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Inside a synesthete's head: A functional connectivity analysis with grapheme-color synesthetes

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ABSTRACT

Grapheme-color synesthesia is a condition in which letters are perceived with an additional color dimension. To identify brain regions involved in this type of synesthesia and to analyze functional connectivity of these areas, 18 grapheme-color synesthetes and 18 matched controls were stimulated with letters and pseudo-letters presented in black and color in an event-related fMRI experiment. Based on the activation-differences between synesthetes and non-synesthetic controls regions of interest were defined. In a second analysis step functional connectivity was calculated using beta series correlation analysis for these seed regions. First we identified one seed region in the left inferior parietal (IPL) cortex (BA7) showing activation differences between grapheme-color synesthetes and controls. Furthermore, we found activation differences in brain areas involved in processing of letters and pseudo-letters, in particular the right IPL cortex (BA7), but also two more clusters in the right hemispheric BA 18 and BA 40. Functional connectivity analysis revealed an increased connectivity between the left IPL seed region and primary/secondary visual areas (BA 18) in synesthetes. Also the right BA 7 showed a stronger connectivity with primary/secondary visual areas (BA 18) in grapheme-color synesthetes. The results of this study support the idea that the parietal lobe plays an important role in synesthetic experience. The data suggest furthermore that the information flow in grapheme-color synesthetes was already modulated at the level of the primary visual cortex which is different than previously thought. Therefore, the current models of grapheme-color synesthesia have to be refined as the unusual communication flow in synesthetes is not restricted to V4, fusiform cortex and the parietal lobe but rather involves a more extended network.

1. Introduction

Genuine synesthesia (Greek: syn=together, aesthesis=sensation) is a condition in which stimulation in one sensory modality elicits a sensation in an unstimulated, other sensory modality. This unusual coupling can also occur within the same sensory modality, as it is the case in grapheme-color synesthesia. Especially in this form of synesthesia, which at first sight appears to involve only vision, broad evidence for participation of higher-level cognitive functions related to speech processing could be shown. Thus, the perception of colors for written symbols depends on the meaning and phonological information of the symbols which was shown in studies in which subjects learned a new language (Asano & Yokosawa, 2012; Mroczko, Metzinger, Singer & Nikolic, 2009) or where the synesthetic perception was related to late perceptual processes in McGurk speech situations (Bargary, Barnett, Mitchell & Newell, 2009).

Synesthesia is a very heterogeneous phenomenon with many distinct types (Day, 2004). Each type is characterized by its specific inducer-concurrent pairing in which the sensory specific stimulus is called inducer and the additional sensation in the unstimulated modality is called concurrent. The different types of synesthesia are named according to their inducer-concurrent pair (Grossenbacher & Lovelace, 2001). In music-color synesthesia, for example, music can elicit colors and shapes (Ward, Huckstep & Tsakanikos, 2006). Certain types like grapheme-color and day-color synesthesia are more likely to co-occur with other types of synesthesia so that there seem to exist different subgroups of synesthesia (Novich, Cheng & Eagleman, 2011). The currently most investigated form is grapheme-color synesthesia, affecting approximately 1% of the population (Simner et al., 2006). In grapheme-color synesthesia, coupling of letters and colors occurs automatically (Mills, Boteler & Oliver, 1999), and each synesthete has his own individual pairing (Cytowic, 2002); hence, one grapheme-color synesthete may perceive the letter as A green

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whereas another as red. Moreover, the synesthetic coupling is characterized by stable inducer concurrent couplings which may persist over long periods of time (Baron-Cohen, Wyke & Binnie, 1987; Simner & Logie, 2007).

The mechanism causing synesthesia is still unknown, but currently different hypothetical models are being discussed. The cross-activation theory states that unusual direct connections between the brain areas that process the inducer (e.g. letters) and the concurrent (e.g. colors), lead to the synesthetic perception (Ramachandran & Hubbard, 2001). These connections are thought to be caused by a pruning deficit in childhood (Maurer & Mondloch, 2004). A recent alternative hypothesis proposes the two-stage model, which assumes that grapheme-color synesthesia is caused by a direct cross-activation of color and grapheme related brain areas, together with an additional, more sensitive parietal binding mechanism (Hubbard, 2007; Hubbard, Brang & Ramachandran, 2011). Another theory, the disinhibited-feedback theory assumes that synesthesia occurs through a disinhibition of feedback projections from multimodal centers (Grossenbacher & Lovelace, 2001). In this way the signal is routed from 'higher' multimodal areas down to the areas processing the concurrent, while in non-synesthetes these recurrent signals are inhibited. A third theory states that parietal multimodal integration mechanisms are more sensitive in synesthetes leading to the unusual coupling seen in synesthesia (Esterman, Verstynen, Ivry & Robertson, 2006). Finally, a very recent hypothesis states that synesthetes have a generally hyperconnected brain and that synesthesia can be seen as a phenotypic manifestation of the globally altered network structure (Hanggi, Wotruba & Jancke, 2011).

Taking into account brain imaging evidence supporting the different models, a very heterogeneous picture arises (Rouw, Scholte & Colizoli, 2011). Some studies found a stronger activation of the human brain color center V4 in grapheme-color synesthetes compared to control subjects (Sperling, Prvulovic, Linden, Singer & Stirn, 2006; Nunn et al., 2002; Brang, Hubbard, Coulson, Huang & Ramachandran, 2010; Hubbard, Arman, Ramachandran & Boynton, 2005; van Leeuwen, Petersson & Hagoort, 2010) while others found activity in parietal (Weiss, Zilles & Fink, 2005; Paulesu et al., 1995) and frontal brain areas (Paulesu et al., 1995; Rouw & Scholte, 2007). Those heterogeneous findings seen in grapheme-color synesthesia may result from the relatively small sample sizes utilized in most studies (median: 7, range: between 1 and 42 subjects, see Table 1S in supplemental material 1 for details of included studies), but also because different experimental paradigms were used. Both variables may lead to a high variance between subjects in the recorded activation magnitude (Smith et al., 2005) and therefore lead to more heterogeneous results. It has been suggested previously that at least 12 subjects should participate in a fMRI group study (Desmond & Glover, 2002) but high reliability and sensitivity will only be achieved with more than 20 subjects (Thirion et al., 2007). To our knowledge, up to now only a few studies investigated more than 12 grapheme-color synesthetes with MRI imaging techniques, all pointing to an involvement of the parietal cortex in mediating synesthetic experience: a diffusion tensor imaging (DTI) study (Rouw & Scholte, 2007), two voxel-based morphometry (VBM) study (Weiss & Fink, 2009; Rouw & Scholte, 2010), a surface based morphometry study (Hanggi et al., 2011) and two functional magnetic resonance imaging (fMRI) studies (van Leeuwen et al., 2010; Rouw & Scholte, 2010). The DTI study shows that the structural connectivity within the superior parietal and the inferior temporal cortex is increased in grapheme-color synesthetes (Rouw & Scholte, 2007). The VBM study found increased grey matter volumes in synesthetes in both the fusiform and the intraparietal cortex (Weiss & Fink, 2009). The fMRI study of Rouw & Scholte, 2010 showed higher activation in the intraparietal sulcus, the inferior frontal gyrus and the parieto-occipital junction in the left hemisphere for synesthetes, whereas van Leeuwen et al. (2010) found additional activation in the left superior parietal lobule in synesthesia. Parietal involvement has also been found by resting state EEG analysis, in particular, that in synesthetes the parietal lobe is connected functionally stronger with other brain areas (Jäncke & Langer, 2011). Taken together, there is growing evidence that mechanisms involving both the parietal and the frontal cortices play an important role in synesthesia, while the role of V4 area is still being discussed (Hupe, Bordier & Dojat, 2012). Up to now it is unclear how these areas communicate with other parts of the brain in synesthetes and if connectivity differences could be related to synesthetic perception.

Functional connectivity analysis of fMRI data is well suited to tackle this problem, as it is defined as the analysis of the temporal relationship between spatially remote neurophysiological events, therefore characterizing functional interactions (Friston, Frith, Liddle & Frackowiak, 1993). This approach assumes that regions involved in processing the same task should correlate their activity. In this study we therefore used a correlation-based approach according to Rissmann, Gazzaley & D'Esposito (2004) as it allows identifying networks involved in a certain cognitive task. Interestingly, using this method it could be shown previously that the inferior parietal cortex of auditory-visual synesthetes is connected functionally stronger with primary visual and auditory areas than in non synesthetes (Neufeld et al., 2012b).

The aim of this study was two-fold: first, we wanted to estimate brain activation underlying synesthetic perception in 18 grapheme-color synesthetes in order to define seed areas for further connectivity analysis and increase the knowledge about those brain areas involved in this type of synesthesia. Second, we wanted to study the functional connectivity of areas involved in grapheme-color synesthesia in order to evaluate the aforementioned hypothetical models. In particular, we sought to understand if the inferior parietal cortex identified as crucial in auditory-visual synesthesia (Neufeld et al., 2012a,2012b), played a similar role in grapheme-color synesthetes.

2. Methods

2.1. Subjects

18 grapheme-color synesthetes and 18 non-synesthetic control subjects participated in the experiment. The groups were matched for age (synesthetes: 34 ± 15 years, controls: 34 ± 13 years), gender (4 males per group), handedness (2 left handed per group) and general intelligence (synesthetes: 114.6 ± 10.7, controls: 115.7 ± 17.3) as assessed by the MWT-B ('Mehrfach Wortschatz Test'); (Lehrl, Triebig & Fischer, 1995). Subjects were also matched for their vividness of visual imagination (VVIQ; (Marks, 1973) synesthetes: 60 ± 13, controls 65 ± 15), as Barnett proposed differences in the vividness of imagination as a possible confounding factor in synesthesia research (Barnett & Newell, 2008). The VVIQ-test consists of a questionnaire in which subjects rate the visual quality of 4 different aspects of 4 imagined scenes involving persons, landscapes and everyday activities (shopping) on a scale between 1 and 5 where 1 means a picture-like image and 5 means without any visual qualities. The imagined scenes are rated twice, once with eyes open and once with eyes closed. The VVIQ score is the mean overall 32 questions (16 ratings with open eye and 16 rating with closed eyes). All 36 subjects gave written informed consent and the study was approved by the local ethic committee of the Hannover Medical School. The subjects participated voluntarily and received a small monetary recompense for their participation.

2.2. Assessing grapheme-color synesthesia

Synesthesia was assessed using an offline MATLAB version of the synesthesia battery (http://www.synesthete.org/), and an extensive interview. In the synesthesia battery, numbers from 0 to 9 (10) and the letters from the alphabet from A to Z (26) were presented and synesthetes had to select a color which matched their synesthetic experience best, while controls had to chose a color