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Medical Hypotheses (2007) ~~x, xxx–xxx~~
2008, Vol. 70(4): 903–904

medical hypotheses

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Psychopharmacology of synesthesia; the role of serotonin S2a receptor activation

Synesthesia is a hereditary condition seen in 4% of the general population – different tones evoke different colors or every grapheme (visually presented number or alphabet) is tinged with a specific color [1–3]. The synesthetically [4] induced color vanishes at low contrast and can lead to perceptual texture segregation and apparent motion [5]; evidence that it is an early sensory process. We proposed that grapheme – color synesthesia is caused by ''anatomical cross wiring'' between the color area V4 and ''number area'' which lie next to each other in the fusiform gyrus. Recent DT imaging has confirmed this [6]. These effects are seen only in a subset of synesthetes we call ''lower synesthetes'' (about 15% of all synesthetes). We also suggested that in another group (''higher synesthetes'') the cross wiring is at a higher more cognitive level in the vicinity of the angular gyrus; this too is consistent with DT imaging results.

In addition to cross wiring (caused by ''defective pruning'' genes) there may also be a pharmacological basis for some types of synesthesia. We report four observations (including three new ones) which support this and present a specific pharmacological model.

(1) LSD produces synesthesia. It selectively activates serotonin S2a receptors suggesting that S2a receptors are involved in synesthesia.
(2) We encountered two subjects in whom Prozac inhibited synesthesia. Prozac being an SSRI increases serotonin and activates S1 receptors – hyperactivation of which is known to inhibit S2a [7].
(3) In another subject Wellbutrin (a norepinephrine and dopamine reuptake inhibitor) abolished synesthesia temporarily, presumably also by inhibiting S2a receptors (norepinephrine indirectly mediates serotonin release) [8].
(4) Finally we encountered a subject who experienced grapheme – color synesthesia (various shades of bluish hue) for the first time in his life when he took 5 mg melatonin. He ''passed'' the objective texture segregation test suggesting that his experience of colors is genuine and sensory. The synesthesia could be turned off or on by withholding or administering melatonin. Serotonin is metabolized into melatonin in the brain which feeds back to inhibit serotonin production. This reduces S1 activation and consequently dis-inhibits S2a receptors leading to synesthesia.

All four findings fit. We propose that serotonin S2a receptors are the ''synesthesia receptors'' in the brain. Their activity can be modulated by various drugs (or indeed by meditation) as noted above. The last subject mentioned above had number – form synesthesia (seeing numbers sequentially represented in specific locations in space) suggesting that he may have already had a mild genetic propensity for grapheme – color synesthesia as well (depending how extensively in the brain the defective pruning gene is expressed). Consuming melatonin allowed the tendency to reach threshold causing overt grapheme – color synesthesia.

We are currently exploring the effect of other S2a antagonists (such as Haloperidol and Methysergide) in inhibiting synesthesia. Our model would also predict a higher incidence of synesthesia in schizophrenics and implicates gene HTR2A on chromosome 13q as the underlying cause of synesthesia. These key questions may be well supported by the use of Positron Emission Tomography with [^{11}C]MDL 100,907 (a selective S2a receptor ligand).

0306-9877/$ - see front matter
doi:10.1016/j.mehy.2007.09.007

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