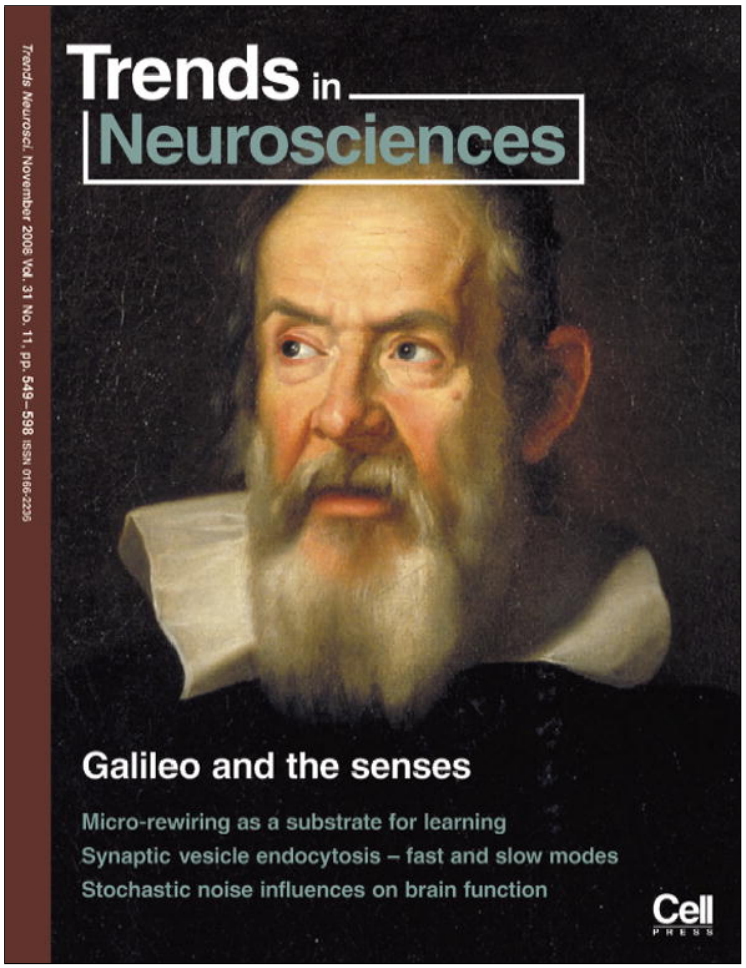

induce the grapheme-colour synaesthetic experience in non-synaesthetes and, therefore, in the absence of excess connections. By using a posthypnotic suggestion, we induced a grapheme-colour synaesthesia with stable associations and similar phenomenology and behaviours to those observed in developmental synaesthesia [15].

Although we agree with Bargary and Mitchell's case that identifying the genes that might predispose to synaesthesia might be crucial for identifying the cause(s) of synaesthesia, there are good reasons to believe that disinhibition has as great a role in synaesthesia as abnormal connectivity. We, therefore, suggest that we do not prematurely inhibit or disinhibit possible mechanisms.

References

1 Muggleton, N. *et al.* (2007) Disruption of synaesthesia following TMS of the right posterior parietal cortex. *Neuropsychologia* 45, 1582–1585
2 Bargary, G. and Mitchell, K.J. (2008) Synaesthesia and cortical connectivity. *Trends Neurosci.* 31, 335–342
3 Grossenbacher, P.G. and Lovelace, C.T. (2001) Mechanisms of synesthesia: cognitive and physiological constraints. *Trends Cogn. Sci.* 5, 36–41
4 Cohen Kadosh, R. and Henik, A. (2007) Can synaesthesia research inform cognitive science? *Trends Cogn. Sci.* 11, 177–184
5 Rouw, R. and Scholte, H.S. (2007) Increased structural connectivity in grapheme-color synesthesia. *Nat. Neurosci.* 10, 792–797
6 Hebb, D.O. (1949) *The Organization of Behavior*, Wiley
7 Hensch, T.K. (2005) Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* 6, 877–888
8 Knudsen, E.I. (2004) Sensitive periods in the development of the brain and behavior. *J. Cogn. Neurosci.* 16, 1412–1425
9 Cohen Kadosh, R. *et al.* Synaesthesia: learned or lost? *Dev. Sci.* (in press)
10 Beeli, G. *et al.* (2008) Time course of neural activity correlated with colored-hearing synesthesia. *Cereb. Cortex* 18, 379–385
11 Goller, A.I. *et al.* Seeing sounds and hearing colors: an event-related potential study of auditory-visual synaesthesia. *J. Cogn. Neurosci.* (in press)
12 Brosch, M. *et al.* (2005) Nonauditory events of a behavioral procedure activate auditory cortex of highly trained monkeys. *J. Neurosci.* 25, 6797–6806
13 Dixon, M.J. *et al.* (2004) Not all synaesthetes are created equal: projector versus associator synaesthetes. *Cogn. Affect. Behav. Neurosci.* 4, 335–343
14 Ward, J. *et al.* (2007) Varieties of grapheme-colour synaesthesia: a new theory of phenomenological and behavioural differences. *Conscious Cogn.* 16, 913–931
15 Cohen Kadosh, R. *et al.* Induced cross-modal synesthetic experience without abnormal neuronal connections. *Psychol. Sci.* (in press)

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Letters Response

Response to Cohen Kadosh and Walsh: Synaesthesia: evaluating competing theories

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We are grateful to Cohen Kadosh and Walsh [1] for raising several important and interesting points in relation to our article. Our intent was to stimulate, not stifle, debate on the mechanisms that underlie synaesthesia by considering it in the context of known principles of cortical connectivity. We would like to point out that we did not 'conclude' that structural differences are the primary cause of developmental synaesthesia, but, rather, presented arguments and reviewed evidence that we think favour that hypothesis. This included data from a recent diffusion-tensor-imaging study, which provided evidence for altered structural connectivity in the brains of synaesthetes [2,3]. These findings are consistent with a structural difference as the primary cause of synaesthesia, but Cohen Kadosh and Walsh [1] are absolutely correct in pointing out that such correlations do not indicate the direction of causality. Altered activity patterns during crucial periods of development, due to a primarily functional difference, would also be likely to result in secondary structural differences.

However, the result of this study was only one of many factors that, to our minds, make a structural hypothesis plausible. We find the structural hypothesis appealing because it is detailed, parsimonious and consistent with the known effects of neurodevelopmental mutations. Our main difficulty with the various versions of the disinhibition hypothesis is that none has been presented in sufficient neuroanatomical and neurophysiological detail to assess. For a model of disinhibition to be heuristically useful it should propose answers to the following questions. Which circuits are disinhibited? By what mechanism would just those circuits be disinhibited? How would their disinhibition result in cortical cross-activation and synaesthetic associations, without more widespread effects?

Cohen Kadosh and Walsh [1] propose, as an example, that mutations in genes affecting γ-aminobutyric acid (GABA)ergic neurotransmission might lead to an inhibitory imbalance in the cortex, resulting in a failure of cortical areas to specialize during crucial periods of cognitive development [4]. How this would result in a failure to specialize is not made clear, however, nor are any arguments given as to how this would lead specifically to the kinds of extra associations that occur in synaesthesia, as opposed to more widespread neurological defects. In fact, in the specific case of genes affecting GABAergic neurotransmission, mutations in many of these result in epilepsy

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[5], and disturbances in this pathway have also been implicated in schizophrenia [6]. By contrast, the appeal of neurodevelopmental genes as candidates is that mutations in such genes are known to result in very specific types of miswiring between [7], and/or within [8], particular areas, which could plausibly lead to cross-activation and, independently, to altered unisensory processing (see later).

Cohen Kadosh and Walsh [1] also cite two recent electroencephalography studies as supporting a disinhibition hypothesis [9,10]. These studies found, in coloured-hearing synaesthetes, alterations in auditory-evoked potentials (AEPs) to sounds that induced a synaesthetic experience. Our group has recently conducted a study of visual-evoked potentials (VEPs) in grapheme-colour synaesthetes and found robust differences in the amplitude of very early components of the VEP to simple visual stimuli that do not induce synaesthesia [11]. The results of these studies are, thus, equally consistent with structural-wiring differences in early sensory cortices that alter responsiveness to all stimuli and that might be independent of those that cause the synaesthetic experience itself.

Finally, Cohen Kadosh and Walsh [1] suggest that fundamentally different mechanisms might underlie different types of synaesthesia. We have reviewed genetic evidence that we think argues against this idea. In a survey of families with multiple synaesthetes we found that, although many families showed only the most common type of synaesthesia (linguistic-colour), very different types of synaesthesia can co-occur in some families [12,13] and also in individuals [14]. The most parsimonious explanation is that a common mechanism underlies different types. Thus, a predisposition to develop synaesthesia might be inherited, but the specific type and the particular associations that emerge would be determined by other factors, such as gene–gene interactions, intrinsic developmental variation and experience [12,15]. Mechanistically, this might arise if connectivity differences in the brains of synaesthetes were initially widespread but resolved differently in different parts of the brain under the influence of these other factors.

Although we favour a structural hypothesis for the reasons stated here, we recognize that these arguments are far from conclusive. We look forward to more discussions on the possible mechanisms whereby disinhibition might lead to synaesthesia, either directly, by acutely causing cross-activation, or indirectly, by altering the normal activity of the brain during crucial periods of development. We strongly agree with what we take to be the broad outlook of Cohen Kadosh and Walsh; that is, whatever the primary cause of synaesthesia, an understanding of the interplay between structural and functional changes over the course of development, both prenatal and postnatal, will be necessary to fully understand this fascinating phenomenon [15,16].

References

1 Cohen Kadosh, R. and Walsh, V. (2008) Synaesthesia and cortical connections: cause or correlation? *Trends Neurosci.* 31, 549–550
2 Rouw, R. and Scholte, H.S. (2007) Increased structural connectivity in grapheme-color synesthesia. *Nat. Neurosci.* 10, 792–797
3 Hänggi, J. *et al.* The multiple synaesthete E.S. – neuroanatomical basis of interval-taste and tone-colour synaesthesia. *Neuroimage* (in press)
4 Cohen Kadosh, R. *et al.* Synaesthesia: learned or lost? *Dev. Sci.* (in press)
5 Turnbull, J. *et al.* (2005) Sacred disease secrets revealed: the genetics of human epilepsy. *Hum. Mol. Genet.* 14, 2491–2500
6 Lewis, D.A. *et al.* (2005) Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* 6, 312–324
7 Dufour, A. *et al.* (2003) Area specificity and topography of thalamocortical projections are controlled by ephrin/Eph genes. *Neuron* 39, 453–465
8 Cang, J. *et al.* (2005) Ephrin-As guide the formation of functional maps in the visual cortex. *Neuron* 48, 577–589
9 Beeli, G. *et al.* (2008) Time course of neural activity correlated with colored-hearing synesthesia. *Cereb. Cortex* 18, 379–385
10 Goller, A.I. *et al.* Seeing sounds and hearing colors: an event-related potential study of auditory-visual synaesthesia. *J. Cogn. Neurosci.* (in press)
11 Barnett, K.J. *et al.* (2008) Differences in early sensory-perceptual processing in synesthesia: a visual evoked potentials study. *Neuroimage*, DOI: 10.1016/j.neuroimage.2008.07.028 (www.sciencedirect.com)
12 Barnett, K.J. *et al.* (2008) Familial patterns and origins of individual differences in synaesthesia. *Cognition* 106, 871–893
13 Ward, J. *et al.* (2005) A comparison of lexical-gustatory and grapheme-colour synaesthesia. *Cogn. Neuropsychol.* 22, 28–41
14 Simner, J. and Hubbard, E.M. (2006) Varieties of synaesthesia interact in cognitive tasks: evidence for implicit associations and late connectivity in crosstalk theories. *Neuroscience* 143, 805–814
15 Mitchell, K.J. (2007) The genetics of brain wiring; from molecule to mind. *PLoS Biol.* 5, e113
16 Karmiloff-Smith, A. (2006) The tortuous route from genes to behavior: a neuroconstructivist approach. *Cogn. Affect. Behav. Neurosci.* 6, 9–17

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