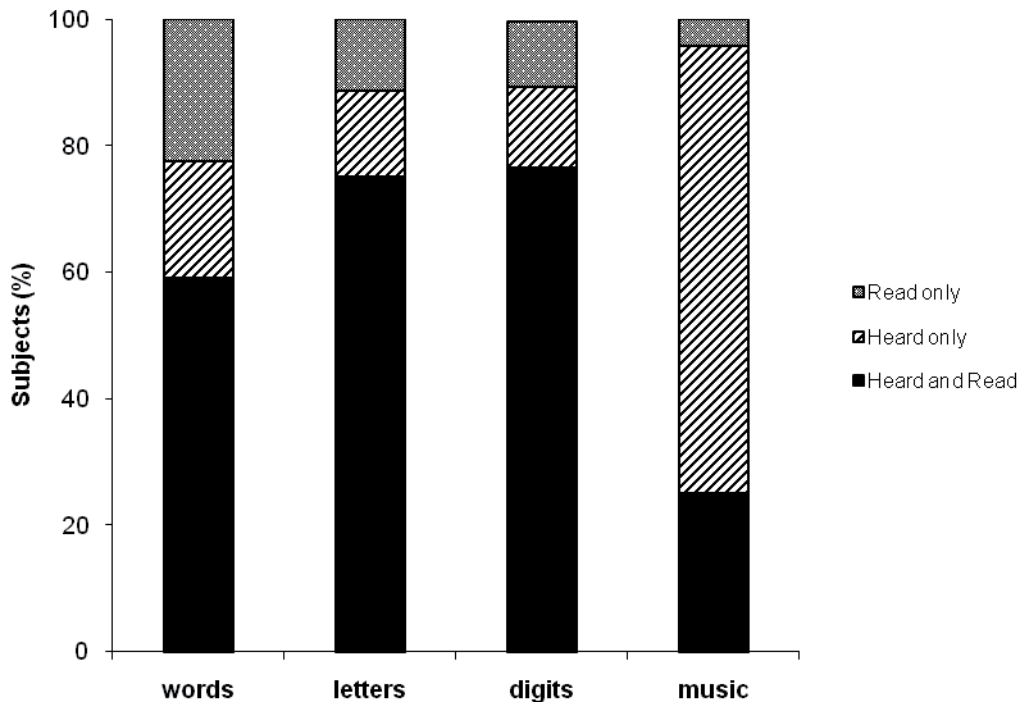


Fig. 4. Subjects reporting GC and/or music-color synaesthesia. Although both could be elicited by heard and/or read stimuli, in many cases the concurrents depended on the sensory modality in which the inducer was presented.

Synaesthesia for Time Units: A total of 62% of our subjects perceived a spatial pattern while reading/hearing time-related words (e.g., “the year is oval” or “the week is rectangular”). Of these, 93% reported the spatial pattern in addition to a color. For 67% of subjects with synaesthesia for time units, thinking of time-units was sufficient to elicit a spatial pattern. As shown by the prevalent combinations of synaesthesia types in Fig. 3, spatial-sequence synaesthesia accompanied GC synaesthesia in the large majority of cases who reported two or more types of inducer.

Synaesthesia for Pain and Touch: Fourteen percent of subjects experienced synaesthesia for pain and 8% for touch. Not all forms of pain and touch elicited synaesthetic

perceptions and the reported inducers were specific: bodily aches (e.g., headache, bellyache), a cut or being stroked are examples of painful inducers. The concurrents presented as colors and forms or patterns - a bright yellow sting, a violet headache, the image of a fragmented glass panel induced by a finger cut. One person reported pain as a concurrent, which was evoked by auditory stimulation, namely brief sounds.

Types and Characteristics of Concurrent Perceptions

Color was the most frequent concurrent reported by our sample (97%), followed by spatial configurations (62%; Fig. 5). Reports of colored concurrents showed that in most cases the color appeared instantly (89%) and static (73%). The remainder reported that the color moved in a specific direction (16%); only in one case did it move randomly. According to 71% of subjects, the synaesthetic color did not interfere with the physical color of the inducer (e.g. black ink color for graphemes). The two hues were discernable as the concurrent's color was brighter, more intense, dazzling, or transparent. The visual modality clearly dominated the concurrents, whereas auditory concurrents were extremely rare.

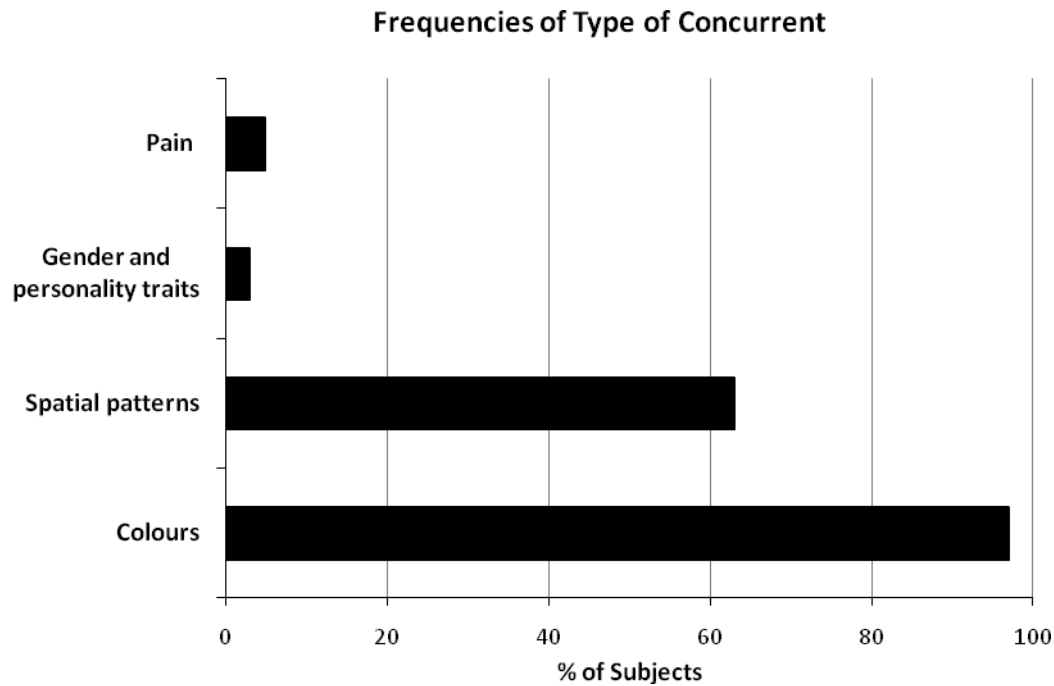


Fig. 5. Frequency rates for the different types of concurrents in the sample. Excepting one subject who reported tones as only concurrent, all participants perceived synaesthetic colors in addition to at least one other concurrent such as spatial patterns, gender, personality traits, taste, temperature or movement.

Cross-modal and Intramodal Synaesthesia

Ninety-two percent of subjects had at least one form of cross-modal synaesthesia: in most cases (89%), auditory inducers evoked visual concurrents. The reverse coupling - a visual stimulus eliciting auditory concurrents - was never reported. For 19% of the subjects with cross-modal synaesthesia the inducer was somatosensory, and gave rise to visual concurrents in all cases but two in which the concurrent was auditory. The reverse association between auditory inducers and somatosensory concurrents occurred in two cases as well. In one case auditory stimuli induced gustatory concurrents. Association between olfactory inducers and visual concurrents were reported by 11% of the participants, and visual inducers and gustatory concurrents were associated in only one case. Seventy-six percent described intramodal

synaesthesia. In all those cases the inducers were written-only graphemes, words, digits and/or musical notes, and evoked color concurrents. A summary of the frequency-weighted cross-modal and intramodal associations is given in Figure 6.

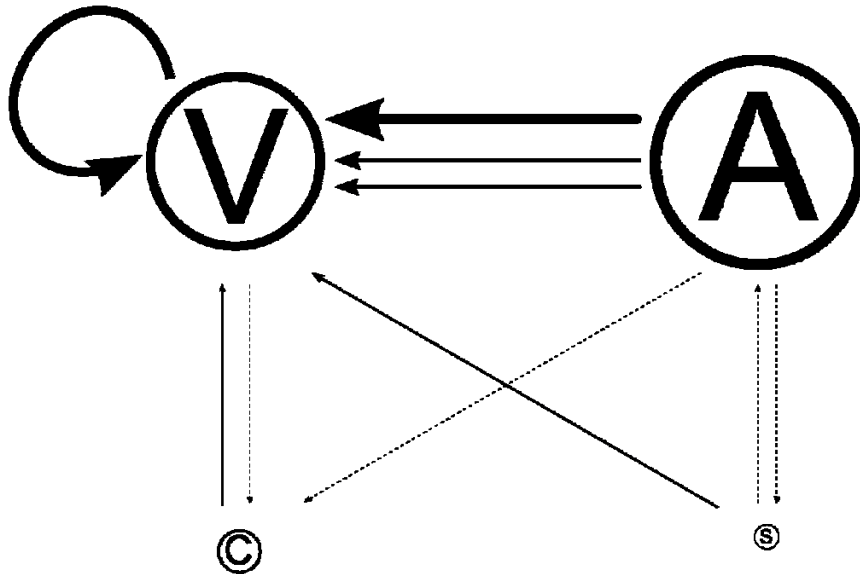


Fig. 6. Schematic representation of the intramodal and cross-modal associations in the sample. Circle size represents frequency of inducer modality. Arrows indicate the direction of the association, thickness reflects their prevalence; dotted line indicate a prevalence <10%. Connections between the auditory and visual modalities stand for phoneme-color, heard music-color and sound-color synaesthesia (top to bottom). The visual format is not only the most common for concurrents, but also the only one that itself engenders visual concurrents, color being the most common concurrent submodality. V = visual, A = auditory, C = chemosensory, S = somatosensory modality.

Characteristics of Synaesthesia and Development over Time

For 33% of subjects the intensity had changed over time, so that the synaesthetic perception had become stronger (28% of these subjects), weaker (28%), or that the subjects had become more aware of it (14%). In 9% of these cases, the color elicited by a specific inducer had changed over time. Although the type of inducer had remained constant during life for most subjects (82%), some participants (5%) reported an expansion within the same sensory modality. Further variations such as spreading to a different sensory modality (3%) or narrowing of the number of

inducers eliciting synaesthesia (3%) were reported. Another 6% of subjects reported changes over time that they did not specify.

We asked the participants whether they could voluntarily control their synaesthesia and either induce or stop the concurrent's occurrence. Thirty-three percent of the subjects indicated that they could smother or ignore as well as evoke the concurrent at will, while the remaining subjects could not control it completely or only with much effort. Although this finding is inconsistent with the noted automaticity of synaesthesia, 52% of these subjects were confirmed synaesthetes according to their consistency score (91%). Also, 59% of the subjects reported that attention affected their synaesthetic perceptions. Other factors that altered the synaesthetic experience included: level of concentration, fatigue, insufficient sleep, fever, emotional involvement as well as some substances (coffee, alcohol, and medicaments). Whereas caffeine and medicaments enhanced synaesthesia, fatigue could either strengthen or weaken the sensations.

Discussion

Self-reports of 63 synaesthetes yielded the following main conclusions: heard- and read-GC synaesthesia was the most commonly reported type, followed by synaesthesia for spatial patterns for time units and for music and sounds. The inducer's modality was important in the majority of cases, and its particular features rather than its meaning determined the precise appearance of the concurrent. A substantial proportion of respondents found that their concurrent experiences had

changed over time and/or were influenced by factors including attention, fatigue, fever, emotion, and substances such as caffeine.

Demographic Characteristics

In agreement with previous studies, we found a marked preponderance of females in our sample (Baron-Cohen et al., 1996; Rich et al., 2005; Barnett et al., 2008a). This bias may reflect a genetically-based difference, but a higher propensity of women to respond to this type of questionnaires may certainly contribute. Indeed, the two studies that sampled university students and museum visitors without prior regard to their synaesthetic status found essentially no gender difference (1.1:1 and 0.9:1, respectively, Simner et al., 2006a). Compared to the estimated prevalence of synaesthesia, participants often reported that they had synaesthetes among their family members who in most cases was the mother and had the same type of synaesthesia as the participant. Although this lends further support to a genetic influence, associations with specific childhood memories were mentioned by six subjects. Reminiscent of a synaesthete who learned her colors from a toy (Witthoft and Winawer, 2006), they corroborate the assumption that particular synaesthetic associations are acquired through experience. Possibly, the particular inducer-concurrent pairings reflect early learning experiences in those who have a genetic predisposition for synaesthesia (Rich et al., 2005; Simner et al., 2009).

Our subjects' involvement in artistic and creative activities is consistent with the finding that around one fourth of the synaesthetes are artists or have artistic

professions (Cytowic, 1989, 26%; Domino, 1989, 23%; Rich et al., 2005, 24%). Interestingly, a relation between vividness of visual images associated with sound, and a tendency to enjoy and become involved in imaginative experiences has been reported by Rader and Tellegen (1987). Moreover, results from self-report scales and behavioral testing show that synaesthetes report more vivid imagery than controls (Barnett and Newell, 2008) and have stronger imagery skills at least for a grapheme based task (Spiller et al., 2008). Creativity mirrors the ability to form new combinations among things; in this, synaesthetes might profit from their richer perceptual repertoire.

	N	Female : Male	Synaesthesia prevalence (%)	Main Synaesthesia- type prevalence (%)	Method of recruitment/ data collection
Baron-Cohen et al. (1996)	22 S 6 NS	6.3 : 1	0.05	100 GC 40.9 MC 13.6 SC	newspaper advertisement
Rich et al. (2005)	192 S 50 NS	6.1 : 1	0.05	87 GC ~ 25 MC and SC	newspaper advertisement
Sagiv et al. (2006)	114 S 311 NS	3.5 : 1		87.7 GC 80 NF 14.2 LG	Internet
Simner et al. (2006a): 2 studies	22 S 478 NS; 13 S 1177 NS	1.1 : 1 0.9 : 1	4.4 1.1	72 GC 9 PC 4 PS	university students; museum visitors
Barnett et al. (2008a)	92 S 310 NS	6 : 1	23	45.3 GC 42 SP 18.7 MC 4.7 SC	Internet and newspaper advertisement

Table I. Prevalence data from surveys of synaesthesia. S= Synaesthetes; NS= Non-synaesthetes; GC= grapheme-color, MC= music-color; SC= sounds-color synaesthesia; PC=people-color synaesthesia; PS= people-smell synaesthesia; SP= spatial patterns for time units; NF= number-form synaesthesia; LG=lexical-gustatory synaesthesia.

Prevalence of Types of Synaesthesia

Although results from our study mostly agree with previous surveys based on larger samples, we also observed some striking differences in prevalence rates. GC synaesthesia was most often reported (86%): our prevalence estimate for this form of synaesthesia lies between that one of Baron-Cohen et al. (100%; 1996) and that one of Barnett et al. (45.3%; 2008a) (Table I). Unlike Baron-Cohen et al. (1996), we found color synaesthesia for digits to be more frequent than synaesthesia for letters and words. In addition, our data showed the majority of subjects responded to both auditory and visually presented graphemes and words. Although there is some evidence for phoneme-color synaesthesia being rarer than grapheme-color synaesthesia, with prevalence estimates of 7.4% vs. 63.5%, (Sean Day, <http://home.comcast.net/~sean.day/html/types.htm>), to our knowledge no survey reported on it. The 41% prevalence of colored-music synaesthesia in Baron-Cohen et al. (1996) coincides with ours and both are higher than the 25% and 18.7% reported by Rich et al. (2005) and Barnett et al. (2008a), respectively. However, the 33% of our sample who reported colored concurrents for natural and artificial sounds is higher than in other studies. Baron-Cohen et al. (1996) reported only 13% for auditory stimuli that excluded words and music, and Rich et al. (2005) found a rate of about 25% for music/sound synaesthesia in their 192 synaesthetes. Moreover, unlike Barnett et al. (2008a), who found that 42% of their 92 synaesthetes described spatial patterns for time-related words, we found 62% in our sample. Probably, the discrepancies reflect differences in sample size and composition as well as in subject

recruitment, and data collection methods - whether examples are presented, how questions are formulated - may play an additional role.

Rates of self-reported associators versus projectors, 90% vs. 10% in our sample, are more biased towards associators than those reported by Barnett et al. (72% vs. 12%; 2008a). Dixon et al. (2004) reported yet closer fractions (58% vs. 41%) for a sample of 12 subjects, and Van Leeuwen et al. (2010) classified their 21 GC-synaesthetes into six associators, seven projectors who experienced the color overlaid onto the graphemes, and eight 'mental screen' projectors who experience the color in external space but not in the vicinity of the graphemes. If the last group is counted among the associators (Ward et al., 2007), this group comes up to 67%. All together, these data account for a higher prevalence of associators among synaesthetes.

Inducer Modality and Properties

According to our synaesthetes' self-reports, the modality of the inducer (seen vs. heard) appeared to carry greater weight in music-color synaesthesia than in synaesthesia for words, letters and digits (Fig. 4). Seventy-one of the participants with synaesthesia for music perceived colors exclusively when listening to notes being played. People with synaesthesia for words, letters, and/or digits most often responded to both written and spoken stimuli (70%), while the heard-only and read-only fractions come in at up to 15%. Unfortunately, we do not know whether any, or how many, of our subjects with heard-only music synaesthesia could read music, thus limiting our conclusions concerning their inducer modality.

If a person cannot read music, the notes do not correspond to tones and may thus fail to elicit concurrents. Likewise, an illiterate synaesthete would probably not associate heard words and phonemes with written letters, and thus experience color only when hearing or speaking language. Also, reading music is often taught later than reading text, so that written notes may be learned too late to acquire the automaticity of synaesthetic concurrents. This could be tested among music-students who learned to read notes at a very young age. In the present sample, reported examples of musical inducers were exclusively instruments or tone-pitch. Not even a subject with absolute pitch named a note, suggesting that notes as such, and the concept of tones they represent, are comparatively unlikely inducers. Accordingly, De Thornley Head (2006) showed that synaesthetes consistently matched color with pitch, without interference from note-name information, even when the name was misleading.

If the age at which the child is exposed to the inducers is important in developmental synaesthesia, the format in which the inducers are more commonly encountered in early life would take priority over the one acquired later. Like notes, letters of languages such as Greek or Arabic would be less likely to induce colors in people who, like German pupils, learn Roman letters in kindergarten or elementary school, and foreign script in their teens, if at all. While this might increase the probability of 'heard-only' grapheme synaesthesia for foreign languages, their phonemes and the visual forms of their characters could still elicit concurrents as long as they resemble those of the familiar language(s) (Mills et al., 2002; Witthoft and Winawer, 2006). By analogy, written notations would need to be learned at a time in life where the new

format can easily be linked to a previously established auditory one. One would expect that corresponding phonemes and graphemes induce the same concurrents in those cases. Note that this was true in our sample for all subjects with heard-and-read synaesthesia for words, letters and digits.

An alternative explanation for these results is that the visual, acoustic and semantic levels of representation are intercalated in the synaesthetic process independent of the age the person learns to read and write. That the sound of a letter is accompanied by its visual and semantic representation in eliciting a concurrent is evidenced by Bargary et al. (2009) for phoneme-color synaesthesia and by Ward and Simner (2003) for phoneme-taste synaesthesia. In addition, Dixon et al. (2000) demonstrated that activating the concept of a digit by mental calculation was sufficient to induce the color relative to this digit in a subject with color synaesthesia for written digits. Together, these results hint at a connection among an inducer's visual, acoustic, and semantic level of representation. Further experimental testing and broader surveys are needed to shed more light on these issues.

Modalities of Synaesthesia

We found that intramodal visual and cross-modal auditory-visual synaesthesia were most prevalent. Whereas dense connections among visual areas might explain the high prevalence of intramodal visual synaesthesia, it is more difficult to explain the high frequency of auditory-visual or somatic-visual synaesthesia. Our findings suggest high unidirectional disinhibition/cross-modal connection between the

auditory and visual area as well as between the somatosensory and the visual area. Consistently, there is evidence that more than half of visually responsive neurons also respond to auditory and/or somatosensory stimuli (Macaluso, 2006). Projections from auditory parabelt regions to both V1 and V2 as well as direct inputs to peripheral V1 from the primary auditory cortex (Falchier et al., 2002; Rockland and Ojima, 2003) and somatosensory input to auditory association cortex have been found in the monkey (Schroeder et al., 2001). The high prevalence of specific cross-modal synaesthetic associations might therefore suggest that the synaesthetic associations track normal cross-modal anatomical pathways. It is unclear, however, why the visual modality appears to be the “preferred” site for concurrents both in cross-modal and intramodal synaesthesia. Possibly, the high differentiation of the visual system in neural sub-systems specialized in the processing of color, form, orientation, and movement offers a broader range of possibilities for cross-submodal as well as for cross-modal connectivity compared to other sensory systems.

Development and Stability of Synaesthesia

Both the concurrents’ occurrence and their intensity may vary across time. Our self-report data confirm previous findings (Rich et al., 2005) and show that even the type of inducer or the concurrent colors’ intensity was subject to change (11% and 33% respectively). Accordingly, in their 12-month longitudinal test on children, Simner et al. (2009) showed that synaesthetes acquired on average 6.4 new grapheme-color associations and proposed that a linear acquisition would predict that synaesthetes

will have acquired all 36 grapheme-color associations only by 10/11 years. These data not only account for changes in synaesthesia over time, but also show that changes might be detected only in specific time-windows in the life of a synaesthete. Although our data on variability of synaesthesia are not based on a follow-up, it is unlikely that changes may be detected by means of a consistency test few months apart from the first test: further specification of the age at which participants remember the changes to occur might help defining the time-window to look at when addressing variability issues in synaesthesia.

Moreover, some substances and mental/physical states (e.g. caffeine, fatigue) reportedly affect the perception of a concurrent. Such variations are incompatible with the notion that synaesthesia is completely stable over time and raises questions about the adequacy of the consistency test. This test assesses the genuineness of self-reported synaesthesia through the comparison of concurrents listed at two or more points separated in time by weeks or months, and is often regarded as the gold standard that distinguishes synaesthetes from non-synaesthetes. However, the consistency estimate for synaesthesia is commonly lower than 100%, and ranges between 73-100%. Rich et al. (2005) suggested that changes of the perceived color over time may explain the less-than-perfect consistency. Surely, variations of the color concurrents across consistency test and retest would not necessarily rule out that synaesthesia is authentic (Ward and Mattingley, 2006), and a synaesthete failing the test-retest could still pass a perceptual reality test (Proulx and Stoerig, 2006). Although high levels of consistency are desirable for particular studies, adhering to

a strict consistency criterion may exclude authentic synaesthetes from one's sample. Moreover, individuals with implicit synaesthesia, who report strong grapheme-color association but score in a medium range in the consistency test (Steven et al., 2004), will likely be neglected.

To preserve the anonymity of our respondents, we did not collect long-term consistency data for the larger part of our sample. Nevertheless, several observations support the veracity of the respondents' self-reports. Firstly, participants reported not only the form/s of their synaesthesia, but indicated the synaesthetic sensations evoked by items listed in the questionnaire, and reported specific examples of inducers and concurrents of their own. Secondly, all participants completed the questionnaire. Given that this required time and dedication, people with no authentic synaesthesia would probably have left it uncompleted. Finally, color concurrents, if not chosen from the color palette, were reported as detailed descriptions of complex colors. This agrees with what is typical of synaesthetes' color reports. Rather than using labels such as "blue" or "brown", they denote their color concurrents as "strong medium blue" (for number 5, participant 8), "inconspicuous weak brown" (for the word *pensioner*, participant 2), or "dark purple with yellow blobs" (for the word *January*, participant 2).

Conclusions

To conclude, our self-report data showed that the modality of the inducer plays an important role in eliciting a concurrent and that the latter predominantly depends on

specific visual and/or auditory features rather than the semantic value of the inducer. Cases linking the origin of synaesthesia to childhood experiences indicate that environmental factors might combine with a genetic predisposition in the induction of synaesthesia. The finding that synaesthetes can ignore or attenuate their synaesthetic perception challenges the presumed automaticity of synaesthesia and calls for objective evidence. The prevalence of auditory stimuli as inducers and of visual qualia as concurrents appears interesting in the light of the ontology and the neural basis of synaesthesia and may further inform neurocognitive models on synaesthesia. Finally, although based on time-point self-reports, our data question the stability of synaesthesia over time, an issue from which future research may benefit. The exclusion of low-consistency synaesthetes may result in a generalization of findings to a population which is actually more varied.

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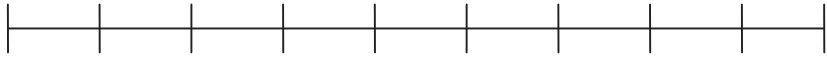
Supplementary material

Questions present in the questionnaire, which focused on the characteristics of the respondent's synaesthesia.

- Please describe your synaesthesia: Please include all the things that can generate your Synaesthesia and briefly describe your synaesthetic perception/s.

- Do these things always elicit synaesthesia?
 Yes No, not always (please describe when)

- Does the same synaesthetic trigger always induce the same experiences?
 Yes No (please describe)

- How intense is your current synaesthetic experience on a scale from 1 (very weak) to 10 (strong)?

1 2 3 4 5 6 7 8 9 10

- Are your synaesthetic experiences in the form of a perception (namely, you *actually see* colors while for ex. reading letters or hearing sounds) or do these impressions appear more associative in your "interior eye"?
 perception interior eye both

- Are your synaesthetic perceptions accompanied by special textures?
 No Yes, namely...

- Do your synaesthetic colors look like the colors of objects?
 Yes No, they are different because...

- When did your synaesthesia occur the first time?
 - I had it all my life
 - At the age of ...

- At what age did you learn that your sensory experience was actually synaesthesia?

- Has the intensity of your synaesthetic experiences changed over time?
 - No
 - it has become stronger
 - it has become weaker
 - other changes (Please describe)

- Has the range of stimuli which *trigger* your synaesthesia (noises, tastes, etc.) changed over time?
 - no change
 - it has become smaller
 - it has become larger within a same sensory modality (for ex. heard words → heard words and music)
 - it has spread to other senses (for ex., noises → noises and tastes)
 - other changes (please describe)

- If you have different forms of synaesthesia, how do you experience them?
 - simultaneously
 - separated
 - involuntarily varying
 - I can decide how

- Can you control your synaesthesia (can you stop or voluntarily elicit the synaesthetic perception)?
 - no
 - yes
 - other (please describe)

¹ Grapheme-color synaesthesia includes grapheme, phoneme, and lexical color synaesthesia unless otherwise specified.

Study 2

Perceptual and Conceptual ERP Components of Synaesthesia: a Cued-Congruency Task Applied to Grapheme-Colour Synaesthetes and Semantic Controls

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Abstract

In synaesthetes, stimulation of one sensory pathway provokes a concurrent sensory experience in a different sensory modality or sub-modality. Results of synaesthetic Stroop and priming tests indicate that the perception of a colour concurrent affects veridical colour processing in synaesthetes. We here examined stimulus-concurrent congruency both in grapheme-colour synaesthetes and in non-synaesthetes trained on grapheme-colour associations. Electrophysiological (EEG) and behavioural measurements were collected during a priming task that included grapheme-grapheme and grapheme-colour patch pairs. To investigate implicit bidirectional synaesthesia an additional inverted colour patch-grapheme condition was included. Both groups showed longer reaction time and more negative-going N400 and N300 event-related potential (ERP) components on incongruent trials. Whereas ERP-effects in the non-synaesthetes were largely confined to the late cognitive components N300, P300, and N400, the synaesthetes also showed faster and congruency-related perceptual effects (N170). Implicit bidirectional synaesthesia involved both early- and late-stage cognitive processes. Our results point to perceptual alterations in synaesthesia that go beyond associative learning.

Keywords: synaesthesia; grapheme; colour; congruency; ERP; bidirectionality; N170; N300; N400.

Introduction

In synaesthesia, stimulation of one sensory or cognitive stream leads to associated experiences in a second, unstimulated stream (Hubbard, 2007). An individual with grapheme-colour synaesthesia typically perceives a colour when reading, hearing and/or imagining an alphanumeric symbol or a word (the inducer). The colour, which is called concurrent, appears to affect the processing of the veridical colour, as repeatedly demonstrated by results at the synaesthetic Stroop test as well as priming tasks (Wollen and Ruggiero, 1983; Mills et al., 1999; Dixon et al., 2000; Mattingley et al., 2001; Palmeri et al., 2002; Smilek et al., 2002; Nikolic et al., 2007). However, whether the concurrent colours are a perceptual phenomenon is still a matter of discussion (Robertson, 2003; Gheri et al., 2008). Evidence favouring the perceptual nature comes from behavioural (Ramachandran and Hubbard, 2001; Smilek et al., 2001) and electrophysiological studies (Barnett et al., 2008; Beeli et al., 2008). While Barnett et al. (2008) showed enhanced C1 and P1 components in synaesthetes compared to controls in response to stimuli with high spatial frequency and high contrast respectively, Beeli et al. (2008) reported longer latencies and lower amplitudes of the auditory evoked potentials N1 and P2 in synaesthetes. Two case studies (Sagiv and Ward, 2006; Cohen Kadosh et al., 2007) and a group study of grapheme-colour synaesthetes showed early congruency effects (Brang et al., 2011). However, a colour priming study reported no N170 effect (Gebuis et al., 2009).

Moreover, non-synaesthetes who were trained on associations between colour labels and uncoloured polygons (MacLeod and Dunbar, 1988) or alphabetic stimuli (Meier

and Rothen, 2009) showed priming effects resembling those of the synaesthetes. Up to now, only Brang et al. (2011) investigated the electrophysiological correlates of congruency violation both in synaesthetes and in trained controls. Their results showed increased amplitudes of the N400, a component that signals semantic violations (Kutas and Hillyard, 1984) and accompanies both linguistic and non linguistic processing as long as the material is meaningful (Barrett et al., 1988; Orgs et al., 2008; Sitnikova et al., 2008; Cornejo et al., 2009; Proverbio and Riva, 2009). Brang et al. (2011) also reported increased N300 amplitudes on non-congruent trials; however, this effect varied across the different experimental paradigms and was restricted to a particular group of their trained controls. Unlike the N400 that increases with semantic *violation*, the N300 presumably indexes suppression as a function of meeting semantic *expectation* (Hamm et al., 2002; Franklin et al., 2007). Indeed, Brang et al. (2011) found an N300 effect in trained controls during an explicit visualization task likely to enhance expectation.

To further specify the neural mechanisms of synaesthesia, we recorded the EEG of 7 grapheme-colour synaesthetes and 7 non-synaesthetes trained to memorize specific grapheme-colour associations. Differently from Brang et al. (2011), who used a single training session, we trained our synaesthetes for six days. Moreover, we reduced the context. Instead of sentences leading up to the crucial colour word (Brang et al., 2008), we presented a black grapheme that served as cue to induce semantic expectation in two of our three experimental conditions. The black grapheme was followed by a briefly presented coloured grapheme (grapheme-grapheme condition)

or colour patch (grapheme-patch condition); their colour was as often congruent as incongruent to the synaesthetic or associated colour of the grapheme. These two conditions roughly mimicked a perceptual variability of colour concurrents among synaesthetes, as some report the colour concurrent as laying on the grapheme, while others describe it as a floating patch (Rich and Mattingley, 2002).

By means of a third condition, which involved a coloured patch as a cue and a black grapheme as a target, we aimed at investigating bidirectionality in synaesthesia. Cohen Kadosh et al. (2007) demonstrated that colour activated the number form area in the fusiform gyrus of a grapheme-colour synaesthete who reported overt bidirectional synaesthesia. Covert co-activation of digits by colours in synaesthetes has been shown with electrophysiological and behavioural measurements (Knoch et al., 2005; Gebuis et al., 2009; Weiss et al., 2009), and elicits considerably smaller response time effects than explicit bidirectionality. To learn whether our synaesthete and non-synaesthete participants would show any behavioural and EEG evidence of 'inverted priming', the third condition was included.

Taken together, we here asked at which perceptual and cognitive processing level congruency effects occur in grapheme-colour synaesthetes and in individuals trained on grapheme-colour associations. We expected response times and late 'cognitive' ERP components to increase on incongruent trials in both groups, and wondered whether the early 'perceptual' N170 would discriminate synaesthesia from associative learning. By means of our third inverted patch condition disrupting the

expectation of the target without affecting prime-target congruency, we also tested whether the N300 and N400 component reflect distinct cognitive processes.

Methods

Participants

Seven grapheme-colour synaesthetes (all women) and 7 non-synaesthetes (6 women) participated in the study. Synaesthetes (mean age=40.7, SD=9.7) were significantly older than controls (mean age=25.4, SD=3.7; $t_{(12)}=3.85$, $p<0.01$) and described their grapheme-colour synaesthesia in our Internet Synaesthesia Questionnaire (<http://www.psych.uni-duesseldorf.de/abteilungen/ebp/forschung/syntest> 2009). No synaesthete reported colours to elicit association with graphemes, indicating that synaesthesia was explicitly unidirectional. An unprompted retest on an average of 30 graphemes (letters and digits) took place 6 months (SD=3.7) after the first test on the same Internet Website and a consistency score was calculated; in two cases, the Synaesthesia Battery (Eagleman et al., 2007) was used for the retest. . In line with previous reports (Baron-Cohen et al., 1993), average consistency was 90% (SD=6%). Three synaesthetes were projectors, as they described the colour as appearing near the grapheme or between their head and the stimulus, and 4 were associators, who reported the colours to appear in their “mind’s eye” (Dixon et al., 2004). All subjects had normal or corrected to normal vision and were right-handed (self reported handedness). They provided written informed consent prior to EEG and received either financial compensation or university credits for their participation. The study

was approved by the local Ethics Committee of the Heinrich-Heine-University of Düsseldorf, in accordance with the Declaration of Helsinki.

Training procedure for control subjects

Control subjects were trained on associations between specific colours and an average of 30 graphemes consisting of different alphabetic letters and digits from 1 to 9. Types and number of the grapheme-colour pairs used to train the non-synaesthetes corresponded to those of four synaesthetes. Subjects daily practised these associations at home on each of six days with a computer program that presented all correct grapheme-colour associations followed by three exercises. In the first, a grapheme was surrounded by three randomly located colour patches, and subjects had to choose the correct patch for the grapheme. In the second, 4 graphemes and 4 colour patches were presented in one slide, and subjects had to assign the correct colour to each grapheme. In the last exercise, the procedure was inverted. Participants only saw colour patches and had to report the associated grapheme/s. Correct and incorrect colours came from the same sample and were easily distinguishable. Each exercise included all grapheme-colour pairs and exercise solutions. Participants were asked to report the start and end time of training and the number of incorrect or missing answers. To ensure that the training had been accomplished, prior to EEG recording control subjects were tested on one exercise and were allowed to proceed only if the error rate was less than 20% of the total grapheme stimuli.

Materials and Procedure

We used three experimental conditions that varied the role of graphemes and colours as prime and target stimuli, respectively. In the first, the grapheme-grapheme (G) condition, a black grapheme preceded the presentation of the same grapheme in colour. The colour could be congruent or incongruent to the grapheme, depending on the inducer-concurrent associations of synaesthetes and the grapheme-colour associations learned by controls. This condition allowed us to control for stimulus shape. In the second, the grapheme-patch (GP) condition, the prime was again a black grapheme, but the target was a colour patch. To investigate bidirectional synaesthesia, a colour patch served as a prime and a black grapheme as a target in a third inverse-patch (IP) condition. The paradigms are schematically represented in Fig. 1. The order in which they were presented was counterbalanced within each group. Depending on how many graphemes elicited synaesthesia, an average of 120 stimuli (range 92-144) was equally divided between the congruent and the incongruent condition of each paradigm. Prime-target pairs were randomized. Each grapheme occurred twice in the congruent and twice in the incongruent condition. To avoid induction of new associations, incongruent colours were paired only once with the same grapheme. The same colours were used in congruent and incongruent conditions, balancing the total luminance between conditions.

During testing, participants were seated comfortably in a shielded room and viewed a computer screen (Mitsubishi) that subtended 14.4 by 10.6° at a distance of about 160 cm. Grapheme stimuli measured 3.6 (on average) by 2.9°, and patch stimuli were 3.9

by 3.9°. Stimuli were presented in the centre of a grey background (59.2 cd/m²). Each trial began with the presentation of a grey background that lasted for 2.5-3 s. No fixation cross was used, as it elicited colour concurrents in some synaesthetes and might have affected the results. A 1,000 ms prime stimulus then appeared in the centre of the screen. After an interstimulus interval of 400 ms, a target stimulus was presented for 200 ms. Subjects were asked to respond as soon as possible, by pressing a button with the left index finger when the target did not match the prime and another button with the right index finger when the target matched the prime. The response time window ended 1,300 ms after stimulus onset. The intertrial interval varied between 2.5-3 s, independent from reaction time. Stimuli were presented using Presentation[®] software (Neurobehavioural Systems, <http://www.nbs.neurobs.com/>). Participants were instructed to refrain from blinking until sometime after pressing a button. To ensure that the task was clear and to train subjects on the control of the blinks, 8 practice trials were given before each paradigm.

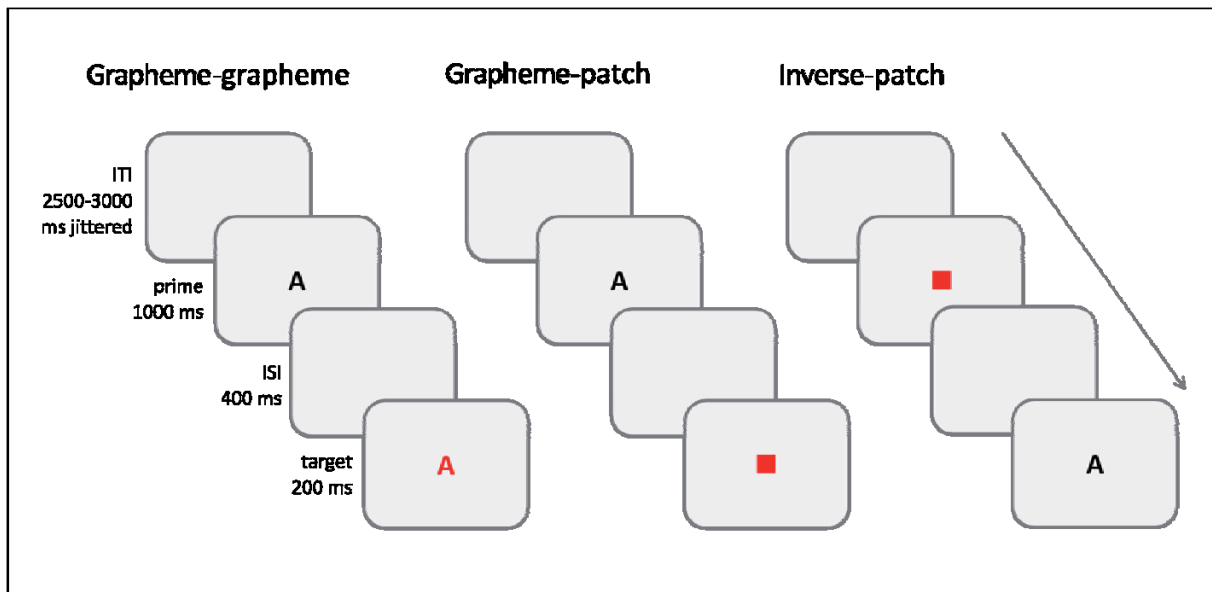


Fig. 1. Schematic representation of the 3 experimental conditions. The colour of target stimuli in the grapheme-grapheme and grapheme-patch condition could be either congruent or incongruent with the prime, according to inducer-concurrent associations of synaesthetes as well as to grapheme-colour pairs learned by controls. In the inverse-patch condition, the prime consisted in a colour patch and the target was a black grapheme, which could be congruent or incongruent with the prime.

Behavioural analysis

Repeated measures ANOVA with the between-subject factor Group (2 levels, synaesthetes and trained non-synaesthetes), and the within-subjects factor of Condition (3 levels, G, GP, and IP) and Congruency (2 levels, congruent and incongruent) were applied to reaction time and accuracy. Outliers (± 2 SD from the subject and condition mean) were calculated separately for congruent and incongruent trials and excluded from analysis.

EEG recording

The EEG of the participants was continuously recorded with Ag/AgCl electrodes placed on an electrode cap (Easy Cap) with 47 scalp sites arranged according to the International 10-20 system. Horizontal eye movements were measured with two

electrodes (bipolar) placed at the outer canthi. Vertical eye movements and blinks were monitored with two electrodes (bipolar), one above and one below the right eye. All electrodes were average-referenced online. Impedances were below 6 Ω . The EEG had a band pass from 0.03 to 250 Hz and was amplified with Brain Products (<http://www.brainproducts.com>) QuickAmp amplifier 72-channels, digitized at 1,000 Hz and stored on a computer hard disk.

ERP analysis

ERPs were time-locked to the onset of the target stimulus. After global trend correction, raw data were filtered with a band-pass filter between 0.5 and 30 Hz, and re-referenced to linked mastoids (electrodes TP9 and TP10). Epochs included the signal from 200 ms to 1,000 ms around the target stimulus; the 200 ms period preceding the stimulus onset served as a baseline. Following artifact rejection and ocular correction according to the algorithm of Gratton, Coles & Donchin (1983), segments were created for congruent and incongruent conditions and averaged accordingly. Incorrect responses were excluded from analysis. Artifact rejection resulted in the elimination of an average of 4.2% of segments for the synaesthetes and 10.4% for trained non-synaesthetes ($F_{(1,12)} = 2.81$, $p=0.119$). We analysed peak latency for the N170 component on a pool of electrodes including PO3, POz, PO4, O1, Oz and O2. Mean amplitude differences were calculated for 3 contiguous time windows for each participant based on visual inspection of the grand average. The first, from 150 to 200 ms post stimulus onset, targeted the N170, the second, 200 to

320 ms, the N300, and the third, 320 to 420 ms, the N400. The mean amplitude analyses of the N170 were performed separately for electrodes CP3, CPz, CP4, P3, Pz, P4, O1, Oz and O2. N300 and N400 analyses included the following sites that were not pooled: F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, PO9, O1, Oz, O2, PO10. Data from the three paradigms were subjected to separate repeated measures ANOVAs with the between subject factor Group (2, synaesthetes and trained non-synaesthetes), and the within subject factors Condition (3, G, GP, IP), Congruency (2, congruent and incongruent), Electrodes Position indicating Anteriority (4, frontal, central, parietal, occipital) and Laterality (5, lateral right and left, medial right and left, central). If an interaction between electrode site/s and another factor was significant, further ANOVAs were performed for each electrode group separately and *t*-tests corrected for multiple comparisons were applied for *post-hoc* testing (see Supplemental material). For all analyses, original degrees of freedom are reported; however, where appropriate, *p* values were subjected to Greenhouse-Geisser correction (Greenhouse and Geisser, 1959).

Results

Behavioural Results

Training forms returned by 5 subjects indicated that their daily training lasted 18 min on average (SD=4.6), and resulted in a significant decrease in the number of errors/misses between the first and the last training day ($t_{(4)}=2.62$, $p<0.05$); the average error rate was 4.3% (~1.4 graphemes) on the last day. Two subjects failed to

return the training form. All subjects reached criterion in the test session preceding the EEG recording.

The overall analysis of response times (RTs) showed a significant main effect of Condition, with significantly longer reaction time in the IP than in the other two conditions ($F_{(2,24)}=7.02, p<0.01$; contrast IP-G: $F_{(1,12)}=15.24, p<0.01$; contrast IP-GP: $F_{(1,12)}=5.77, p<0.05$). A significant interaction Condition \times Congruency ($F_{(2,24)}=3.61, p<0.05$) and Condition \times Congruency \times Group ($F_{(2,24)}=4.30, p<0.05$) emerged. Follow-up analysis was conducted on the different paradigms separately. In the G and GP condition RTs were prolonged for incongruent compared to congruent colours (G: $F_{(1,12)}=23.77, p<0.001$; GP: $F_{(1,12)}=20.00, p=0.001$). In the G condition, synaesthetes and controls showed similar reaction times ($F_{(1,12)}=1.81, p=0.20$), but controls showed a trend toward significantly shorter reaction time than synaesthetes in the GP condition ($F_{(1,12)}=3.51, p=0.08$); possibly, the exclusive use of colour patches in the training procedure familiarized controls with this particular colour representation. Interestingly, in the IP condition we also found a significant main effect of Congruency ($F_{(1,12)}=32.81, p<0.001$) due to longer RTs on incongruent trials as well as a Group \times Congruency interaction ($F_{(1,12)}=4.69, p=0.05$). A *post-hoc* analysis showed a congruency effect both for synaesthetes ($t_{(6)}=-2.92, p=0.02$) and controls ($t_{(6)}=-4.97, p<0.02$). Mean reaction time of synaesthetes and controls in the 3 paradigms are shown in Fig. 2. Accuracy differed neither between groups ($F_{(1,12)}=1.51, p=0.21$) nor paradigms ($F_{(2,24)}=1.61, p=0.22$), and no interaction of Group \times Accuracy ($F_{(2,24)}=1.29, p=0.29$) was found.

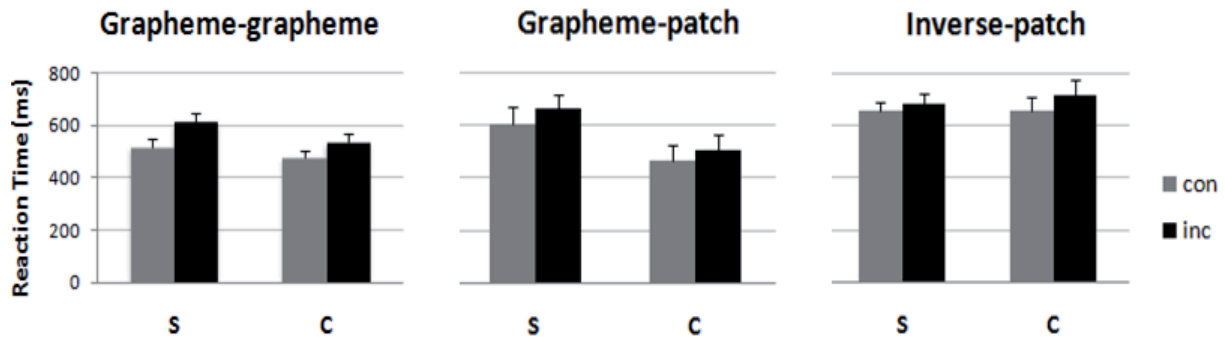


Fig. 2. Mean reaction time and standard error of the mean of synaesthetes (S) and trained controls (C) in the congruent (con) and incongruent (inc) condition of the cued-congruency task in the 3 paradigms.

EEG Results

ANOVA on the N170 peak latency across paradigms resulted in a main effect of Group ($F_{(1,12)}=4.62, p=0.05$). ANOVA on mean amplitudes on the 150-200 ms time-window showed two significant interactions, namely Group \times Congruency in the G condition ($F_{(1,12)}=22.02, p<0.01$) and Group \times Congruency \times Laterality in the GP condition ($F_{(2,24)}=5.22, p<0.05$).

Separate ANOVAs on the 200-320 and the 320-420 time-window chosen for the N300 and N400 respectively, showed significant interactions Congruency \times Position, Congruency \times Laterality and Congruency \times Position \times Laterality (Table I). The factor Group was involved in one significant Position \times Group interaction in the 320-420 time-window in the GP condition only ($F_{(3,36)}=4.12, p<0.05$). Results from follow-up analyses are hereafter reported for the N170, N300, and N400 components separately.

	N300			N400		
Conditions	G	GP	IP	G	GP	IP
<i>Congruency</i>	$F_{(1,12)} = 25.21^{* **}$	$F_{(1,12)} = 1.34$ n.s.	$F_{(1,12)} = 0.09$ n.s.	$F_{(1,12)} = 1.34$ n.s.	$F_{(1,12)} = 1.37$ n.s.	$F_{(1,12)} = 16.34^{**}$
<i>Congruency</i> <i>x Position</i>	$F_{(3,36)} = 9.80^{**}$	$F_{(3,36)} = 17.71^{**}$	$F_{(3,36)} = 0.55$ n.s.	$F_{(3,36)} = 17.71^{**}$	$F_{(3,36)} = 19.69^{***}$	$F_{(3,36)} = 3.73^*$
<i>Congruency</i> <i>x Laterality</i>	$F_{(4,48)} = 26.68^{***}$	$F_{(4,48)} = 4.79^*$	$F_{(4,48)} = 2.46$ n.s.	$F_{(4,48)} = 4.79^*$	$F_{(4,48)} = 2.16$ n.s.	$F_{(4,48)} = 14.60^{***}$
<i>Position</i> <i>x Laterality</i> <i>x Congruency</i>	$F_{(12,144)} = 4.33^{**}$	$F_{(12,144)} = 3.25^{**}$	$F_{(12,144)} = 1.79$ n.s.	$F_{(12,144)} = 3.25^{**}$	$F_{(12,144)} = 5.49^{***}$	$F_{(12,144)} = 2.21$ n.s.
<i>Group</i> <i>Anteriority</i>	$F_{(3,36)} = 3.32$ n.s.	$F_{(3,36)} = 2.38$ n.s.	$F_{(3,36)} = 4.21$ n.s.	$F_{(3,36)} = 1.95$ n.s.	$F_{(3,36)} = 4.12^*$	$F_{(3,36)} = 3.14$ n.s.
<i>Group</i> <i>Congruency</i>	$F_{(1,12)} = 0.25$ n.s.	$F_{(1,12)} = 1.69$ n.s.	$F_{(1,12)} = 1.33$ n.s.	$F_{(1,12)} = 3.69$ n.s.	$F_{(1,12)} = 1.63$ n.s.	$F_{(1,12)} = 0.00$ n.s.
<i>Amplitude</i> <i>difference</i> <i>S (μV)</i>	-1.72	-1.52	-0.10	-1.16	-0.67	-1.01
<i>Amplitude</i> <i>difference</i> <i>C (μV)</i>	-1.30	-2.99	-0.19	-1.36	-2.30	-1.45

Table I. Results from ANOVAs (top rows) and mean amplitude difference between the incongruent and the congruent condition for synaesthetes (S) and controls (C) (bottom rows). Results for the N300 and N400 components are shown separately for each experimental condition. G = Grapheme-grapheme; GP = Grapheme-patch; IP = Inverse patch. n.s. = non significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

N170

The peak latency of the N170 was significantly shorter in synaesthetes than controls both in the G ($F_{(1,12)} = 6.07$, $p = 0.03$) and the IP paradigm ($F_{(1,12)} = 4.89$, $p < 0.05$) (Fig. 3).

While synaesthetes showed an averaged peak latency of 133 ms in G and 129 in IP, the controls' means were 155 and 149 respectively. Separate analysis of the effect of

congruency for the two groups in the 150-200 ms time-window revealed a significant Congruency effect in synaesthetes in G ($F_{(1,6)}=59.18, p<0.001$) and IP conditions ($F_{(1,6)}=9.40, p<0.05$), but not controls (G: $F_{(1,6)}=0.82, p=0.40$; IP: $F_{(1,6)}=0.64, p=0.45$). No group difference emerged in GP ($F_{(1,12)}=2.10, p=0.17$). Moreover, in GP the congruency effect did not reach significance in synaesthetes ($F_{(1,6)}=4.43, p=0.08$) and was absent in controls ($F_{(1,6)}=0.75, p=0.42$).

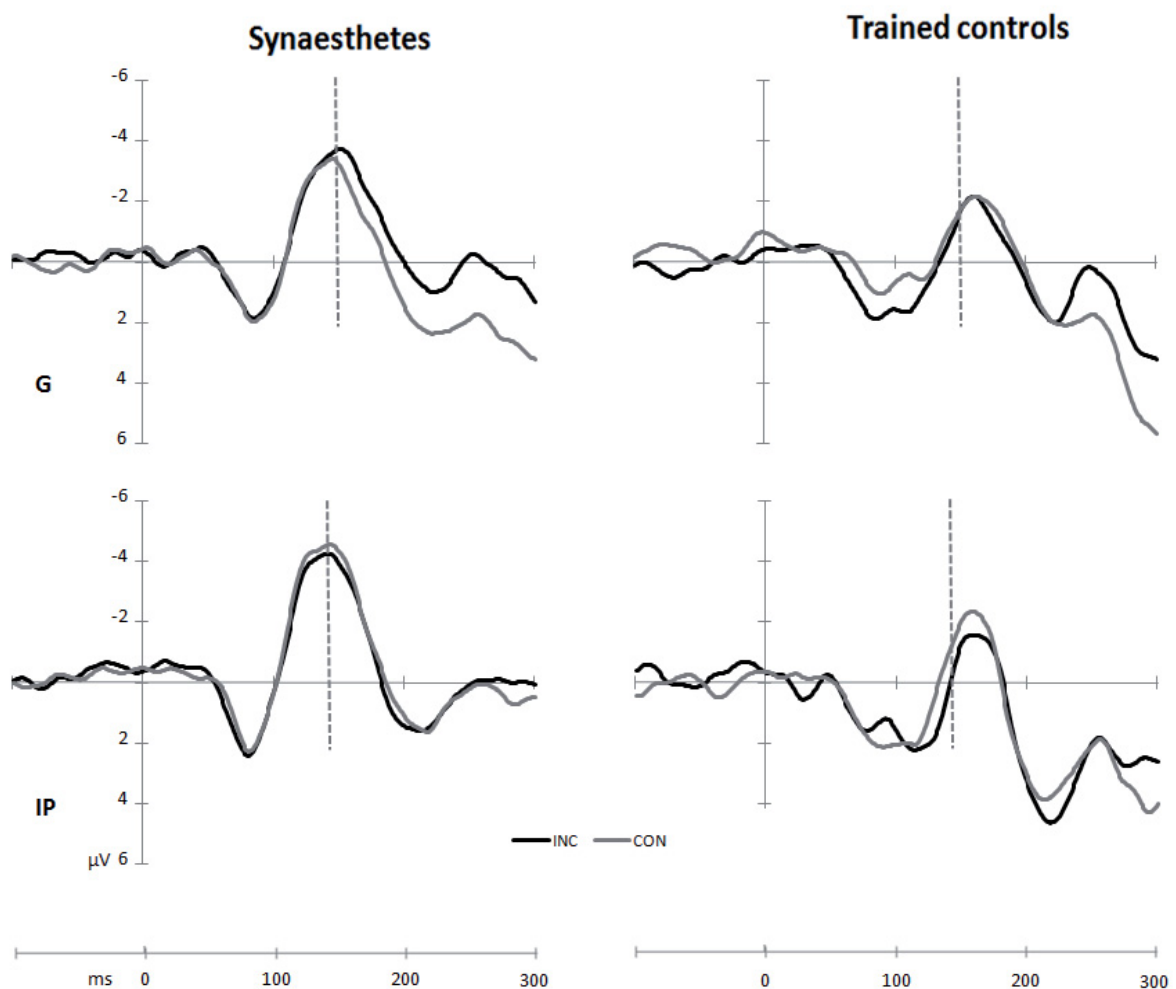


Fig. 3. Grand average ERPs representing mean responses of a parieto-occipital pool of electrodes including PO3, POz, PO4, O1, Oz, and O2 in the Grapheme-grapheme (G) and Inverse-patch (IP) paradigm. The dashed lines represent the synaesthetes' N170 peak and are plotted onto the control group's ERP to illustrate their later peak.

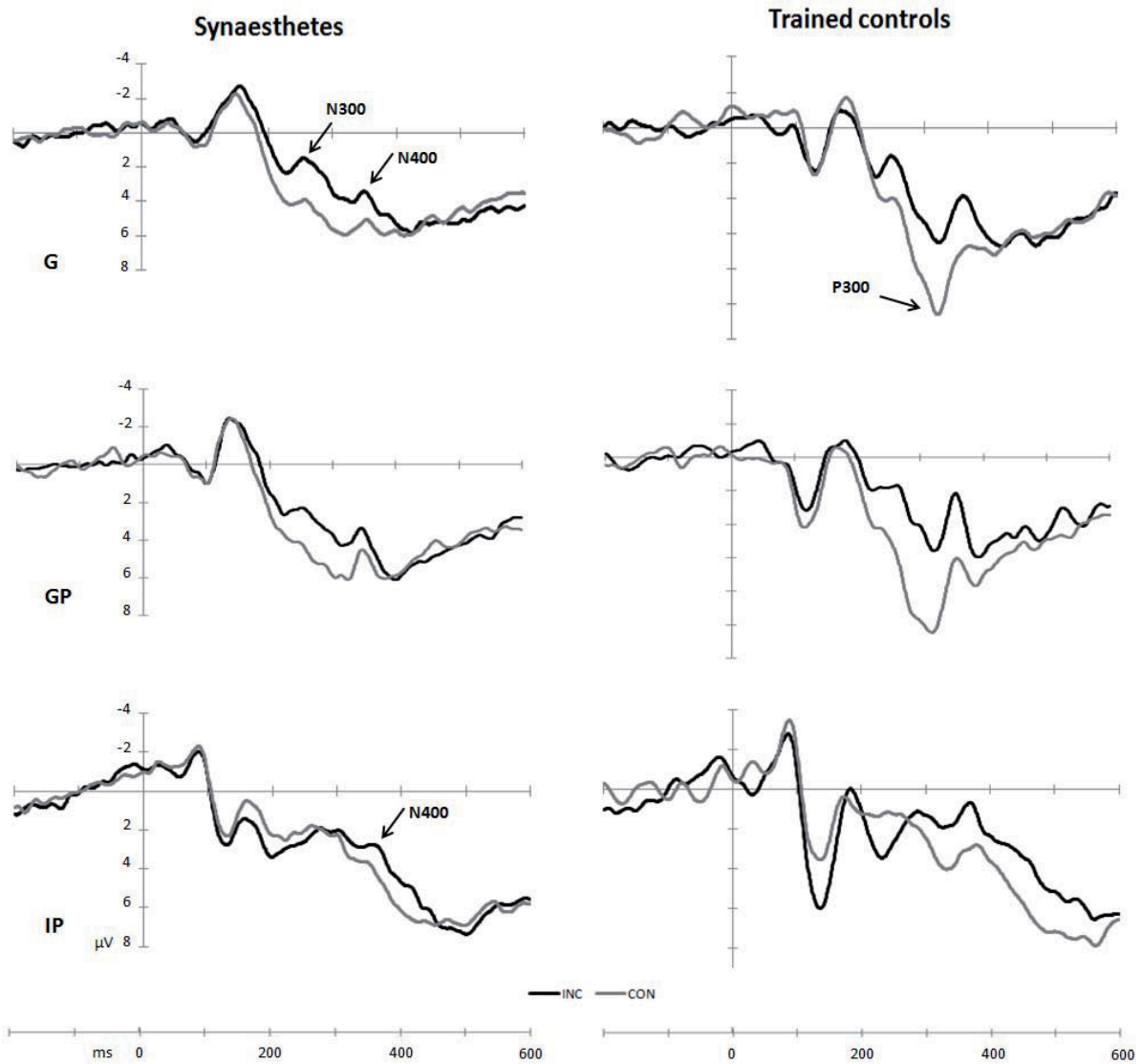


Fig. 4. Grand average ERPs from POz of synaesthetes and trained controls in the congruent (CON) and incongruent (INC) condition in the 3 paradigms Grapheme-grapheme (G), Grapheme-patch (GP) and Inverse-patch (IP). The N300-N400 biphasic negativity is visible in G and GP, but in IP the N300 effect of congruency is no longer visible. Compared to synaesthetes, controls show larger P300 amplitudes in the congruent condition of the G and GP paradigms.

N300

Follow-up repeated measures ANOVAs showed a significant main effect of Congruency in the 200-320 ms time-window (Fig. 4). In both G and GP condition, the incongruent condition elicited a more negative N300 component than the congruent condition, at central (G: $F_{(1,12)}=21.45$, $p<0.01$; GP: $F_{(1,12)}=5.34$, $p<0.05$), parietal (G:

$F_{(1,12)}=24.57, p<0.001$; GP: $F_{(1,12)}=14.33, p<0.01$) and occipital sites (G: $F_{(1,12)}=9.24, p<0.05$; GP: $F_{(1,12)}=8.99, p<0.05$). The interaction Congruency \times Laterality was significant at central (G: $F_{(4,48)}=18.38, p<0.001$; GP: $F_{(4,48)}=13.78, p<0.001$), parietal (G: $F_{(4,48)}=5.68, p<0.01$; GP: $F_{(4,48)}=4.75, p<0.05$), and at occipital sites (G: $F_{(4,48)}=3.15, p=0.05$; GP: $F_{(4,48)}=2.80, p=0.07$), with larger congruency effects over the right hemisphere than on the left one. In the IP condition, no main effect of Congruency was found in the 200-320 time-window at different Position levels, but a significant interaction Congruency \times Laterality emerged at central ($F_{(4,48)}=3.15, p<0.05$) and parietal sites ($F_{(4,48)}=3.34, p<0.05$).

N400

A main effect of Congruency was also observed in the 320-420 ms time-window in all conditions at parietal (G: $F_{(1,12)}=20.34, p<0.01$; GP: $F_{(1,12)}=6.12, p<0.05$; IP: $F_{(1,12)}=27.19, p<0.001$) and occipital sites (G: $F_{(1,12)}=4.12, p=0.06$; GP: $F_{(1,12)}=7.70, p<0.05$; IP: $F_{(1,12)}=4.83, p<0.05$). In the IP condition the N400 effect emerged also at central sites ($F_{(1,12)}=9.41, p<0.05$). Significant interactions of Congruency \times Laterality were again observed at central sites in all conditions (G: $F_{(4,48)}=4.77, p<0.01$; GP: $F_{(4,48)}=4.17, p<0.05$; IP: $F_{(4,48)}=10.40, p<0.001$). In G and IP the N400 effect was also present at parietal (G: $F_{(4,48)}=2.44, p=0.05$; IP: $F_{(4,48)}=10.70, p<0.001$), and occipital sites (G: $F_{(4,48)}=3.37, p=0.05$; IP: $F_{(4,48)}=5.94, p<0.01$). Both synaesthetes and controls showed larger congruency effects over the right hemisphere. The N400 and N300 effects and amplitudes for the two groups are depicted in Fig. 4.

Discussion

Summary

The present study investigated processing of the congruency of colour-grapheme associations in synaesthetes and trained controls, to determine to what degree learned grapheme-colour associations resemble those of grapheme-colour synaesthetes.

Results show that incongruent grapheme-colour pairs induced a semantic violation in synaesthetes as well as trained controls. Both longer reaction time and more pronounced N400 and N300 components were observed when the colour of a grapheme did not match its synaesthetic or associated colour. Behavioural results agree with those from previous studies on synaesthetes (Mattingley et al., 2001; Palmeri et al., 2002; Nikolic et al., 2007) and extend the finding of similar group performance (van Leeuwen et al., 2010) to trained controls. However, synaesthetes showed faster processing and higher susceptibility to grapheme-colour congruency, as indicated by the reduced latency and the mean amplitude congruency effect of the early sensory N170 ERP component. Moreover, early-stage cognitive processes may play a role in bidirectional synaesthesia and possibly in the differentiation between associator and projector synaesthetes.

Differences between synaesthetes and trained controls

Congruency modulated the N170 component in synaesthetes, but not in trained controls. That synaesthetes in the present study were substantially older than

controls renders this finding particularly interesting, as aging induces a delay of the N170 component for faces and letters (Deiber et al., 2010).

In the G condition, the congruency effect consisted in a more negative-going N170 in congruent trials, and in the IP condition, the pattern was reversed so that incongruent trials evoked more pronounced N170 amplitude. Results from the G condition agree with those from the comparable condition in a previous study on grapheme-colour synaesthetes and trained controls (Brang et al., 2011). Cohen Kadosh et al. (2007) also found a N170 congruency effect in a synaesthete, but not naive controls, who attended to coloured stimuli during a modified Stroop test.

The N170, which is assumed to reflect orthographic processing (Bentin et al., 1999) appears to be modulated by colour congruency, indicating that synaesthetes' processing of 'synaesthetic' and 'physical' colour affects grapheme encoding at early processing stages. As proposed by Sagiv and Ward (2006), the congruently coloured letter may be easier to categorize and therefore enhance the N170. Remarkably, the present and a previous study (Brang et al., 2011) show that the N170 mean amplitude congruency effect in synaesthetes does not reach statistical significance when the target stimulus is a colour patch. In addition, the peak latency of the N170 component is similar between groups in the GP condition. These findings suggest that both perceptual colour competition of incongruent pairs and faster processing of congruent pairs occur when synaesthetes visually perceive alphanumeric stimuli and that these processes are related to letter categorization.

An alternative explanation for the early mean amplitude congruency effect exclusively shown by synaesthetes regards their high expertise with grapheme-colours. Tanaka et al. (2001) reported on a N170 component which was distributed similarly to ours and larger when experts categorized objects within rather than outside their domain of expertise. Synaesthetes normally report experiencing their inducer-concurrent associations all their life long and are very selective as for the exact nuance of the colour concurrent. Their higher expertise with the correct grapheme-colour association compared to controls may therefore be responsible for the early congruency effect.

Group differences in brain responses were not restricted to early processing, but emerged also around 300 ms after stimulus onset in the congruent condition of G and GP (Fig. 4). In addition to the N300 and N400 effects that we here primarily addressed, trained controls generated a pronounced P300 in congruent trials which is completely absent in synaesthetes. Mean amplitudes in a 300-340 time-window revealed a slight interaction between Group and Congruency in the G condition ($F_{(1,12)}=4.09, p=0.06$). It reflected a significant group difference with controls showing larger P300 than synaesthetes on congruent ($t_{(12)}=-2.58, p<0.03$) but not incongruent trials ($t_{(12)}=-1.75, p=0.10$). Similarly, a group difference was observed for congruent ($t_{(12)}=-2.29, p<0.05$) but not incongruent trials ($t_{(12)}=-0.84, p=0.41$) in the GP paradigm. The presence of a P300 in trained controls indicates strong engagement of explicit memory processes and suggests different neural mechanism in synaesthesia and associative learning.

Similarities between synaesthetes and trained controls

The lack of a group difference in the 300-340 ms time-window on incongruent trials may be due to the novelty of incongruent grapheme-colour associations both for synaesthetes and trained controls. Indeed, no group difference emerged in the IP condition, which was high load for both groups regardless of congruency, as indicated by the longer reaction time and latency of the P300. As task difficulty increased, the pattern of activation of synaesthetes increasingly resembled that of controls. Similar parietal P300 amplitudes for synaesthetes and controls were found by Schiltz et al. (1999) in an oddball paradigm that used letters and numbers as stimuli. The concurrent colour perception for their synaesthetes was unrelated to the target status of a stimulus. Analogously, in the incongruent condition in our study, inducer and concurrent were unrelated. This equally applied to synaesthetes and controls and may have resulted in similar patterns of P300 activation between groups.

Other late-stage components, the N300 and the N400, also showed a similarity between groups. The N300 mean amplitude effect indicates that electrophysiological components preceding the N400 reflect the interference elicited by incongruent grapheme-colour pairs. However, the disappearance of the N300, but not the N400 effect, in the IP condition suggests that different cognitive processes are related to these two components. In the IP condition, the target was equivocal, as one colour prime could be associated with more than one grapheme. This probably weakened target expectancy in a manner that abolished the N300. Conversely, Brang et al.

(2011) found an N300 effect in trained controls who executed an explicit visualization task likely to enhance the expectation. The N300 effect therefore appears related to semantic expectation rather than violation (Hamm et al., 2002; Franklin et al., 2007). The presence of a N300 mean amplitude effect in our two subjects groups and in the explicit visualization control group of Brang et al.'s (2011) study suggests that both synaesthesia and associative learning access imagistic representation. As proposed by McPherson and Holcomb (1999), the N300 may reflect a process similar to that of the N400, but specific to object or imagistic representations. It is possible that in synaesthesia and associative learning the presentation of an alphanumeric stimulus or a colour activates imagery processes related to the associated stimulus. Indeed, partially overlapping neural paths for synaesthesia and visual imagery have been reported (Rich et al., 2006).

The N400 mean amplitude effect shown by synaesthetes supports our hypothesis that synaesthetic associations are semantically processed. The significant interaction Congruency x Laterality reflected a larger N400 congruency effect over the right hemisphere. Possibly, the interaction at central sites depended on the readiness potential. Subjects responded to incongruent stimuli with the left hand, so that a contralateral negative potential would be expected. However, the congruency effect was also present at right parietal and occipital sites, displaying a distribution typical of N400 topography. A right-hemispheric bias of the N400 effect over centro-parietal sites for written words in sentences has been acknowledged (Kutas and Federmeier, 2011) and recently extended to auditory stimuli (Groppe et al., 2010). Moreover, our

findings agree with previous evidence showing a slight right-hemispheric negative activation at centro-parietal sites during a congruency test with a colour patch target in synaesthetes (Gebuis et al., 2009; Brang et al., 2011). Differently from Brang et al. (2011), who reported group differences in the distribution pattern in their graphemes condition (comparable to our G condition), our groups showed similar N400 topography both when lexical and non-lexical stimuli were used. Although colored patches were used in both trainings, different training duration and procedures might explain this discrepancy. Brang et al.'s (2011) controls were trained on 10 grapheme-colour pairs for 15 minutes. Our more extensive and variegated training may have shaped the semantic system of our controls more successfully, thus giving rise to similar N400 patterns between groups. This finding does not necessarily imply that synaesthetic associations are learned, but suggests that synaesthesia and associative learning rely on partially similar neural substrates.

Bidirectionality

In the IP condition, synaesthetes but not controls showed a congruency effect in the amplitude of the N170. In agreement with prior results (Gebuis et al., 2009), this finding invokes the possibility of covert bidirectional synaesthesia that engages early sensory in addition to semantic processes. In a combined ERP and functional magnetic resonance (fMRI) study of a synaesthete with explicitly bidirectional grapheme-colour synaesthesia, Cohen Kadosh et al. (2007) provided evidence for

colour automatically activating the number form area even though no digits were presented.

The N400 effect our synaesthetes show in the GP and IP conditions implies that the two directions of information flow between inducer and concurrent share semantic processes. Because controls trained on the inverted colour-grapheme pairs showed similar late ERP components as synaesthetes, the N400 effect found in synaesthetes may be related to knowledge or memory recall of grapheme-colour associations in both groups. This result together with group differences at earlier stage of processing indicates similar neural mechanisms which subserve both directions. As yet bidirectional synaesthesia has not been integrated in any neurocognitive theory on the neural mechanisms of synaesthesia.

Synaesthete subtypes

A distinction between projector synaesthetes, who report experiencing their photisms in external space, and associator synaesthetes, who report experiencing their photisms “in the mind’s eye”, has been proposed (Dixon et al., 2004). Rouw and Scholte (2007; 2010) as well as Van Leeuwen et al. (2010; 2011) suggest that these experiential differences map onto differences in connectivity and functional neuranatomy. According to Rouw and Scholte (2007), projectors have stronger hyperconnectivity in inferotemporal cortex and predominantly engage visual and auditory cortical regions (2010). Results of van Leeuwen et al. (2011) suggest that projectors engage functional subdivisions of the fusiform gyrus. In contrast, associators rely more on parietal regions implicated in binding (van Leeuwen et al.,

2010; 2011) respectively on more memory-related hippo- and parahippocampal structures (Rouw and Scholte, 2010). Although our synaesthetes' group is too small to allow any firm conclusions on subgroup differences, we compared their ERPs with a repeated measure ANOVA with between-subjects factor Subgroup (2 levels, associators and projectors) and the within-subjects factors Position, Laterality and Congruency as in the main analysis. An interaction of Position x Subgroup characterized all paradigms in the 150-200 ms time-window (G: $F_{(2,10)}=7.02, p<0.05$; GP: $F_{(2,10)}=5.91, p<0.05$; IP: $F_{(2,10)}=16.68, p<0.01$). This was due to an N170 enhancement at centro-parietal sites in projectors, but at occipital sites in associators. Although this result agrees with topographical differences between synaesthete subtypes, it cannot be mapped onto the candidate structures. Moreover, our projectors' response times did not differ from the associators' although Dixon et al. (2004) reported that projectors showed significantly larger benefits from congruency.

Conclusions

The present study provides behavioural and physiological evidence for similar semantic and dissimilar perceptual processes at work in synaesthesia and associative learning. Synaesthetes showed congruency-related and faster perceptual activation than non-synaesthetes who, as a consequence of training seemed to rely more on memory-related cognitive processes. However, both synaesthetes and trained controls processed the inducer semantically. While synaesthesia appears to invoke facilitatory perceptual as well as semantic cognitive processes, the training

modulated only the latter in our control participants. Evidence showing that increasing expertise with grapheme-colour associations eventually evokes early congruency effects and reduces the P300 amplitude in non-synaesthetes, would provide incontrovertible support for a hypothetical continuum between synaesthesia and normal cognition.

Acknowledgements

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Supplementary material

	N170	N300	N400
Grapheme-grapheme	P3 ($t_{(6)} = -6.24^{***}$)	Cz ($t_{(13)} = 6,09^{***}$)	P7 ($t_{(13)} = 5,41^{***}$)
	O1 ($t_{(6)} = -5.56^{***}$)	C4 ($t_{(13)} = 7,12^{***}$)	P3 ($t_{(13)} = 3,83^{**}$)
	Oz ($t_{(6)} = -5.09^{**}$)	P3 ($t_{(13)} = 4,09^{**}$)	Pz ($t_{(13)} = 4,04^{**}$)
	O2 ($t_{(6)} = -3.68^{**}$)	Pz ($t_{(13)} = 4,44^{**}$)	P4 ($t_{(13)} = 3,63^{**}$)
		P4 ($t_{(13)} = 6,42^{***}$)	O1 ($t_{(13)} = 3,41^{**}$)
		O1 ($t_{(13)} = 4,43^{**}$)	
		O2 ($t_{(13)} = 3,61^{**}$)	
Grapheme-Patch	/	C4 ($t_{(13)} = 4,07^{**}$)	O1 ($t_{(13)} = 2,74^*$)
		P3 ($t_{(13)} = 3,23^{**}$)	Oz ($t_{(13)} = 2,76^*$)
		Pz ($t_{(13)} = 3,37^{**}$)	
		P4 ($t_{(13)} = 5,50^{***}$)	
		P8 ($t_{(13)} = 3,88^{**}$)	
		Oz ($t_{(13)} = 3,98^{**}$)	
		O2 ($t_{(13)} = 4,11^{**}$)	
Inverse-grapheme	CPz ($t_{(6)} = 5,37^{**}$)	/	Cz ($t_{(13)} = 3,67^{**}$)
	CP4 ($t_{(6)} = 6,86^{***}$)		C4 ($t_{(13)} = 4,81^{***}$)
	P4 ($t_{(6)} = 8,16^{***}$)		P3 ($t_{(13)} = 4,17^{**}$)
			Pz ($t_{(13)} = 4,05^{**}$)
			P4 ($t_{(13)} = 5,30^{***}$)
			P8 ($t_{(13)} = 6,22^{***}$)
			Oz ($t_{(13)} = 3,20^{**}$)
			O2 ($t_{(13)} = 4,51^{**}$)

Electrode sites showing significant congruency effect according to post hoc t-test corrected for multiple comparisons. Results for the N170, N300 and N400 components are shown separately for each experimental condition. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Study 3

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) one or more categories of ordinal stimuli are perceived as arranged in peripersonal space. Using event related fMRI, we examined the neural bases of SSS and colour synaesthesia (C) for spoken words in a late-blind developmental synaesthete, JF, to learn 1. whether visual cortex would still be recruited, and 2. to what extent the correlates of SSS correspond to those of spatial imagery. JF reported days of the week and months of the year as coloured and spatially ordered in peripersonal space (S+C); parts of the days and festivities of the year were spatially ordered but not coloured (S). Two experimental conditions, S and S+C, were compared. Words that denote time-units and triggered no concurrents were used in a control condition. Stimuli were matched for semantic and syntactic characteristics; the task required the detection of order reversals. Results show that both the S and the S+C condition activated the occipito-parietal, infero-frontal and insular cortex, but only the S+C condition engaged the colour area hOC4v. Whereas the latter result shows the continued recruitment of visual colour cortex in a late-blind synaesthete, the spatial geometry of SSS appears to be related to occipitoparietal areas also engaged by spatial imagery in blind (Vanlierde et al., 2003) and sighted non-synaesthetes (Mellet et al., 1996). Inferior frontal activation may be related to spatial memory and detection, while the insula may contribute to audiovisual integration related to the processing of inducers and concurrents as well as to engagement in a task-dependent vestibular process.

Keywords: synaesthesia, spatial, sequence, blindness, imagery

Introduction

In synaesthetes, the stimulation of one sensory or cognitive pathway provokes an additional involuntary experience (a concurrent) in a second sensory or cognitive pathway. Together with coloured-grapheme and coloured-phoneme synaesthesia, *spatial sequence synaesthesia* (SSS) is one of the most prevalent forms (Sagiv et al., 2006). In SSS, one or more categories of ordinal stimuli like numbers or weekdays, are perceived as ordered in peripersonal space in a two- or three-dimensional structure like real-world objects (Galton, 1883; Seron et al., 1992; Hubbard et al., 2005; Sagiv et al., 2006; Eagleman, 2009). While a number of behavioural studies aimed at testing the authenticity of SSS have been conducted (Sagiv et al., 2006; Smilek et al., 2007; Price and Mentzoni, 2008), the functional neuroanatomy of SSS remains to be determined. The present paper aims at shedding light on the neural correlates of spatial sequence and colour synaesthesia in a late-blind man.

Apart from an anecdotal report by Locke (1690), there are only few reports of visual concurrents in late-blind persons prior to a study by Steven and Blakemore (2004). Of their six late-blind participants who retained their synaesthetic colour experiences, four had been without any form of genuine colour vision for over 10 years, meaning that colour vision was retained over a long period. 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), auditory (Weeks et al., 2000; Roeder et al., 2002), verbal (Burton et al., 2002; Amedi et al., 2003), and memory processing (Raz et al., 2005). Differences between sighted individuals

and the late-blind appear less pronounced (Goyal et al., 2006). It is however remarkable that 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 et al., 2006). Whereas the capacity of perceiving colour is normally not retained during blindness, it is noted that blind persons can function with regard to spatial navigation (Jones, 1975). However, the underlying processes and the brain areas involved in spatial processing in the blind remain to be determined. Studies applying spatial localization tasks in the auditory domain showed that both sighted and congenitally blind subjects strongly activate posterior parietal areas (Weeks et al., 2000). All together, these data suggest that the posterior parietal areas might be engaged in SSS in a late blind individual.

Literature on sighted non-synaesthetes provides abundant evidence that the parietal cortex plays a role in representing space and in binding objects to each other (Colby and Goldberg, 1999; Corbetta et al., 2000; Robertson, 2003). In particular, the posterior parietal together with the frontal cortex has been shown to be functionally specialized for controlling spatial attention (Stein, 1989; Silver et al., 2005). More evidence comes from human lesion studies: Balint's syndrome, which is associated with bilateral occipito-parietal damage (Rizzo and Vecera, 2002), is noted to cause the loss of spatial information beyond one's own body. Also, a better understanding of the role of the parietal cortex in visual spatial processing comes from studies that focus on sequences such as numbers, as these are represented in a spatial mental line

according to their ordinal characteristics. The mental number line was elegantly demonstrated by the spatial-numerical association of response codes (SNARC) effect (Dehaene et al., 1993), which applies also to non-numerical categories such as days of the week (Gevers et al., 2004), months of the year, letters (Gevers et al., 2003), and even to semantic information presented in pictures (Turriziani et al., 2009).

Results from functional magnetic resonance imaging (fMRI) (Pinel et al., 2001; Acuna et al., 2002; Ischebeck et al., 2008; Van Opstal et al., 2008; Franklin and Jonides, 2009; Kaufmann et al., 2009) and repetitive Transcranial Magnetic Stimulation (rTMS) (Goebel et al., 2001; Goebel et al., 2006; Turriziani et al., 2009) studies consistently showed that the posterior parietal cortex is crucially involved in the representation of numerical as well as non numerical sequences. That the parietal cortex is likely to play a role also in the spatial processing involved in SSS is suggested by a few studies in sighted subjects: Spalding and Zangwill (1950) reported that an occipital-parietal injury 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 a bilateral activation in the posterior intraparietal sulci during a number order task (Tang et al., 2008). All together, these data are in agreement with the hypothesis that the mental number line is only a special case of the mental manipulation of visuospatial information supported by the parietal areas (Pinel et al., 2001).

We hypothesized that a non-numerical form of synaesthesia, namely SSS for time-units, would activate the posterior parietal cortex. The synaesthesia reported by the

late blind subject from Steven and Blakemore (2004), namely the experience of colour and spatial sequences for time-units, gave us the opportunity to investigate this issue. Although involvement of the parietal cortex in the processing of time-units was suggested in a following study (Steven et al., 2006), these authors focussed predominantly on JF's colour concurrents. With the present study we aim at disentangling the contributions of colour and spatial sequence synaesthesia. We created two experimental conditions in which either one or both types of concurrent were elicited, allowing us to separately assess the neural correlates of both synaesthesias, and a control condition in which no synaesthesia was triggered. We expected the activation of colour sensitive brain areas in the posterior ventral cortex during the synaesthetic condition that elicited coloured concurrents, and a parietal contribution to the spatial processing of the synaesthetic non-numerical sequences. Besides, two factors were implemented in our study: first, given the evidence that semantic and syntactic aspects of processing are both functionally distinct and involve different subparts of the neuronal network underlying word processing (Caramazza and Hillis, 1991; Friederici et al., 2000; Shapiro et al., 2005), stimuli in the different conditions were controlled for these characteristics. Second, to enhance the intensity of the synaesthetic experiences, we followed Piazza et al. (2006) and Hubbard et al. (2009), who reported that SSS for numbers is more intensely triggered when the task or the stimuli induce a strong notion of sequence. We therefore required our subject to use the semantic and the spatial information present in his synaesthesia in order to perform the task.

Another aim of the present study is to investigate possible commonalities between SSS and spatial imagery. The assumption that synaesthetic perception and imagery utilize the same spatial frames of reference as other forms of perception, although not deeply investigated yet, has been previously addressed (Ward et al., 2006). One study showed that both coloured-grapheme synaesthetes and matched controls activated the putative colour area V4 during normal colour imagery (not involving synaesthesia), but the synaesthetes showed activation in the left medial lingual gyrus during a synaesthetic task (Rich et al., 2006). In their study of JF, Steven et al. (2006) found that V4 and adjacent areas were activated during colour synaesthesia, but imagining colours activated a region anterior to V4, previously associated with colour imagery in sighted people (Howard et al., 1998). These studies exclusively compared colour imagery with coloured synaesthesia. It remains to be determined whether SSS shares neural correlates with spatial imagery. On the basis of results from self-report scales and behavioural tests of visual imagery, Price (2009) proposed that the tendency to develop SSS could be driven by a general tendency to experience particularly strong visuospatial imagery across all domains, thus placing SSS on a continuum with normal cognition. In the present study we attempt to identify the functional anatomy of SSS and to understand to what extent it recruits the same neural areas as spatial imagery.

Methods

Subject

JF, a right-handed male engineer, 60 years of age at the time of testing, lost his sight 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 experienced sequence-space synaesthesia for auditorily presented categorical stimuli. Time-units, pay-scales, military groupings, and orchestral instruments were arranged in a body-centered space, and time-units as well as orchestral instruments were additionally perceived as coloured. JF now has coloured-Braille, i.e. touch-induced visual synaesthesia (Steven and Blakemore, 2004). Our study focused on his synaesthesia for time-units, in which days of the week and months of the year are perceived as coloured, rectangular shapes and are arranged in body-centered visual space. JF likened this arrangement to a stone path in a garden, on which he would walk starting from a reference point constituted by the current day. JF also reported sequence-space synaesthesia for parts of the days and for festivities of the year; the position of festivities followed the months in which they occurred. Unlike days and months, bank holidays and parts of the day did not induce colours.

Results of a 18-months apart consistency test confirm that JF's synaesthetic experiences were stable over time with a consistency score of 94.7%. Written informed consent was obtained from the participant prior to scanning and the study

was approved by the local ethics committee of the Heinrich-Heine-University of Düsseldorf, in accordance with the Declaration of Helsinki.

Procedure

In our event-related fMRI study words spoken by a native English speaker were presented through scanner-compatible headphones. Three conditions were compared. For the 2-concurrents synaesthetic condition (S+C) we presented words referring to days of the week and months of the year, which in JF elicited coloured, shaped, and sequence-space synaesthesia. For the 1-concurrent synaesthetic condition (S), parts of the day ('morning', 'afternoon') and holidays of the year ('Christmas', 'Easter') were presented, i.e. words that elicited sequence-space synaesthesia but neither colour nor shape. For the non-synaesthetic control (Con) condition, we used time-units ('second', 'season', 'year') that failed to evoke synaesthetic sensations (see Table I for a list of stimuli). To enhance SSS through the task (Piazza et al., 2006; Hubbard et al., 2009), we organized stimuli into trials of seven words of the same time-unit type. The words were either presented in standard direction ('Monday', Tuesday', 'Wednesday'.., or 'Monday', Wednesday', 'Friday'..), with one change in direction ('Monday', 'Wednesday', 'Tuesday'), or with two such changes ('Monday', 'Thursday', 'Wednesday', 'Tuesday', 'Friday', 'Saturday'). These switches were introduced to make JF 'move' forward and backward in his synaesthetic space while performing the task. Stimulus duration was 561 ms on average and the inter-stimulus interval was 2.5 sec. 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). Twelve trials per condition were presented in randomized order. Trials were interleaved by a rest time of 10 sec. All sequences were unique with regard to the combination of the 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 in the Con condition: ($F_{(2,47)} = 6.94, p < .01$; <http://corpora.informatik.uni-leipzig.de/?dict=en>), all sequences were practiced prior to the fMRI session to avoid large familiarity effects. Response devices were the keyboard for the practice session and an MR-scanner compatible Lumitouch response box inside the MR scanner. Total runtime was ~22 minutes (974 MR images).

Stimulus presentation

Presentation software (version 10.2, Neurobehavioral Systems Inc., 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.

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 msec, TR = 2280 msec, flip angle = 80°, 224 mm FOV, 64 x 64 matrix, 3.5 x 3.5 x 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 msec, TR = 2,300 msec, 256 mm FOV, 256 x 256 matrix, 1 mm³ resolution).

Conditions	S+C (colour and spatial sequence synaesthesia)	S (spatial synaesthesia, no colour)	Con (no synaesthesia)
	Monday	Morning	Picosecond
	Tuesday	Midday	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		Eon
	October		
	November		
	December		
Word rareness	7.6	12.0	10.8

Table I. *Time-units used in the three conditions. S+C = 2-concurrents synaesthesia condition, S = 1-concurrent synaesthesia condition, Con = control condition. The S+C and S conditions included two groups of stimuli, whereas the Con condition consisted of one larger group. On 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^{7.6} the number of occurrences a word in the S+C condition).*

Data Analysis

MR data were pre-processed and analysed with SPM8 software (Wellcome Department of Imaging Neuroscience, www.fil.ion.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 normalization the images were resampled to a 2x2x2 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 in an event-related design. The design matrix contained regressors for each of the three experimental conditions (S+C, S, Con) and for prompts, responses and rest periods. 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 $P < .001$ at the whole brain level, with a

cluster-level statistic of $P_{FWECorr} < .05$. 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 single conditions versus Rest. For this purpose, the statistical threshold was raised to a $P_{FWECorr} < .01$ at the whole brain level, with a cluster-level statistic of $P_{FWECorr} < .001$ and a minimum cluster size of 100 voxels. Corresponding brain regions and Brodmann areas were retrieved from the Münster T2T-Converter (www.neuro03.uni-muenster.de/ger/t2tconv/conv3d.html) and verified with the SPM8 Anatomy toolbox (Eickhoff et al., 2005).

Results

Behavioural results

JF correctly indicated the number of switches in all trials except one in the S+C and one in the Con condition, leading to an accuracy of 92 % in these two conditions and 100% in the S condition. He responded significantly faster in the S+C compared to the Con condition ($F_{(2,33)} = 5.419$ $p < .01$; see Fig. 1a). Reaction times to trials with no changes in direction were slower compared to those with 1 change in direction ($F_{(2,33)} = 4.184$ $p < .05$; Fig. 1b). Reaction times for trials with 1 and 2 switches in directions did not show any significant difference.

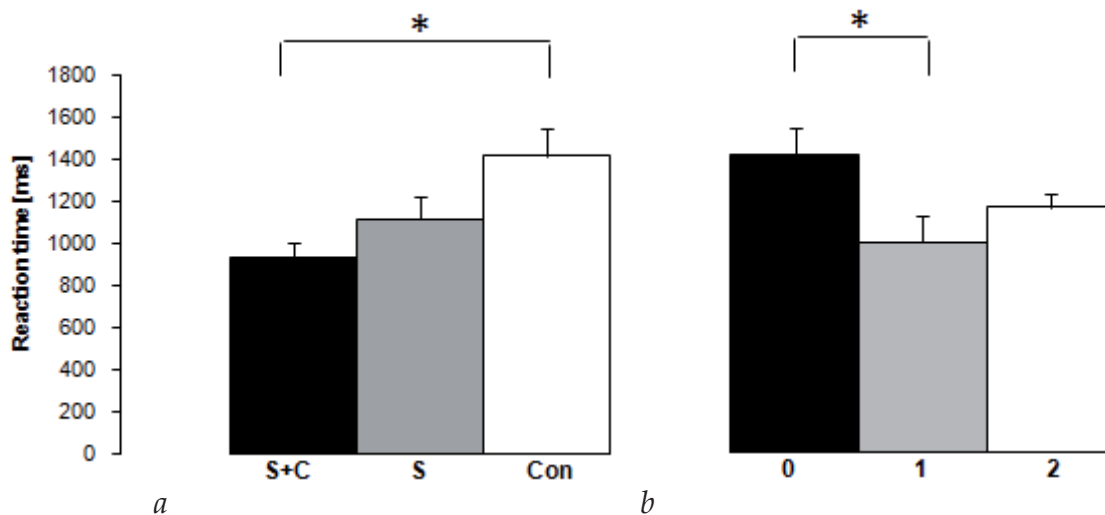


Fig. 1a. Average and standard error of the mean reaction time in the three conditions. S+C = 2-concurrents synaesthesia condition, S = 1-concurrent synaesthesia condition, Con = control condition. b. Average and standard error of the mean reaction time in trials with no switch, one switch and two switches in direction. Trials were collapsed across conditions. * ($p < .05$)

fMRI results

The contrast Time-Words > Rest (S+C, S, Con > Rest) revealed extensive activation (Fig. 2): specifically, the superior temporal gyrus was bilaterally active, together with the right inferior parietal cortex and the right superior and inferior frontal gyrus.

Significant activation in bilateral occipital cortex, right inferior parietal cortex, right inferior frontal cortex and insula were found when the synaesthetic conditions were compared to the control (S+C, S > Con). A plot of the different occipital contributions of these conditions is represented in Fig. 3.

Contrasting the S+C condition with the Con condition, a significant activation of the left colour area V4 emerged at the coordinates (-30, -68, -12) (Fig. 4a), an area which belongs to the cytoarchitectonic area hOC4v (V4) and lies close to that one found by Steven et al. (2006) (-29, -67, -18). This contrast also showed significant frontal activation ($P_{FDRcorr} = .002$), 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 to belong to the inferior parietal cortex. The middle occipital gyrus was bilaterally activated.

For the $S > Con$ contrast, we expected to find posterior parietal activation and no effect in V4 due to the synaesthesia without colour elicited by the S stimuli. Indeed, significant activation emerged at coordinates (44, -82, 30), a region having 80% probability to be the inferior parietal cortex and situated more rostrally compared with the parietal activation in the S+C condition. The $S > Con$ contrast also revealed significant activation in middle and superior occipital cortex as well as right superior temporal, and inferior frontal gyri; the last focus extended into the anterior insula (Fig.4b). This contrast did not show any activation in V4. No significant effects were found for the contrast of $S+C > S$ at the whole brain level, whereas the 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. The $Con > Rest$ contrast showed significant activation in the right inferior and superior parietal lobule in addition to the superior temporal and the right inferior frontal gyrus bilaterally. A summary of the significantly activated areas is presented in Table II.

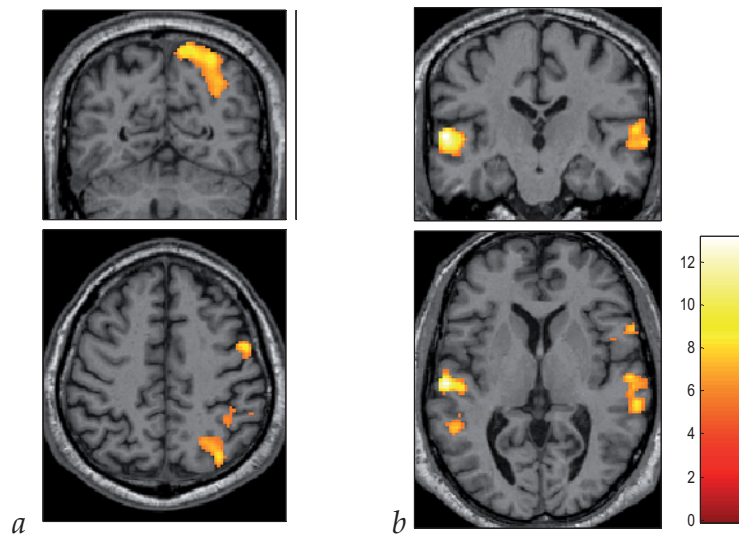


Fig. 2. Coronal and horizontal view of the parietal (a) and temporal (b) activation in the contrast Words > Rest at coordinates (31, -63, 44) and (-58, -20, 4) respectively.

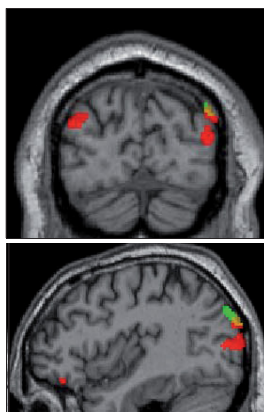


Fig. 3. Plot of the S+C > Con contrast (red), of the S > Con contrast (green), and of the overlap of the two contrasts (orange). Significant activation of the superior and middle occipital gyrus (see table 2), with the S condition showing a more rostral activation compared to the S+C condition in the right hemisphere (coordinates 40, -87, 23).

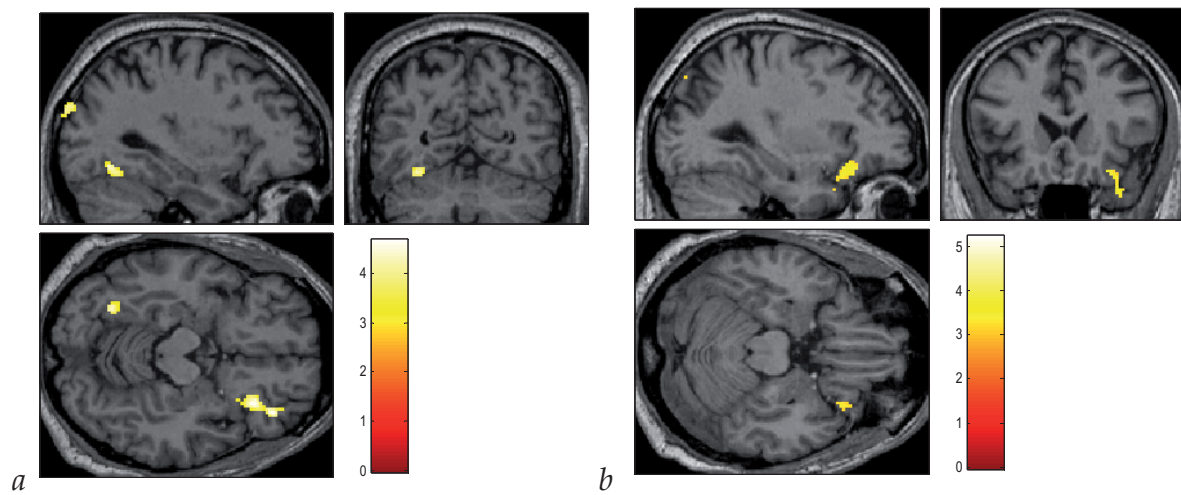


Fig. 4a. Saggital, transversal and coronal view of the activations of the visual colour area V4, the occipito-parietal, infero-frontal and insular cortex in the S+C condition (coordinates -30,-63,-14). b. Saggital, transversal and coronal view of the activations of the infero-frontal and insular cortex in the S condition (31,19,-21).

	<i>Side</i>	<i>MNI Coordinates</i>			<i>Cluster size</i>	<i>BA</i>	<i>P</i>
		<i>x</i>	<i>y</i>	<i>z</i>	<i>(voxels)</i>		
S+C, S, Con > Rest							
SPL, IPC	R	50	-36	54	1428	7	<.001
STG	L	-58	-20	4	397	22	<.001
STG	R	58	-16	0	531	22	<.001
MTG	L	-56	-48	6	100	21	<.001
IFG	R	48	10	14	414	44	<.001
SFG	R	28	-6	62	317	6	<.001
S+C, S > Con							
SOG, IPC	R	42	-86	26	236	19	<.001
SOG	L	-26	-94	26	162	19	<.001
IFG, IS	R	30	20	-20	226	47	<.001
S+C > Con							
IFG, MFG, IS	R	28	26	-12	192	47	<.001
IPC	R	40	-88	26	66	19	<.05*
MOG, SOG	L	-28	-96	24	113	19	= .007
MOG	R	38	-90	8	94	18	= .018
hOC4v	L	-30	-68	-12	56	19	<.05*
S > Con							
IPC, SOG	R	44	-82	30	100	19	= .013
MOG, SOG	L	-26	-94	26	83	19	<.05
IFG, IS, STG	R	30	20	-20	77	47	<.04
S > Rest							
SPL, IPC	R	16	-64	60	642	7	<.001

Table II. Anatomical regions, MNI coordinates for peak activations, cluster size, Brodmann areas, and P-values revealed by comparing condition as listed in column 1. S+C = 2-concurrents synaesthesia condition, S = 1-concurrent 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 FWEcorr value at cluster level corrected for entire brain volume.* $P_{FDRcorr}$ value.

Discussion

The present study reports on colour synaesthesia and spatial sequence synaesthesia for time-units in a late blind subject. In the next sections, we discuss first the behavioural findings and then the fMRI results, which will be examined according to the anatomical location of the increased activation and the respective functional significance. Finally, neural commonalities between SSS and spatial imagery will be discussed in the light of findings from other imaging studies.

Behavioural data

The average reaction time in the S+C condition was significantly shorter than in the Con condition, suggesting that the switches in direction within the sequences of synaesthetic stimuli were easier to detect than in the control sequences. One explanation for this finding is that the visualization of items that was triggered in the S+C condition facilitated processing. The synaesthetic process has determined the perception of the stimuli in a visual dimension in addition to the auditory one. The bimodal stimulation in the S+C condition might have resulted in intersensory facilitation and thus have determined a faster task performance compared to the Con condition. Although there was no difference in task accuracy between the S+C and the Con condition, we cannot exclude the alternative possibility that the first

condition has involved less effort and therefore shorter reaction times compared to the second one.

Not surprisingly, JF took longer to respond on trials with no changes in direction compared to those with one change: this might depend on a late inspection of the items before giving the answer, in order to ascertain its correctness. This 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 and Gelade, 1980).

fMRI data

V4 , occipital, and parietal cortex

Language comprehension activated both left and right perisylvian areas, thus replicating previous findings on congenitally blind individuals (Roeder et al., 2002). These together with previous findings in sighted subjects (Creutzfeldt et al., 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 et al. (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 one onto the other.

Moreover, we observed activation of extra-striate visual areas in our late-blind subject during presentation of synaesthesia-inducing auditory stimuli. The combined synaesthetic conditions S+C and S evoked occipito-parietal, infero-frontal and insular activation. 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. To the Brodmann Area (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 and Zangwill, 1950; Steven et al., 2006), the occipito-parietal region is likely to be involved in SSS. Besides, it is worth noting that activation of middle and superior occipital areas has been found alongside V4 in colour processing tasks (Bartels and Zeki, 2000; Mullen et al., 2007). It might therefore also contribute to the synaesthetic colour 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. Dehaene et al. (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 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 reflects a basic feature of the mental number line (Pinhas et al., 2010). Indeed, the Con condition elicited activation in the right intraparietal sulcus. 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.

In addition to the bilateral occipital (BA19) and the right inferior parietal cortex, the S+C condition activated the left colour area V4. As hypothesized, V4 was not activated in the S condition, which elicited non-coloured synaesthesia. Although the S+C condition elicited coloured concurrents and the S condition did not, V4 activation did not emerge when subtracting the S from the S+C condition. The activation of V4 replicates results from previous fMRI studies on coloured-hearing synaesthesia (Nunn et al., 2002; Gray et al., 2006; Steven et al., 2006) and grapheme-colour synaesthesia (Hubbard et al., 2005; Sperling et al., 2006). 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.

Inferior frontal cortex

The significant activation of the inferior frontal cortex both in the S+C and S condition 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 sequence-space synaesthesia, 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 et al., 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 et al., 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.

It is worth noting that the right inferior frontal activation has been observed in previous fMRI studies on synaesthesia (Paulesu et al., 1995; Aleman et al., 2001), 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 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 and Goldman-Rakic, 2000; Gruber and von Cramon, 2001) and, more specifically, to spatial working memory (Diwadkar et al., 2000; Curtis, 2006; Ricciardi et al., 2006). Interestingly, rTMS of the right inferior frontal gyrus suppresses the SNARC effect (Rusconi et al., 2009). 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 et al., 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.

Insular cortex

Both the S+C and the S conditions 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

hypothesized role of the insula as an ideal neuroanatomical locus for synaesthesia (Ramachandran and Hubbard, 2001a). Due to its connectivity with diverse auditory, somatosensory, olfactory, limbic and para-limbic structures (Hadjikhani and Roland, 1998; Banati et al., 2000), 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, 2001b) and is involved in audio-visual integration of conceptually related objects (Naghavi et al., 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 perceived ordered sequences could for example have worked as a vestibular stimulus. Positron emission tomography studies show that the insula is one of the cerebral projections of the vestibular system in man (Bottini et al., 1994) and is active during body representation (Bonda et al., 1995). In particular, vestibular symptoms have been related to the lesion of the anterior insula (Papathanasiou et al., 2006), which appears to be part of a specific mental navigation network encoding spatial information in an egocentric 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 and would confirm that internally generated experiences such as synaesthesia can lead to similar brain activations as real vestibular stimuli. Although the control condition involved a sequence as well, it did not invoke any moving in space, which could explain higher insula activity in the S+C and S conditions.

Finally, a possible role of the insula in the affect-laden component of synaesthesia should be taken in consideration. In the light of the extensive interconnections of the anteroventral portions of the insula with limbic structures (Mesulam and Mufson, 1982) and of previous findings of right anterior insula activation related to emotionally arousing words (Maddock et al., 2003), it is a possibility that the affective component involved in synaesthesia played a role in the insula activation in our study.

SSS and visuospatial imagery

A second question we aimed to answer with our study was whether visuospatial imagery and SSS share neural correlates. Published evidence suggests that parieto-occipital as well as frontal cortex plays a role in spatial imagery (Levine et al., 1985; Mellet et al., 1995; Ghaem et al., 1997). 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 et al., 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). The similarity between brain activation patterns related to imagined spatial stimuli in non synaesthetes and those related to SSS in our subject accounts for common neural activations between the imagery process and this kind of synaesthesia. 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 categorization/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 might apply in SSS.

A parallel line of research focusing on eye movements brings some evidence for shared neural activation between imagery and perception, in that it shows that patterns of eye-movements are similar when an image is imagined, and thus not physically presented, as when the image is actually viewed (Brandt and Stark, 1997). Besides, a relationship between the SNARC effect and gaze direction has repeatedly been observed (Fischer et al., 2004; Schwarz and Keus, 2004; Loetscher et al., 2010; Fernandez et al., in press). Interestingly, the spatial shift along the mental number line related to mental calculation has been shown to rely on neural circuits in the

posterior parietal area shared with those involved in updating spatial information during saccadic eye movements (Knops et al., 2009). If the parietal circuitry associated with spatial coding is co-opted during shifts on the mental number-line, this may also occur in SSS despite its non-numerical inducers. Future studies might shed light on the role of the eye movements in SSS as well as in the SNARC effect for non-numerical stimuli such as time-units. This would contribute to understand the interplay between SSS and the imagined number line and whether they lay on a perceptual continuum.

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. This pattern of neural activation corresponds to that observed during spatial imagery in blind and sighted non-synaesthetes. Further studies of non-synaesthetes who perform the same task and of SSS synaesthetes may show whether and how this network differs from that activated in these groups.

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Discussion

Demographic characteristics of synaesthetes and features responsible for eliciting and/or modulating synaesthesia were investigated in the survey study. To shed light on the neural mechanisms of this condition, time-course and functional neuroanatomy of synaesthetic experience were examined in two common forms of synaesthesia: grapheme-colour and spatial sequence synaesthesia.

Results from the survey study indicate that synaesthetic inducer-concurrent associations may be acquired. Environmental factors are likely to play a key role in the origin of synaesthesia, possibly in combination with a genetic predisposition. The modulation of synaesthetic experience over time challenges the presumed consistency of synaesthesia and the adequacy of the consistency test, which is commonly used to assess the veracity of reported synaesthesia. Although excluding synaesthetes with low consistency scores is desirable for particular studies, this selection may result in neglecting individuals with implicit synaesthesia. As a consequence, findings would apply only to a subgroup of the synaesthetic population, and would prevent the identification of a possible continuum between synaesthesia and normal cognition. In the light of the prevalence of auditory- and somato-visual synaesthetic associations, the hypothesis of a continuum is of particular interest. Given that auditory- and somato-visual paths were identified also in the normal population, it is likely that synaesthesia shares some neural mechanisms with normal cognitive functioning.

Findings from the EEG and the fMRI study agree in showing that at least some neural processes are shared in synaesthetes and non-synaesthetes. Similar electrophysiological patterns of activation emerge in synaesthetes and semantic controls at a late stage of processing. Synaesthetes semantically process grapheme-colour associations analogously to individuals who are trained to associate alphanumeric stimuli with colours. The fMRI study showed that cortical areas engaged in normal spatial and colour processing are recruited in synaesthetes when they experience spatially arranged coloured concurrents. Specifically, occipitoparietal areas are engaged in the spatial aspects of spatial-sequence synaesthesia and the visual colour area V4 is activated when the synaesthetic experience involves colour perception.

The emergence of an N300 effect both in synaesthetes and controls points to a possible role of imagistic representation in synaesthesia: when synaesthetes visualize an inducer, imagery processes similar to those occurring in non-synaesthetes who recall grapheme-colour associations are likely to occur. Results from the fMRI study also support the link between imagery and synaesthesia. In a blind synaesthete, the perception of spatial geometry in spatial sequence synaesthesia is related to areas that are also engaged during spatial imagery both in blind and in sighted non-synaesthetes.

Alongside results which account for shared neural mechanisms in synaesthetes and non-synaesthetes, striking group differences emerged in electrophysiological activation. While non-synaesthetes largely engaged memory-related cognitive

processes, synaesthetes showed congruency-related and faster perceptual activation (N170). These results point to rapid early perceptual processes as a marker of synaesthesia and question the disinhibited feedback model.

Finally, findings from the EEG study account for bidirectional neural mechanisms in synaesthesia. Similar patterns of activation emerged in a direct and in a reversed cued-congruency task in synaesthetes who do not perceive a grapheme while looking at a colour. It is thus possible that the inverse colour-grapheme associations remain at an unconscious level in synaesthetes, may be depending on a functionality-related suppression. Colours are commonly used to improve stimuli categorization and to efficiently group items. Indeed, the fact that synaesthetes report their condition to be an advantage in learning and memorizing accounts for a functional aspect involved in synaesthesia. Possibly, the lack of functionality of the inverse colour-grapheme associations may cause this direction of flow of information to be neglected in synaesthetes.

Overall, the present data call for further enquiry of early processes in synaesthetes and for possible shared neural mechanisms between synaesthesia and normal cognition. Similarity between neural correlates of synaesthesia and imagery remains to be tested on a larger sample of sighted individuals as well as on forms of synaesthesia different from grapheme-colour and spatial-sequence synaesthesia. An important contribution to the understanding of the continuum between synaesthesia and normal cognition might come from studies including associators and projector synaesthetes as well as individuals with implicit synaesthesia. The comparison of

those groups with non-synaesthetes may shed light not only on commonalities between the synaesthetic and the normal population, but also on the different levels of awareness at which integration processes occur.

References

- Acuna, B. D., Eliassen, J. C., Donoghue, J. P. & Sanes, J. N. (2002). Frontal and parietal lobe activation during transitive inference in humans. *Cereb Cortex*, 12(12): 1312-21.
- Aleman, A., Rutten, G. J., Sitskoorn, M. M., Dautzenberg, G. & Ramsey, N. F. (2001). Activation of striate cortex in the absence of visual stimulation: an fMRI study of synesthesia. *Neuroreport*, 12(13): 2827-30.
- Amedi, A., Malach, R., Hendler, T., Peled, S. & Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. *Nat Neurosci*, 4(3): 324-30.
- Amedi, A., Raz, N., Pianka, P., Malach, R. & Zohary, E. (2003). Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. *Nat Neurosci*, 6(7): 758-66.
- Armel, K. C., & Ramachandran, V. S. 1999. Acquired synesthesia in retinitis pigmentosa. *Neurocase*, 5:293-296.
- Asher, J. E., Lamb, J. A., Brocklebank, D., Cazier, J. B., Maestrini, E., Addis, L., Sen, M., Baron-Cohen, S. & Monaco, A. P. (2009). A whole-genome scan and fine-mapping linkage study of auditory-visual synesthesia reveals evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12. *Am J Hum Genet*, 84(2): 279-85.
- Banati, R. B., Goerres, G. W., Tjoa, C., Aggleton, J. P. & Grasby, P. (2000). The functional anatomy of visual-tactile integration in man: a study using positron emission tomography. *Neuropsychologia*, 38(2): 115-24.
- Bargary, G. & Mitchell, K. J. (2008). Synaesthesia and cortical connectivity. *Trends Neurosci*, 31(7): 335-42.
- Barnett, K. J., Foxe, J. J., Molholm, S., Kelly, S. P., Shalgi, S., Mitchell, K. J. & Newell, F. N. (2008a). Differences in early sensory-perceptual processing in synesthesia: a visual evoked potential study. *Neuroimage*, 43(3): 605-13.

- Barnett, K. J., Finucane, C., Asher, J. E., Bargary, G., Corvin, A. P., Newell, F. N. & Mitchell, K. J. (2008b). Familial patterns and the origins of individual differences in synaesthesia. *Cognition*, 106(2): 871-93.
- Barnett, K. J. & Newell, F. N. (2008). Synaesthesia is associated with enhanced, self-rated visual imagery. *Conscious Cogn*, 17(3): 1032-9.
- Baron-Cohen, S., Harrison, J., Goldstein, L. H. & Wyke, M. (1993). Coloured speech perception: is synaesthesia what happens when modularity breaks down? *Perception*, 22(4): 419-26.
- Baron-Cohen, S., Burt, L., Smith-Laittan, F., Harrison, J. & Bolton, P. (1996). Synaesthesia: prevalence and familiarity. *Perception*, 25(9): 1073-9.
- Barrett, S. E., Rugg, M. D. & Perrett, D. I. (1988). Event-related potentials and the matching of familiar and unfamiliar faces. *Neuropsychologia*, 26(1): 105-17.
- Bartels, A. & Zeki, S. (2000). The architecture of the colour centre in the human visual brain: new results and a review. *Eur J Neurosci*, 12(1): 172-93.
- Battelli, L., Pascual-Leone, A. & Cavanagh, P. (2007). The 'when' pathway of the right parietal lobe. *Trends Cogn Sci*, 11(5): 204-10.
- Beeli, G., Esslen, M. & Jancke, L. (2008). Time course of neural activity correlated with colored-hearing synesthesia. *Cereb Cortex*, 18(2): 379-85.
- Bentin, S., McCarthy, G. & Wood, C. C. (1985). Event-related potentials, lexical decision and semantic priming. *Electroencephalogr Clin Neurophysiol*, 60(4): 343-55.
- Bentin, S., Mouchetant-Rostaing, Y., Giard, M. H., Echallier, J. F. & Pernier, J. (1999). ERP manifestations of processing printed words at different psycholinguistic levels: time course and scalp distribution. *J Cogn Neurosci*, 11(3): 235-60.
- Bonda, E., Petrides, M., Frey, S. & Evans, A. (1995). Neural correlates of mental transformations of the body-in-space. *Proc Natl Acad Sci U S A*, 92(24): 11180-4.
- Brandt, S. A. & Stark, L. W. (1997). Spontaneous eye movements during visual imagery reflect the content of the visual scene. *J Cogn Neurosci*, 9: 27-38.

- Bottini, G., Sterzi, R., Paulesu, E., Vallar, G., Cappa, S. F., Erminio, F., Passingham, R. E., Frith, C. D. & Frackowiak, R. S. (1994). Identification of the central vestibular projections in man: a positron emission tomography activation study. *Exp Brain Res*, 99(1): 164-9.
- Brang, D., Edwards, L., Ramachandran, V. S. & Coulson, S. (2008). Is the sky 2? Contextual priming in grapheme-color synaesthesia. *Psychol Sci*, 19(5): 421-8.
- Brang, D., Hubbard, E. M., Coulson, S., Huang, M. & Ramachandran, V. S. (2010). Magnetoencephalography reveals early activation of V4 in grapheme-color synesthesia. *Neuroimage*, 53(1): 268-74.
- Brang, D., Kanai, S., Ramachandran, V. S. & Coulson, S. (2011). Contextual Priming in Grapheme-Color Synesthetes and Yoked Controls: 400 msec in the Life of a Synesthete. *J Cogn Neurosci*.
- Burton, H., Snyder, A. Z., Diamond, J. B. & Raichle, M. E. (2002). Adaptive changes in early and late blind: a fMRI study of verb generation to heard nouns. *J Neurophysiol*, 88(6): 3359-71.
- Calvert, G. A., Hansen, P. C., Iversen, S. D. & Brammer, M. J. (2001a). Detection of audio-visual integration sites in humans by application of electrophysiological criteria to the BOLD effect. *Neuroimage*, 14(2): 427-38.
- Calvert, G. A. (2001b). Crossmodal processing in the human brain: insights from functional neuroimaging studies. *Cereb Cortex*, 11(12): 1110-23.
- Caramazza, A. & Hillis, A. E. (1991). Lexical organization of nouns and verbs in the brain. *Nature*, 349(6312): 788-90.
- Chafee, M. V. & Goldman-Rakic, P. S. (2000). Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J Neurophysiol*, 83(3): 1550-66.
- Cohen Kadosh, R., Sagiv, N., Linden, D. E., Robertson, L. C., Elinger, G. & Henik, A. (2005). When blue is larger than red: colors influence numerical cognition in synesthesia. *J Cogn Neurosci*, 17(11): 1766-73.

- Cohen Kadosh, R., Cohen Kadosh, K. & Henik, A. (2007). The neuronal correlate of bidirectional synesthesia: a combined event-related potential and functional magnetic resonance imaging study. *J Cogn Neurosci*, 19(12): 2050-9.
- Colby, C. L. & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annu Rev Neurosci*, 22: 319-49.
- Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvooy, M. P. & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci*, 3(3): 292-7.
- Cornejo, C., Simonetti, F., Ibanez, A., Aldunate, N., Ceric, F., Lopez, V. & Nunez, R. E. (2009). Gesture and metaphor comprehension: electrophysiological evidence of cross-modal coordination by audiovisual stimulation. *Brain Cogn*, 70(1): 42-52.
- Creutzfeldt, O., Ojemann, G. & Lettich, E. (1989). Neuronal activity in the human lateral temporal lobe. I. Responses to speech. *Exp Brain Res*, 77(3): 451-75.
- Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience*, 139(1): 173-80.
- Cytowic, R.E. (1989). *Synesthesia: A union of the senses*. New York: Springer-Verlag.
- de Thornley Head, P. (2006). Synaesthesia: pitch-colour isomorphism in RGB-space? *Cortex*, 42(2): 164-74.
- Dehaene, S., Bossini, S. & Giraux, P. (1993). The mental representation of parity and numerical magnitude. *J Exp Psychol Gen*, 122, 371-396.
- Dehaene, S., Piazza, M., Pinel, P. & Cohen, L. (2003). Three parietal circuits for number processing. *Cogn Neuropsychol*, 20(3): 487-506.
- Dehay, C., Kennedy, H. & Bullier, J. (1988). Characterization of transient cortical projections from auditory, somatosensory, and motor cortices to visual areas 17, 18, and 19 in the kitten. *J Comp Neurol*, 272(1): 68-89.
- Deiber, M. P., Rodriguez, C., Jaques, D., Missonnier, P., Emch, J., Millet, P., Gold, G., Giannakopoulos, P. & Ibanez, V. (2010). Aging effects on selective attention-

- related electroencephalographic patterns during face encoding. *Neuroscience*, 171(1): 173-86.
- Diwadkar, V. A., Carpenter, P. A. & Just, M. A. (2000). Collaborative activity between parietal and dorso-lateral prefrontal cortex in dynamic spatial working memory revealed by fMRI. *Neuroimage*, 12(1): 85-99.
- Dixon, M. J., Smilek, D., Cudahy, C. & Merikle, P. M. (2000). Five plus two equals yellow. *Nature*, 406(6794): 365.
- Dixon, M. J., Smilek, D. & Merikle, P. M. (2004). Not all synaesthetes are created equal: projector versus associator synaesthetes. *Cogn Affect Behav Neurosci*, 4(3): 335-43.
- Dixon, M. J., Smilek, D., Duffy, P. L., Zanna, M. P. & Merikle, P. M. (2006). The role of meaning in grapheme-colour synaesthesia. *Cortex*, 42(2): 243-52.
- Domino, G. (1989). Synaesthesia and creativity in fine art students: An empirical look. *Creativity Research Journal*, 2: 17-29.
- Doricchi, F., Guariglia, P., Gasparini, M. & Tomaiuolo, F. (2005). Dissociation between physical and mental number line bisection in right hemisphere brain damage. *Nat Neurosci*, 8(12): 1663-5.
- Eagleman, D.M., Kagan, A.D., Nelson, S.N., Sagaram, D. & Sarma, A.K. (2007). A standardized test battery for the study of synesthesia. *Journal of Neuroscience Methods* 159: 139-145.
- Eagleman, D. M. (2009). The objectification of overlearned sequences: a new view of spatial sequence synesthesia. *Cortex*, 45(10): 1266-77.
- Edquist, J., Rich, A. N., Brinkman, C. & Mattingley, J. B. (2006). Do synaesthetic colours act as unique features in visual search? *Cortex*, 42(2): 222-31.
- Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K. & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage*, 25(4): 1325-35.

- Elias, L. J., Saucier, D. M., Hardie, C. & Sarty, G. E. (2003). Dissociating semantic and perceptual components of synaesthesia: behavioural and functional neuroanatomical investigations. *Brain Res Cogn Brain Res*, 16(2): 232-7.
- Emrich, H.M., Schneider, U. & Zedler, M. (2002). *Welche Farbe hat der Montag? Synästhesie: das Leben mit verknüpften Sinnen*. S. Hirzel Verlag, Stuttgart.
- Esterman, M., Verstynen, T., Ivry, R. B. & Robertson, L. C. (2006). Coming unbound: disrupting automatic integration of synesthetic color and graphemes by transcranial magnetic stimulation of the right parietal lobe. *J Cogn Neurosci*, 18(9): 1570-6.
- Falchier, A., Clavagnier, S., Barone, P. & Kennedy, H. (2002). Anatomical evidence of multimodal integration in primate striate cortex. *J Neurosci*, 22(13): 5749-59.
- Federmeier, K. D. & Kutas, M. (2001). Meaning and modality: influences of context, semantic memory organization, and perceptual predictability on picture processing. *J Exp Psychol Learn Mem Cogn*, 27(1): 202-24.
- Fernández, S.R., Rahona, J.J., Hervás, G., Vázquez, C. & Ulrich, R. Thinking about numbers influences the choice of gaze direction. *Cortex* (in press).
- Fischer, M. H., Warlop, N., Hill, R. L. & Fias, W. (2004). Oculomotor bias induced by number perception. *Exp Psychol*, 51(2): 91-7.
- Franklin, M. S., Dien, J., Neely, J. H., Huber, E. & Waterson, L. D. (2007). Semantic priming modulates the N400, N300, and N400RP. *Clin Neurophysiol*, 118(5): 1053-68.
- Franklin, M. S. & Jonides, J. (2009). Order and magnitude share a common representation in parietal cortex. *J Cogn Neurosci*, 21(11): 2114-20.
- Friederici, A. D., Opitz, B. & von Cramon, D. Y. (2000). Segregating semantic and syntactic aspects of processing in the human brain: an fMRI investigation of different word types. *Cereb Cortex*, 10(7): 698-705.
- Frishkoff, G. A., Tucker, D. M., Davey, C. & Scherg, M. (2004). Frontal and posterior sources of event-related potentials in semantic comprehension. *Brain Res Cogn Brain Res*, 20(3): 329-54.

- Galton, F. (1883). *Inquiries into Human Faculty and its Development*. London: Dent & Sons.
- Ganis, G., Kutas, M. & Sereno, M.I. (1996). The search for “common sense”: an electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience*, 8(2): 89-106.
- Gebuis, T., Nijboer, T. C. & Van der Smagt, M. J. (2009). Multiple dimensions in bi-directional synesthesia. *Eur J Neurosci*, 29(8): 1703-10.
- Gevers, W., Reynvoet, B. & Fias, W. (2003). The mental representation of ordinal sequences is spatially organized. *Cognition*, 87(3): B87-95.
- Gevers, W., Reynvoet, B. & Fias, W. (2004). The mental representation of ordinal sequences is spatially organized: evidence from days of the week. *Cortex*, 40(1): 171-2.
- Ghaem, O., Mellet, E., Crivello, F., Tzourio, N., Mazoyer, B., Berthoz, A. & Denis, M. (1997). Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *Neuroreport*, 8(3): 739-44.
- Gheri, C., Chopping, S. & Morgan, M. J. (2008). Synaesthetic colours do not camouflage form in visual search. *Proc Biol Sci*, 275(1636): 841-6.
- Goebel, S., Walsh, V. & Rushworth, M. F. (2001). The mental number line and the human angular gyrus. *Neuroimage*, 14(6): 1278-89.
- Goebel, S. M., Calabria, M., Farne, A. & Rossetti, Y. (2006). Parietal rTMS distorts the mental number line: simulating 'spatial' neglect in healthy subjects. *Neuropsychologia*, 44(6): 860-8.
- Goller, A. I., Otten, L. J. & Ward, J. (2009). Seeing sounds and hearing colors: an event-related potential study of auditory-visual synesthesia. *J Cogn Neurosci*, 21(10): 1869-81.
- Goyal, M. S., Hansen, P. J. & Blakemore, C. B. (2006). Tactile perception recruits functionally related visual areas in the late-blind. *Neuroreport*, 17(13): 1381-4.
- Gratton, G., Coles, M.G. and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 55(4): 468-484.

- Gray, J. A., Parslow, D. M., Brammer, M. J., Chopping, S., Vythelingum, G. N. & ffytche, D. H. (2006). Evidence against functionalism from neuroimaging of the alien colour effect in synaesthesia. *Cortex*, 42(2): 309-18.
- Greenhouse, S. W. & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, 24: 95–112.
- Groppe, D. M., Choi, M., Huang, T., Schilz, J., Topkins, B., Urbach, T. P. & Kutas, M. (2010). The phonemic restoration effect reveals pre-N400 effect of supportive sentence context in speech perception. *Brain Res*, 1361: 54-66.
- Grossenbacher, P. G. & Lovelace, C. T. (2001). Mechanisms of synesthesia: cognitive and physiological constraints. *Trends Cogn Sci*, 5(1): 36-41.
- Gruber, O. & von Cramon, D. Y. (2001). Domain-specific distribution of working memory processes along human prefrontal and parietal cortices: a functional magnetic resonance imaging study. *Neurosci Lett*, 297(1): 29-32.
- Hadjikhani, N. & Roland, P. E. (1998). Cross-modal transfer of information between the tactile and the visual representations in the human brain: A positron emission tomographic study. *J Neurosci*, 18(3): 1072-84.
- Haenggi, J., Wotruba, D. & Jancke, L. (2011). Globally altered structural brain network topology in grapheme-color synesthesia. *J Neurosci*, 31(15): 5816-28.
- Hamm, J. P., Johnson, B. W. & Kirk, I. J. (2002). Comparison of the N300 and N400 ERPs to picture stimuli in congruent and incongruent contexts. *Clin Neurophysiol*, 113(8): 1339-50.
- Harrison, J. & Baron-Cohen, S. (1995). Synaesthesia: reconciling the subjective with the objective. *Endeavour*, 19(4): 157-60.
- Holcomb, P. J. & Grainger, J. (2006). On the time course of visual word recognition: an event-related potential investigation using masked repetition priming. *J Cogn Neurosci*, 18(10): 1631-43.
- Howard, R. J., ffytche, D. H., Barnes, J., McKeefry, D., Ha, Y., Woodruff, P. W., Bullmore, E. T., Simmons, A., Williams, S. C., David, A. S. & Brammer, M.

- (1998). The functional anatomy of imagining and perceiving colour. *Neuroreport*, 9(6): 1019-23.
- Hubbard, E. M., Arman, A. C., Ramachandran, V. S. & Boynton, G. M. (2005). Individual differences among grapheme-color synesthetes: brain-behavior correlations. *Neuron*, 45(6): 975-85.
- Hubbard, E. M. & Ramachandran, V. S. (2005). Neurocognitive mechanisms of synesthesia. *Neuron*, 48(3): 509-20.
- Hubbard, E. M., Manohar, S. & Ramachandran, V. S. (2006). Contrast affects the strength of synesthetic colors. *Cortex*, 42(2): 184-94.
- Hubbard, E. M. (2007). Neurophysiology of synesthesia. *Curr Psychiatry Rep*, 9(3): 193-9.
- Hubbard, E. M., Ranzini, M., Piazza, M. & Dehaene, S. (2009). What information is critical to elicit interference in number-form synaesthesia? *Cortex*, 45(10): 1200-16.
- Innocenti, G. M., Berbel, P. & Clarke, S. (1988). Development of projections from auditory to visual areas in the cat. *J Comp Neurol*, 272(2): 242-59.
- Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., Egger, K., Streng, H., Scheperjans, F. & Delazer, M. (2008). Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. *Hum Brain Mapp*, 29(8): 894-909.
- Jaencke, L., Beeli, G., Eulig, C. & Hanggi, J. (2009). The neuroanatomy of grapheme-color synesthesia. *Eur J Neurosci*, 29(6): 1287-93.
- Jones, B. (1975). Spatial perception in the blind. *Br J Psychol*, 66(4): 461-72.
- Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S. & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature*, 363(6430): 623-5.
- Kaufmann, L., Vogel, S.E., Starke, M., Kremser, C. & Schocke, M. (2009). Numerical and non-numerical ordinality processing in children with and without

- developmental dyscalculia: Evidence from fMRI. *Cognitive Development* 24(4):486-494.
- Kennedy, H., Batardiere, A., Dehay, C. & Barone, P. (1997). Synaesthesia: Implications for developmental neurobiology. In S. Baron-Cohen & J. E. Harrison (Eds.), *Synaesthesia: Classic and Contemporary Readings*. (pp. 243-256). Malden, MA: Blackwell Publishers.
- Knoch, D., Gianotti, L. R., Mohr, C. & Brugger, P. (2005). Synesthesia: when colors count. *Brain Res Cogn Brain Res*, 25(1): 372-4.
- Knops, A., Thirion, B., Hubbard, E. M., Michel, V. & Dehaene, S. (2009). Recruitment of an area involved in eye movements during mental arithmetic. *Science*, 324(5934): 1583-5.
- Kutas, M. & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature*, 307(5947): 161-3.
- Kutas, M. & Federmeier, K. D. (2011). Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). *Annu Rev Psychol*, 62: 621-47.
- Laeng, B., Svarddal, F. & Oelmann, H. (2004). Does color synesthesia pose a paradox for early-selection theories of attention? *Psychol Sci*, 15(4): 277-81.
- Levine, D. N., Warach, J. & Farah, M. (1985). Two visual systems in mental imagery: dissociation of "what" and "where" in imagery disorders due to bilateral posterior cerebral lesions. *Neurology*, 35(7): 1010-8.
- Locke J. (1960). *An Essay Concerning Human Understanding*. London: T. Basset.
- Loetscher, T., Bockisch, C. J., Nicholls, M. E. & Brugger, P. (2010). Eye position predicts what number you have in mind. *Curr Biol*, 20(6): R264-5.
- Macaluso, E. (2006). Multisensory processing in sensory-specific cortical areas. *Neuroscientist*, 12(4): 327-38.
- MacLeod, C. M. & Dunbar, K. (1988). Training and Stroop-like interference: evidence for a continuum of automaticity. *J Exp Psychol Learn Mem Cogn*, 14(1): 126-35.

- Maddock, R. J., Garrett, A. S. & Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp*, 18(1): 30-41.
- Marks, L. E. (1975). On colored-hearing synesthesia: cross-modal translations of sensory dimensions. *Psychol Bull*, 82(3): 303-31.
- Mattingley, J. B., Rich, A. N., Yelland, G. & Bradshaw, J. L. (2001). Unconscious priming eliminates automatic binding of colour and alphanumeric form in synaesthesia. *Nature*, 410(6828): 580-2.
- Maurer, D., & Maurer, C. (1988). *The world of the newborn*. New York: Basic Books.
- McPherson, W. B. & Holcomb, P. J. (1999). An electrophysiological investigation of semantic priming with pictures of real objects. *Psychophysiology*, 36(1): 53-65.
- Meier, B. & Rothen, N. (2009). Training grapheme-colour associations produces a synaesthetic Stroop effect, but not a conditioned synaesthetic response. *Neuropsychologia*, 47(4): 1208-11.
- Melara, R. D. (1989). Dimensional interaction between color and pitch. *J Exp Psychol Hum Percept Perform*, 15(1): 69-79.
- Mellet, E., Tzourio, N., Denis, M. & Mazoyer, B. (1995). A Positron Emission Tomography Study of Visual and Mental Spatial Exploration. *Journal of Cognitive Neuroscience*, 7(4): 433-445.
- Mellet, E., Tzourio, N., Crivello, F., Joliot, M., Denis, M. & Mazoyer, B. (1996). Functional anatomy of spatial mental imagery generated from verbal instructions. *J Neurosci*, 16(20): 6504-12.
- Mellet, E., Tzourio, N., Denis, M. & Mazoyer, B. (1998). Cortical anatomy of mental imagery of concrete nouns based on their dictionary definition. *Neuroreport*, 9(5): 803-8.
- Mesulam, M. M. & Mufson, E. J. (1982). Insula of the old world monkey. III: Efferent cortical output and comments on function. *J Comp Neurol*, 212(1): 38-52.
- Mills, C.B., Boteler, E.H. & Oliver, G.K. (1999). Digit synaesthesia: a case study using a Stroop-Type test. *Cognitive Neuropsychology*, 16 (2): 181-191.

- Mills, C.B., Viguers, M.L., Edelson, S.K., Thomas, A.T., Simon-Dack, S.L. & Innis, J.A. (2002). The color of two alphabets for a multilingual synesthete. *Perception*, 31(11): 1371-94.
- Mondloch, C. J. & Maurer, D. (2004). Do small white balls squeak? Pitch-object correspondences in young children. *Cogn Affect Behav Neurosci*, 4(2): 133-6.
- Moscovitch, C., Kapur, S., Kohler, S. & Houle, S. (1995). Distinct neural correlates of visual long-term memory for spatial location and object identity: a positron emission tomography study in humans. *Proc Natl Acad Sci U S A*, 92(9): 3721-5.
- Mullen, K. T., Dumoulin, S. O., McMahon, K. L., de Zubicaray, G. I. & Hess, R. F. (2007). Selectivity of human retinotopic visual cortex to S-cone-opponent, L/M-cone-opponent and achromatic stimulation. *Eur J Neurosci*, 25(2): 491-502.
- Myles, K. M., Dixon, M. J., Smilek, D. & Merikle, P. M. (2003). Seeing double: the role of meaning in alphanumeric-colour synaesthesia. *Brain Cogn*, 53(2): 342-5.
- Naghavi, H. R., Eriksson, J., Larsson, A. & Nyberg, L. (2007). The claustrum/insula region integrates conceptually related sounds and pictures. *Neurosci Lett*, 422(1): 77-80.
- Neville, H.J. (1995). Developmental specificity in neurocognitive development in humans. In: Gazzaniga, M. (Ed.), *The Cognitive Neurosciences*. MIT Press, Cambridge.
- Nigam, A., Hoffman, J.E. & Simons, R.F. (1992). N400 to semantically anomalous pictures and words. *Journal of Cognitive Neuroscience*, 4(1): 15-22.
- Nikolic, D., Lichti, P. & Singer, W. (2007). Color opponency in synaesthetic experiences. *Psychol Sci*, 18(6): 481-6.
- Nobre, A. C., Coull, J. T., Maquet, P., Frith, C. D., Vandenberghe, R. & Mesulam, M. M. (2004). Orienting attention to locations in perceptual versus mental representations. *J Cogn Neurosci*, 16(3): 363-73.
- Nunn, J. A., Gregory, L. J., Brammer, M., Williams, S. C., Parslow, D. M., Morgan, M. J., Morris, R. G., Bullmore, E. T., Baron-Cohen, S. & Gray, J. A. (2002).

- Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words. *Nat Neurosci*, 5(4): 371-5.
- Orgs, G., Lange, K., Dombrowski, J. H. & Heil, M. (2008). N400-effects to task-irrelevant environmental sounds: further evidence for obligatory conceptual processing. *Neurosci Lett*, 436(2): 133-7.
- Palmeri, T. J., Blake, R., Marois, R., Flanery, M. A. & Whetsell, W., Jr. (2002). The perceptual reality of synesthetic colors. *Proc Natl Acad Sci U S A*, 99(6): 4127-31.
- Papathanasiou, E. S., Papacostas, S. S., Charalambous, M., Eracleous, E., Thodi, C. & Pantzaris, M. (2006). Vertigo and imbalance caused by a small lesion in the anterior insula. *Electromyogr Clin Neurophysiol*, 46(3): 185-92.
- Paulesu, E., Harrison, J., Baron-Cohen, S., Watson, J. D., Goldstein, L., Heather, J., Frackowiak, R. S. & Frith, C. D. (1995). The physiology of coloured hearing. A PET activation study of colour-word synaesthesia. *Brain*, 118 (Pt 3): 661-76.
- Piazza, M., Pinel, P. & Dehaene, S. (2006). Objective correlates of an unusual subjective experience: A single-case study of number-“form synaesthesia. *Cognitive Neuropsychology*, 23(8): 1162 - 1173.
- Pinel, P., Dehaene, S., Riviere, D. & LeBihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage*, 14(5): 1013-26.
- Pinhas, M., Tzelgov, J. & Guata-Yaakobi, I. (2010). Exploring the mental number line via the size congruity effect. *Can J Exp Psychol*, 64(3): 221-5.
- Price, M. C. & Mentzoni, R. A. (2008). Where is January? The month-SNARC effect in sequence-form synaesthetes. *Cortex*, 44(7): 890-907.
- Price, M. C. (2009). Spatial forms and mental imagery. *Cortex*, 45(10): 1229-45.
- Proulx, M.J. & Stoerig, P. (2006). Seeing sounds and tingling tongues: Qualia in synaesthesia and sensory substitution. *Anthropology & Philosophy*, 7: 135-150.
- Proverbio, A. M. & Riva, F. (2009). RP and N400 ERP components reflect semantic violations in visual processing of human actions. *Neurosci Lett*, 459(3): 142-6.

- Rader, C.M. & Tellegen, A. (1987). An investigation of synesthesia. *Journal of Personality and Social Psychology*, 52(5): 981-987.
- Ramachandran, V. S. & Hubbard, E. M. (2001a). Psychophysical investigations into the neural basis of synaesthesia. *Proc Biol Sci*, 268(1470): 979-83.
- Ramachandran, V.S. & Hubbard, E.M. (2001b) Synaesthesia: A window into perception, thought and language. *Journal of Consciousness Studies*, 12: 3-34.
- Raz, N., Amedi, A. & Zohary, E. (2005). V1 activation in congenitally blind humans is associated with episodic retrieval. *Cereb Cortex*, 15(9): 1459-68.
- Ricciardi, E., Bonino, D., Gentili, C., Sani, L., Pietrini, P. & Vecchi, T. (2006). Neural correlates of spatial working memory in humans: a functional magnetic resonance imaging study comparing visual and tactile processes. *Neuroscience*, 139(1): 339-49.
- Rich, A. N. & Mattingley, J. B. (2002). Anomalous perception in synaesthesia: a cognitive neuroscience perspective. *Nat Rev Neurosci*, 3(1): 43-52.
- Rich, A. N., Bradshaw, J. L. & Mattingley, J. B. (2005). A systematic, large-scale study of synaesthesia: implications for the role of early experience in lexical-colour associations. *Cognition*, 98(1): 53-84.
- Rich, A. N., Williams, M. A., Puce, A., Syngeniotis, A., Howard, M. A., McGlone, F. & Mattingley, J. B. (2006). Neural correlates of imagined and synaesthetic colours. *Neuropsychologia*, 44(14): 2918-25.
- Rizzo, M. & Vecera, S. P. (2002). Psychoanatomical substrates of Balint's syndrome. *J Neurol Neurosurg Psychiatry*, 72(2): 162-78.
- Robertson, L. C. (2003). Binding, spatial attention and perceptual awareness. *Nat Rev Neurosci*, 4(2): 93-102.
- Rockland, K. S. & Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. *Int J Psychophysiol*, 50(1-2): 19-26.
- Roeder, B., Stock, O., Bien, S., Neville, H. & Rosler, F. (2002). Speech processing activates visual cortex in congenitally blind humans. *Eur J Neurosci*, 16(5): 930-6.

- Rouw, R. & Scholte, H. S. (2007). Increased structural connectivity in grapheme-color synesthesia. *Nat Neurosci*, 10(6): 792-7.
- Rouw, R. and Scholte, H.S. (2010). Neural basis of individual differences in synesthetic experiences. *J Neurosci*, 30:6205– 6213.
- Rugg, M. D. & Nagy, M. E. (1987). Lexical contribution to nonword-repetition effects: evidence from event-related potentials. *Mem Cognit*, 15(6): 473-81.
- Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M. P., Dold, G. & Hallett, M. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. *Nature*, 380(6574): 526-8.
- Sagiv, N. & Ward, J. (2006). Crossmodal interactions: lessons from synesthesia. *Prog Brain Res*, 155: 259-71.
- Sagiv, N., Simner, J., Collins, J., Butterworth, B. & Ward, J. (2006). What is the relationship between synaesthesia and visuo-spatial number forms? *Cognition*, 101(1): 114-28.
- Schiltz, K., Trocha, K., Wieringa, B. M., Emrich, H. M., Johannes, S. & Munte, T. F. (1999). Neurophysiological aspects of synesthetic experience. *J Neuropsychiatry Clin Neurosci*, 11(1): 58-65.
- Schroeder, C. E., Lindsley, R. W., Specht, C., Marcovici, A., Smiley, J. F. & Javitt, D. C. (2001). Somatosensory input to auditory association cortex in the macaque monkey. *J Neurophysiol*, 85(3): 1322-7.
- Schwarz, W. & Keus, I. M. (2004). Moving the eyes along the mental number line: comparing SNARC effects with saccadic and manual responses. *Percept Psychophys*, 66(4): 651-64.
- Seron, X., Pesenti, M., Noel, M. P., Deloche, G. & Cornet, J. A. (1992). Images of numbers, or "When 98 is upper left and 6 sky blue". *Cognition*, 44(1-2): 159-96.
- Shapiro, K. A., Mottaghy, F. M., Schiller, N. O., Poeppel, T. D., Fluss, M. O., Muller, H. W., Caramazza, A. & Krause, B. J. (2005). Dissociating neural correlates for nouns and verbs. *Neuroimage*, 24(4): 1058-67.

- Silver, M. A., Ress, D. & Heeger, D. J. (2005). Topographic maps of visual spatial attention in human parietal cortex. *J Neurophysiol*, 94(2): 1358-71.
- Simner, J., Mulvenna, C., Sagiv, N., Tsakanikos, E., Witherby, S.A., Fraser, C., Scott, K. & Ward, J. (2006a). Synaesthesia: the prevalence of atypical cross-modal experiences. *Perception*, 35: 1024-1033.
- Simner, J., Glover, L. & Mowat, A. (2006b). Linguistic determinants of word colouring in grapheme-colour synaesthesia. *Cortex*, 42(2): 281-9.
- Simner, J., Harrold, J., Creed, H., Monro, L. & Foulkes, L. (2009). Early detection of markers for synaesthesia in childhood populations. *Brain*, 132(Pt 1): 57-64.
- Sitnikova, T., Holcomb, P. J., Kiyonaga, K. A. & Kuperberg, G. R. (2008). Two neurocognitive mechanisms of semantic integration during the comprehension of visual real-world events. *J Cogn Neurosci*, 20(11): 2037-57.
- Smilek, D., Dixon, M. J., Cudahy, C. & Merikle, P. M. (2001). Synaesthetic photisms influence visual perception. *J Cogn Neurosci*, 13(7): 930-6.
- Smilek, D., Dixon, M. J., Cudahy, C. & Merikle, P. M. (2002). Concept driven color experiences in digit-color synesthesia. *Brain Cogn*, 48(2-3): 570-3.
- Smilek, D., Callejas, A., Dixon, M. J. & Merikle, P. M. (2007). Ovals of time: time-space associations in synaesthesia. *Conscious Cogn*, 16(2): 507-19.
- Spalding, J. M. & Zangwill, O. L. (1950). Disturbance of number-form in a case of brain injury. *J Neurol Neurosurg Psychiatry*, 13(1): 24-9.
- Sperling, J. M., Prvulovic, D., Linden, D. E., Singer, W. & Stirn, A. (2006). Neuronal correlates of colour-graphemic synaesthesia: a fMRI study. *Cortex*, 42(2): 295-303.
- Spiller, M. J. & Jansari, A. S. (2008). Mental imagery and synaesthesia: Is synaesthesia from internally-generated stimuli possible? *Cognition*, 109(1): 143-51.
- Stein, J. F. (1989). Representation of egocentric space in the posterior parietal cortex. *Q J Exp Physiol*, 74(5): 583-606.
- Steven, M. S. & Blakemore, C. (2004). Visual synaesthesia in the blind. *Perception*, 33(7): 855-68.

- Steven, M. S., Hansen, P. & Blakemore, C. (2004). Implicit Synesthesia: Non-synesthetes with reproducible colour-word associations. *Society for Neuroscience Abstracts*, 664:19.
- Steven, M. S., Hansen, P. C. & Blakemore, C. (2006). Activation of color-selective areas of the visual cortex in a blind synesthete. *Cortex*, 42(2): 304-8.
- Stovner, L. J., Zwart, J. A., Hagen, K., Terwindt, G. M. & Pascual, J. (2006). Epidemiology of headache in Europe. *Eur J Neurol*, 13(4): 333-45.
- Stroop, J.R., 1935. Studies of interference in serial verbal reactions. *J Exp Psychol*, 18: 643-662.
- Tanaka, J. W. & Curran, T. (2001). A neural basis for expert object recognition. *Psychol Sci*, 12(1): 43-7.
- Tang, J., Ward, J. & Butterworth, B. (2008). Number forms in the brain. *J Cogn Neurosci*, 20(9): 1547-56.
- Tomson, S. N., Avidan, N., Lee, K., Sarma, A. K., Tushe, R., Milewicz, D. M., Bray, M., Leal, S. M. & Eagleman, D. M. (2011). The genetics of colored sequence synesthesia: Suggestive evidence of linkage to 16q and genetic heterogeneity for the condition. *Behav Brain Res*, 223(1): 48-52.
- Treisman, A. M. & Gelade, G. (1980). A feature-integration theory of attention. *Cogn Psychol*, 12(1): 97-136.
- Trojano, L., Grossi, D., Linden, D. E., Formisano, E., Hacker, H., Zanella, F. E., Goebel, R. & Di Salle, F. (2000). Matching two imagined clocks: the functional anatomy of spatial analysis in the absence of visual stimulation. *Cereb Cortex*, 10(5): 473-81.
- Turriziani, P., Oliveri, M., Bonni, S., Koch, G., Smirni, D. & Cipolotti, L. (2009). Exploring the relationship between semantics and space. *PLoS One*, 4(4): e5319.
- Van Leeuwen, T. M., Petersson, K. M. & Hagoort, P. (2010). Synaesthetic colour in the brain: beyond colour areas. A functional magnetic resonance imaging study of synaesthetes and matched controls. *PLoS One*, 5(8): e12074.

- Van Leeuwen, T.M., Den Ouden, H.E.M., Hagoort, P. (2011). Effective connectivity determines the nature of subjective experience in grapheme-color synesthesia.
- Van Opstal, F., Verguts, T., Orban, G. A. & Fias, W. (2008). A hippocampal-parietal network for learning an ordered sequence. *Neuroimage*, 40(1): 333-41.
- Vanlierde, A., De Volder, A. G., Wanet-Defalque, M. C. & Veraart, C. (2003). Occipito-parietal cortex activation during visuo-spatial imagery in early blind humans. *Neuroimage*, 19(3): 698-709.
- Walker, P. & Smith, S. (1984). Stroop interference based on the synaesthetic qualities of auditory pitch. *Perception*, 13(1): 75-81.
- Ward, J. & Simner, J. (2003). Lexical-gustatory synaesthesia: linguistic and conceptual factors. *Cognition*, 89(3): 237-61.
- Ward, J., Simner, J. & Auyeung, V. (2005). A comparison of lexical-gustatory and grapheme-color synaesthesia. *Cognitive Neuropsychology*, 22(1): 28-41.
- Ward, J. & Mattingley, J. B. (2006). Synaesthesia: an overview of contemporary findings and controversies. *Cortex*, 42(2): 129-36.
- Ward, J., Huckstep, B. & Tsakanikos, E. (2006). Sound-colour synaesthesia: to what extent does it use cross-modal mechanisms common to us all? *Cortex*, 42(2): 264-80.
- Ward, J., Li, R., Salih, S. & Sagiv, N. (2007). Varieties of grapheme-colour synaesthesia: a new theory of phenomenological and behavioural differences. *Conscious Cogn*, 16(4): 913-31.
- Weeks, R., Horwitz, B., Aziz-Sultan, A., Tian, B., Wessinger, C. M., Cohen, L. G., Hallett, M. & Rauschecker, J. P. (2000). A positron emission tomographic study of auditory localization in the congenitally blind. *J Neurosci*, 20(7): 2664-72.
- Weiss, P. H., Zilles, K. & Fink, G. R. (2005). When visual perception causes feeling: enhanced cross-modal processing in grapheme-color synesthesia. *Neuroimage*, 28(4): 859-68.
- Weiss, P. H. & Fink, G. R. (2009). Grapheme-colour synaesthetes show increased grey matter volumes of parietal and fusiform cortex. *Brain*, 132(Pt 1): 65-70.

- Weiss, P. H., Kalckert, A. & Fink, G. R. (2009). Priming letters by colors: evidence for the bidirectionality of grapheme-color synesthesia. *J Cogn Neurosci*, 21(10): 2019-26.
- Wittchen, H. U. & Pittrow, D. (2002). Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. *Hum Psychopharmacol*, 17 Suppl 1: S1-11.
- Witthoft, N. & Winawer, J. (2006). Synesthetic colors determined by having colored refrigerator magnets in childhood. *Cortex*, 42(2): 175-83.
- Wolff, P. H., Matsumiya, Y., Abrams, I. F., van Velzer, C. & Lombroso, C. T. (1974). The effect of white noise on the somatosensory evoked response in sleeping newborn infants. *Electroencephalogr Clin Neurophysiol*, 37(3): 269-74.
- Wollen, K.A. & Ruggiero, F.T. (1983). Coloured-letter synesthesia. *Journal of Mental Imagery*, 7: 83-6.
- Xiao, X., Qiu, J. & Zhang, Q. (2009). The dissociation of neural circuits in a Stroop task. *Neuroreport*, 20(7): 674-8.

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Erklärung

Die hier vorgelegte Dissertation habe ich eigenständig und ohne unerlaubte Hilfsmittel angefertigt. Die Dissertation wurde in der vorliegenden oder in ähnlicher Form bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Valentina Niccolai

Publications

M. van Duinen, **V. Niccolai** , E. Griez (2010). Challenging Anxiety. A Focus on the Specificity of Respiratory Symptoms. *Current Topics in Behavioral Neurosciences*, 2:229-50.

V. Niccolai, M. van Duinen, E. Griez (2009). Respiratory patterns in panic disorder reviewed: a focus on biological challenge tests. *Acta Psychiatrica Scandinavica*, 22; 120(3):167-177.

V. Niccolai, M. van Duinen, E. Griez (2008). Objective and Subjective measures in recovery from 35%CO₂ challenge. *Canadian Journal of Psychiatry*, 53(11):737-44.

F. Galassi, S. Quercioli, D. Charismas, **V. Niccolai**, E. Barciulli (2007) Cognitive-behavioural group treatment for panic disorder with agoraphobia. *J Clin Psychol*, 63(4):409-16.

Oral presentations

V. Niccolai, T. Van Leeuwen, C. Blakemore, P. Stoerig. (2011). Colour and visuospatial perception in a blind subject: an fMRI case study on synaesthesia. UK Synaesthesia Association Annual Conference. London, United Kingdom.

Conference Posters

V. Niccolai and P. Stoerig. *Synaesthesia for Personality: a case report*. (2009). III International Congress on Synaesthesia, Science and Art. Granada, Spain.

V. Niccolai, S. Sieloff, I. Knoll, P. Stoerig. *An Internet Survey of Synaesthesia*. (2008). Action BM0605: Consciousness: A transdisciplinary, Integrated Approach, COST. Ghent, Belgium.

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