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Refining the Experimental Lever

A Reply to Shanon and Pribram

The commentaries by Shanon (2003) and Pribram (2003) on our original article (Ramachandran & Hubbard, 2001) are stimulating and make a valuable contribution to the knowledge and thinking about synaesthesia, and indeed the mind in general. We were gratified to see the overall level of agreement with our general framework. For example, both of the authors endorse our connection between the perceptual phenomenon of synaesthesia and the cognitive phenomenon of metaphor. Shanon not only endorses our view, but also provides additional data supporting parallels between synaesthesia and metaphor. Pribram is especially complimentary concerning our hypothesis concerning the neural basis of representations, and our suggestions that map-to-map interactions are critical for translations between these representations.

In this reply, we would like to focus on the remaining points which still separate us. Rather than discuss the commentaries point by point, we would like to offer some of our own thoughts in response to their comments. There are four areas we would like to discuss and elaborate on: (1) trends in synaesthetic colours, including the fact that synaesthetic triggers are highly specific, categorical stimuli, such as calendars, numbers and letters, and specific musical pitches; (2) further details of our hypothesis concerning the origin of synaesthesia; (3) the evidence suggesting that synaesthesia is, contrary to Shanon's arguments, genetic; and (4) the connection between synaesthesia and psychedelics.

I: Trends in Synaesthetic Colours

In his commentary, Shanon reports data concerning the non-randomness of synaesthetic associations. The question of whether synaesthetic associations are regular has been one of fundamental importance since the earliest days of research into synaesthesia, and Shanon briefly describes data from a study he conducted examining these regularities in synaesthetic associations (Shanon, 1982; McKellar, 1957). The regularities Shanon and McKellar have noted are

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striking, and should be taken seriously by any theory of synaesthesia. One concern is that these data were obtained on a small sample of subjects (16). However, more recent analyses (Day, 2001; Day, personal communication) have replicated and extend some of Shanon's basic findings in a sample of 167 (now extended to over 300) grapheme–colour synaesthetes. For example, Day reports that 43% of synaesthetes experience A as being red in colour, while E is about equally often blue, yellow or green (17%, 20% and 15%, respectively). I and O are often either black or white (as are 1 and 0, Day personal communication).

One important factor, which we cannot determine from Shanon's small sample, is whether the synaesthetes represented in this data set all experience the same form of synaesthesia or whether some of the synaesthetes in this group were 'higher' synaesthetes while others were 'lower' synaesthetes. Given that different forms of synaesthesia probably depend on cross activation at different stages of cortical processing, it will be important for future studies to take this into consideration. For example, in the case of lower synaesthetes, in whom the colour experience is dominated by perceptual attributes, we would predict that 0 and O and 1 and I, because of their visual similarity, would share similar colours. On the other hand, in the case of higher synaesthetes, in whom order seems to be much more of a determining factor for colour experiences, we might expect that 0 or 1 would have the same colour as Sunday, and so on, as described by Shanon. This distinction needs to be investigated further. Since Day's previous reports describe overall, general trends in synaesthetic experiences, and not patterns and structure within an individual synaesthete's experiences, they do not allow us to further test Shanon's hypothesis.

One possible factor that may lead to the non-randomness observed in synaesthetic pairings is that letters, numbers, and colour names are acquired in development in a non-random order. Certain numbers are more commonly learned early in development (Dehaene & Mehler, 1992), as is the alphabetic order. Finally, it should be noted that children acquire colour terms in a common developmental order, which mimics the colour term typology described by Berlin & Kay (1969). Thus, it could be that the genetic factors described above interact with the learning of letters, numbers and colour terms in a non-random manner, leading to the regularities observed in synaesthetic colour associations.

Alternatively, we suggest that the mapping of the colours to the letters of the alphabet in higher synaesthetes may reflect the manner in which phonemes are mapped in Broca's area. For example, front vowels, intermediate and back, may be mapped systematically in a motor map, and this in turn may cross activate a map that represents numerical sequence. By way of analogy, consider the fact that in the periodic table of elements, the rules of arrangement of elements seemed arbitrary and irrational until the correct measure (i.e., atomic number, rather than atomic weight) was used. Likewise, the mapping of colours to numbers may be non-random (as shown by Shanon) but we are suggesting that, in addition to being non-random, it is also non-arbitrary. Instead, we propose that it may be determined by internal rules of congruence or translation between brain

maps. Further research into regularities in synaesthetic associations will have to take both these developmental and neural considerations into account.

It should be noted that the triggers that lead to synaesthetic experiences are letters, numbers, days of the week, musical tones, and the like. The significance of this fact has been largely overlooked in previous accounts of synaesthesia. Subcortical brain structures do not distinguish between, for example, A and O or Monday and Tuesday, so it is not clear why one should be red and the other black, if synaesthesia were simply a result of subcortical processing, as implied by Shanon (2003). We are not saying that subcortical structures play no role in synaesthesia, but it is clear that cortical representations must play a major role (as Cytowic now admits in the revised edition of his classic book, Cytowic, 1989/2002).

II: The Neural Basis of Synaesthesia

Second, in light of both Shanon's and Pribram's comments, we would like to further explain the thinking that led to our 'cross activation' hypothesis. Our hypothesis concerning synaesthesia and cross activation builds on previous work with phantom limb patients (Ramachandran *et al*., 1992). Phantom limbs occur when a limb has been amputated, but is still felt to be present. Although this phenomenon had been known for over a century (e.g., Weir-Mitchell, 1871) no compelling explanation had been put forward. In a study of monkeys who had their sensory nerves cut (de-afferentation) Pons *et al.* (1991) using single cell recordings found that, 11 years after de-afferentation, primary somatosensory cortex had re-organized, such that regions of cortex that respond to the face had 'invaded' regions of cortex that were previously specialised for the representation of the hand. Pons *et al.* further argued that this re-organisation was a result of neural 'sprouting' or the formation of new cortical connections between the input carried by neurons coming from the face, and regions of cortex that had been previously dedicated to representing the (now missing) hand input.

These physiological observations led one of us (VSR) to propose that phantom limb sensations may also arise through similar cortical sprouting in humans, and tested this by showing that stimulation of the cheek led to *systematic, organised* sensations of the phantom limb being stimulated (Ramachandran *et al.*, 1992). Additionally, MEG experiments (Yang *et al.*, 1994) showed that human cortex reorganised in a manner similar to that observed in monkey physiology studies. Two observations, which we have not made explicit enough in previous writings, are that (1) these cortical to cortical connections led to a novel *perceptual* experience of having the missing limb stimulated through stimulation of the still present facial nerves, and (2) these novel perceptual experiences were *reproducible and involuntary*, two of the hallmarks of synaesthetic experience.

Analogously, we proposed that synaesthesia arises through a mechanism of cross activation similar to that observed in phantom limb patients, and therefore would be predicted to show many of the same features, such that synaesthesia would be expected to be an *involuntary, systematic, organised, reproducible, perceptual* experience. However, instead of occurring within a single brain map,

the cross activation occurs *between* brain maps. Therefore the cross activation we propose in synaesthesia would cause experiences to cross the boundaries of sensory modalities, instead of simply boundaries within the somatosensory homunculus.

Furthermore, this model of synaesthesia may help us to explain the directionality seen in synaesthesia, such as letters and numbers evoking colours, but not vice versa. We suggest that the manner in which different modalities are mapped might make it inherently easier to map in one direction to the other (see Ramachandran & Hubbard, 2001). If a number evokes a colour, the brain has something to ascribe the colour to without internal contradiction because there can be no such thing as 'free-floating' qualia. To see this issue more clearly, consider the case of phantom limb pain. In a patient who experienced phantom limb pain in his elbow, when the phantom limb was 'amputated' through the use of the mirror box treatment, the phantom limb pain in the elbow vanished, because there was no longer any elbow to ascribe the pain to. Similarly, in synaesthesia, there can be no free-floating 'number' qualia. If the colour were to evoke the number, to where would it be ascribed? Where would the number be seen, and how large would the number appear?

Similar to the directionality seen in synaesthetic associations, metaphors, instead of being arbitrary, respect directionality (Lakoff & Johnson, 1980), and this directionality appears to be similar to what is seen in synaesthesia (Day, 1996; Shanon, 1992). We have suggested that this directionality also results from constraints imposed by the neural hardware, which allows some directions of mapping to be more 'natural' than others. If this idea is correct, synaesthesia may provide an experimental lever for exploring how maps in different conceptual and perceptual domains activate each other and what the rules of translation might be. Understanding such map-to-map interactions is fundamental, in our view, for understanding the emergence of the human mind.

We note that this neural theory of synaesthesia does not necessarily contradict the cognitive account of synaesthesia proposed by Shanon and many others. Unless we assume some sort of mind–brain dualism, then accounts at the cognitive level, must in some fashion, reduce to accounts at a neural level. It is possible that the cross activation we have proposed is simply the neural level analogue of Shanon's vague notion of the 'mode of perception that disregards standard differentiation between sensory modalities' just as DNA duplication and transcription is the molecular analogue of 'passing on hereditary information from parent to offspring'. The molecular and hereditary accounts of inheritance are not mutually exclusive explanations, and the same holds for the neural and cognitive accounts of synaesthesia.

Additionally, we are sympathetic to Pribram's suggestion that many apparently excitatory phenomena in neurology can actually emerge from inhibition — and this may well be true of some forms of synaesthesia — but we believe the cross activation model we propose is not in any way inconsistent with this suggestion. As Pribram suggests, an increase in inhibitory connectivity may play a role, but it is probably not the only factor, as the connections that we propose are

most likely excitatory (based on the analogy with the changes in excitatory connectivity that leads to phantom limb experiences). Additionally, while the role of subcortical structures remains open, based on the specificity of the mappings in synaesthesia (see above) we would have to suggest that cortical factors play a critical role in synaesthesia. Perhaps some combination of excitatory and inhibitory processes is at work in synaesthesia. Current imaging data (e.g., Hubbard, Ramachandran & Boynton, in prep; Nunn *et al.*, 2002; Paulesu *et al.*, 1995) cannot answer these questions, as fMRI and PET measure blood-flow changes, and only indirectly measure neural activity, irrespective of whether that activity is excitatory or inhibitory. Future studies making use of alternative techniques such as radio-labelled amino acids to identify excitatory and inhibitory neurotransmitter activity will be required to obtain any meaningful data on these questions.

III: Genetic Factors in Synaesthesia

In the third section of this reply, we would like to discuss further the evidence for a genetic component in synaesthesia. Genetic linkage studies have suggested a genetic component to synaesthesia (Bailey & Johnson, 1997; Baron-Cohen *et al.*, 1996; Cytowic, 1989/2002), and, given that synaesthesia is much more common in females than in males (estimate range between 3:1 and 8:1), it has been suggested that the genetic component may be X-linked dominant (Bailey & Johnson, 1997). However, the evidence for a genetic component in synaesthesia (specifically X-linked dominant) is not simply the fact that the prevalence in the population is consistent with an X-linked dominant trait. In addition, proper pedigree and transmission studies have been undertaken. Evidence consistent with an X-linked dominant trait include:

1) The complete absence of father to son transmission (Baron-Cohen *et al.*, 1993; 1996). Cytowic (1989/2002) reports that 'we have found no confirmed cases of male-to-male transmission, either historically or in our own data' (p. 55).
2) The pedigree studies undertaken to date show perfect transmission (5/5) father to daughter transmission (Baron-Cohen *et al*., 1993; 1996; Cytowic 1989/2002 does not report father to daughter statistics).
3) High transmission rate from mothers to daughters (72% Baron-Cohen *et al.*, 1996; 56% Cytowic, 1989/2002).
4) Lower transmission rate from mothers to sons (25% Baron-Cohen *et al.*, 1996; 40%, Cytowic, 1989/2002).

The lower rate of transmission from mothers to son may then require an explanation. Since we have such poor estimates of the prevalence of synaesthesia to begin with (remember, estimates have ranged between 1:20 and 1:20000, with more recent estimates converging around 1:200–1:500), biases in reporting (i.e., men may be less willing to discuss 'that touchy feely colour stuff') could lead to a reduced number of self-reports relative to women.

However, the genetic story is likely to be more complicated than a pure X-linked dominant account. A recent study of identical (MZ) twin sisters has found that one sister is synaesthetic, while the other is not (Smilek *et al.*, 2002), suggesting that the genetic mutation(s) that lead to synaesthesia may have incomplete penetrance. Additionally, it should be noted that this genetic factor might interact in interesting ways with environmental variables (see above). Second, we have found that synaesthesia can skip generations. We have verified the presence of synaesthesia in subject JC (the same JC discussed in our original article), and through interviews, with his mother and cousin. However, his aunt (on his mother's side) and uncle report that they do not experience synaesthesia (see Figure 1).

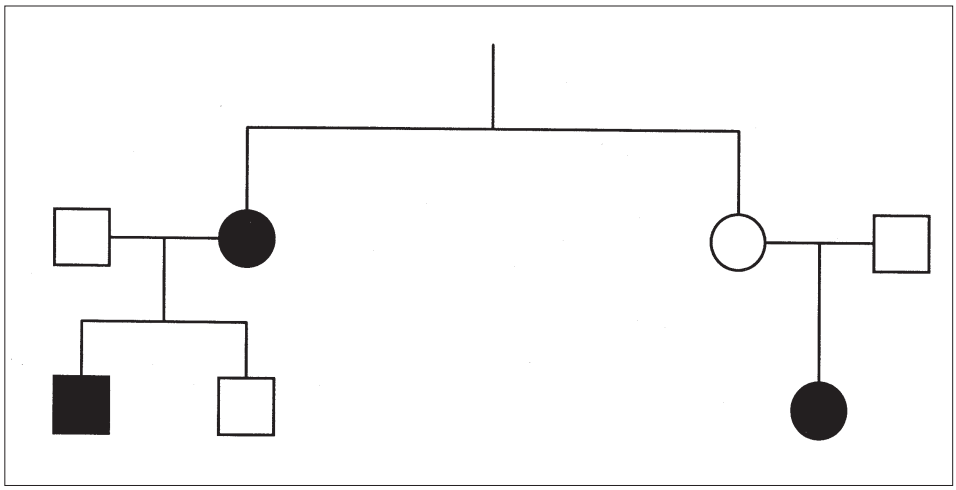

Figure 1. Pedigree of a synaesthetic family, indicating that synaesthesia can skip generations.

The squares indicate males, and the circles indicate females. Filled symbols indicate people who experience synaesthesia, while open symbols indicate family members who do not. The synaesthetic male is JC (See Ramachandran & Hubbard, 2001). His mother and cousin experience synaesthesia, while his mother's sister does not. Although this result suggests that synaesthesia may show incomplete penetrance, it is otherwise consistent with the X-linked dominant theory of synaesthesia previously suggested by others (Bailey & Johnson, 1997; Baron-Cohen *et al*., 1996; Cytowic, 1989/2002).

IV: Synaesthesia and Psychedelics

Finally, we would like to briefly discuss Shanon's comments concerning the relationship between synaesthesia and psychedelics. Shanon is, of course, not the only person to note the similarity between synaesthetic experience and psychedelic experience. Indeed, numerous theorists have made this point critical to their theories of synaesthesia (e.g., Grossenbacher, 1997; Grossenbacher & Lovelace, 2001, and Cytowic, 1989/2002). One question we have is to what extent is the phenomenology of psychedelics is really compatible with the phenomenology of synaestheisa. Shanon's recent reports (Shanon, 2002) provide some useful entrée into these issues, but the question still remains open.

While Shanon has done a great deal of work on the phenomenology of ayahuasca, very little is known about its mechanisms of action. On the other hand, a great deal is known about the mechanisms of action for LSD, another psychedelic commonly associated with synaesthesia. LSD leads to modified activity in two areas: the locus ceruleus (LC), and pyramidal cells in the cortex (Aghajanian and Marek, 1999; Marek and Aghajanian, 1998). The locus ceruleus is a collecting point for a wide variety of sensory inputs, after which it then projects diffusely to the cerebral cortex and the rest of the neuraxis. The locus ceruleus has been likened to a novelty detector, and as such, does not explain the hallucinogenic results. It may, however, explain why LSD users feel like they are experiencing things for the first time. The other site of modified activity reported by Aghajanian and Marek (1999) is the pyramidal cells in the cerebral cortex. Through a direct action on the pyramidal cells, LSD-like hallucinogens facilitate the excitation of these neurons, and it may be this excitatory activity in cortical neurons that leads to synaesthesia like experiences in psychedelics users.

Can these possible mechanisms for LSD-like hallucinogens account for congenital synaesthesia? There are several objections to this account. Synaesthetic associations are quite specific (e.g., the grapheme 'A' leads to the experience of the colour scarlet) as mentioned above. Drug-induced synaesthesia does not seem to have the same specificity. Additionally, drug induced synaesthesia can produce a sensation whose modality the subject cannot determine. The experience may be in between a sound and a sight with no way to determine which was the perceptual event (Smythies, personal communication). This may be a result of the confusion produced by the drugs, or it may be indicative of a more primal mistake by the brain. If one is to conclude that congenital synaesthesia is similar to the drug-induced type one must also explain why a synaesthete does not show the confusion usually associated with psychedelics. Differences in the phenomenology of different psychedelics and between congenital synaesthesia and drug induced synaesthesia will warrant a great deal more study, although research in each of these areas may help us to better understand the neural basis of each.

Conclusions

We have very much enjoyed the commentaries by Shanon and Pribram. Our reply here was meant to focus on remaining questions, and to elaborate on themes that we only touched upon in our original article. We hope that, if nothing else, these comments increase the enthusiasm for studying synaesthesia as a promising experimental lever to study perception, thought and language.

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