Review

Synaesthesia and cortical connectivity

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Synaesthesia is a heritable condition of involuntary sensory cross-activation whereby the presentation of a particular stimulus elicits a secondary sensory-perceptual experience. It is thought to be caused by aberrant cross-activation of one cortical area by another, but models differ as to whether this reflects functional or structural differences in the brains of synaesthetes. Here we consider these models in light of recent experimental findings and argue for structural differences in the brains of synaesthetes, which might be more widespread than expected. We also discuss several plausible developmental mechanisms that could link a putative genetic variant to altered cortical connectivity and illustrate how synaesthesia could be an informative model to investigate how patterns of connectivity between cortical areas are established.

Introduction

Synaesthesia is a condition whereby a stimulus (the inducer) generates a specific and consistent sensory percept or association in another modality or processing stream (the concurrent) [1–3] (Box 1). The best-known example is 'coloured hearing,' where sounds, usually but not exclusively words, induce particular colour percepts. Many different forms exist, however, including words to taste, tastes to shapes, and music to colour or shapes, for example, as well as the association of numbers or calendar units with spatial locations (Figure 1). One of the most common forms, linguistic–colour synaesthesia, involves the association of letters or numerals (graphemes), words, days of the week, months of the year and other linguistic stimuli with specific colours.

The high-level, learned nature of many of the inducing stimuli has focused attention on the cortex as the most likely locus of such cross-activation. Direct evidence to support this has come from various fMRI studies which have shown in grapheme–colour synaesthetes that area V4 of the cortex, an area shown to be critical for colour processing [4], is activated upon presentation of spoken words [5], graphemes [1] and visual words [6]. Other studies (reviewed in Ref. [7]) have found activation in lower or higher visual and/or parietal areas. Parietal activation might reflect a spatial component to the synaesthetic percept or the secondary 'binding' of the inducer and concurrent percepts [7–11].

Most synaesthetes report that such experiences have 'always been there,' consistent with a developmental origin (as distinct from these associations having been explicitly learned or from synaesthesia acquired in response to deafferentation, e.g. [12,13], or temporarily induced by hallucinogens [14]). Importantly, the condition appears to be highly specific; it is not associated with any major cognitive differences or general neurophysiological disturbances. Together with the imaging studies discussed above, these observations suggest that synaesthesia could be caused by mutations in genes that specifically control connectivity (defined either functionally or structurally) between cortical areas during development. Importantly, recent studies have found that very different types of synaesthesia (such as tastes to shapes and music to colour) can co-occur in individuals [15] or in families [16]. What seems to be inherited, therefore, is a tendency to develop synaesthesia in a general sense, but the specific type that emerges in an individual is likely affected by other factors ([16] and see below).

A variety of models have been proposed to explain synaesthesia [1,7,17–21] which have in common the idea of aberrant cross-activation of one cortical area by another, but which differ in two major, independent parameters (Figure 2). The first is whether cross-activation of the concurrent area by the inducer area is direct [1,19,21] or mediated via some other cortical area(s) [17,18]. The second is whether the cross-activation reflects extra connections that are not present in non-synaesthetes (i.e. a structural difference [1,19,21]), or disinhibition of normal connections (i.e. a functional difference [18,20]).

Here we consider these models in the light of known principles of cortical connectivity and present arguments in favour of a structural difference in the brains of synaesthetes. We discuss recent direct experimental evidence supporting this hypothesis and propose several possible developmental mechanisms involved in the establishment of cortical connectivity which could be affected in synaesthetes. Finally, we consider evidence that connectivity differences in the brains of synaesthetes might be more widespread than the apparently discrete phenotype would lead one to expect and discuss how these differences might be resolved differently in individuals to yield a discrete phenotype.

Models of synaesthesia: extra wires or altered function?

Two main arguments have been made in favour of a purely functional difference in synaesthetes. First, certain trends in associations in synaesthetes are similar to cross-modal associations observed in non-synaesthetes (such as lower pitch with darker colours, or yellow with the letter Y), leading some researchers to argue that synaesthetes

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Box 1. Characteristics of synaesthesia

General
Synaesthesia involves the activation of a 'concurrent' percept by an inducing stimulus (the inducer) in another modality or another facet of the same modality. Although initially defined as a cross-sensory phenomenon, it is now recognized that cognitive characters can often act as inducers.

Prevalence
Synaesthesia has until recently been thought to be quite rare (as low as one in ten million [3]). However, current estimates of the population prevalence are in the range of 1–4% [95].

Familiality
It was first recognized by Galton [96] in the 1800s that synaesthesia can run in families, and pedigree studies have provided evidence for Mendelian transmission [3,16,97]. Recent studies [15,16] have found, importantly, that very different types of synaesthesia can occur in the same individual or in the same family.

Biased sex ratio
Synaesthesia is often reported to be more common in women, although exactly how much more common is debated. Estimates of the female:male ratio range from 6:1 [16,97,98] to 1:1 [95]. See Refs [16,95] for a discussion of possible factors contributing to these findings.

Unidirectional
Although cases of bidirectional synaesthesia have been reported (e.g. [38]), it is by far more common for the effect to be unidirectional; for example, music will induce colours but not vice versa.

Stable
The experience in general and the specific pairings of inducers and concurrents in particular tend to be quite stable over the lifetime of the individual.

Idiosyncratic
The particular pairings of inducers and concurrents are highly specific to the individual. This is true even with families or comparing monozygotic twins [16]. The pairings often appear arbitrary (e.g. '7 is pale blue with a pleasant, soft, nice personality'), although they can in some cases be affected by semantic characteristics ('*Barb*ara' may taste of rhu*barb*, for example [99]). They can also be biased by cross-modal associations that are common in the general population, for example, that specific letters pair with specific colours (Y with yellow, for example, which is a more common pairing in synaesthetes than would be expected by chance [16,98,100] [but still only 50%]).

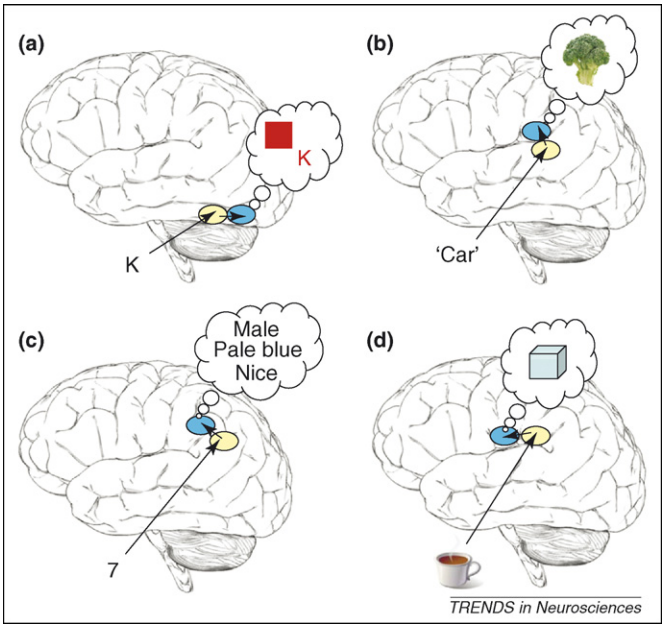

Figure 1. Examples of synaesthesia. Several common types of synaesthesia are represented. All involve aberrant cross-activation from an inducer area (yellow) to a concurrent area (blue). For grapheme–colour synaesthesia **(a)**, the locations of these areas have been identified by fMRI. The concurrent in this case can be a patch of colour projected externally or seen 'in the mind's eye' or projected onto the form of the inducing grapheme. The other panels depict locations of areas that might *plausibly* be involved in words to tastes **(b)**, personification of numbers **(c)** and tastes to shapes **(d)**. Whether these and other types of synaesthesia actually involve adjacent cortical areas is an important outstanding question. (Brain image: Szymon Rusinkiewicz, Doug DeCarlo, Adam Finkelstein and Anthony Santella, Princeton University.).

simply express a more explicit version of these normal cross-modal mechanisms [20,22,23]. An alternative interpretation is that the cross-modal patterns of associations that are active in all people can *bias* the associations that emerge in synaesthesia as letters, words or other inducers are learned, but that the latter are not merely a more overt manifestation of the former [16] (see below).

A second argument (e.g. [3,24]) in favour of a functional difference is that certain hallucinogens (or psychedelic drugs), such as lysergic acid diethylamide (LSD) or psilocybin, which target serotonin receptors, can, in some individuals, induce a state of synaesthesia where stimuli in one sensory modality cross-stimulate another [14,24]. This suggests that cross-modal connections must exist in all individuals but could be disinhibited in synaesthetes. Psychedelic drugs have a wide range of effects on physiology, perception, mood and many cognitive processes, however, and are reported as only rarely inducing synaesthesia [14], which does not usually involve the kinds of discrete, paired and stable associations observed in developmental synaesthesia. In light of this, the idea that mutations in serotonin pathway genes could specifically cause synaesthesia [24], without having more widespread effects (e.g. [25]), seems less likely.

By contrast, it is rather easier to imagine how mutations in genes directly controlling cortical connectivity could lead to synaesthesia. Below, we consider the phenomenology of developmental synaesthesia (Box 1) in the context of known principles of cortical connectivity and the developmental processes that establish it, and present arguments for direct cross-activation mediated by a structural difference in the brains of synaesthetes.

Principles of cortical connectivity

Connections between cortical areas tend to have a hierarchical and reciprocal relationship, with one area sending predominantly driving, feedforward connections to another and the latter sending mainly modulatory, feedback connections to the first [26–31]. (The situation of strong reciprocal driving interactions is not thought to exist in the healthy brain [32].) Feedforward and feedback connections can be distinguished based on their laminar sites of origin and termination [27–29], their effects on receptive field properties [27,31,33] and types of synaptic neurotransmitter receptors [34]. The hierarchical relationship between any two areas can be determined by functional experiments [33,35–37] and anatomically by the ratio of feedforward and feedback connections in each direction [28,29].

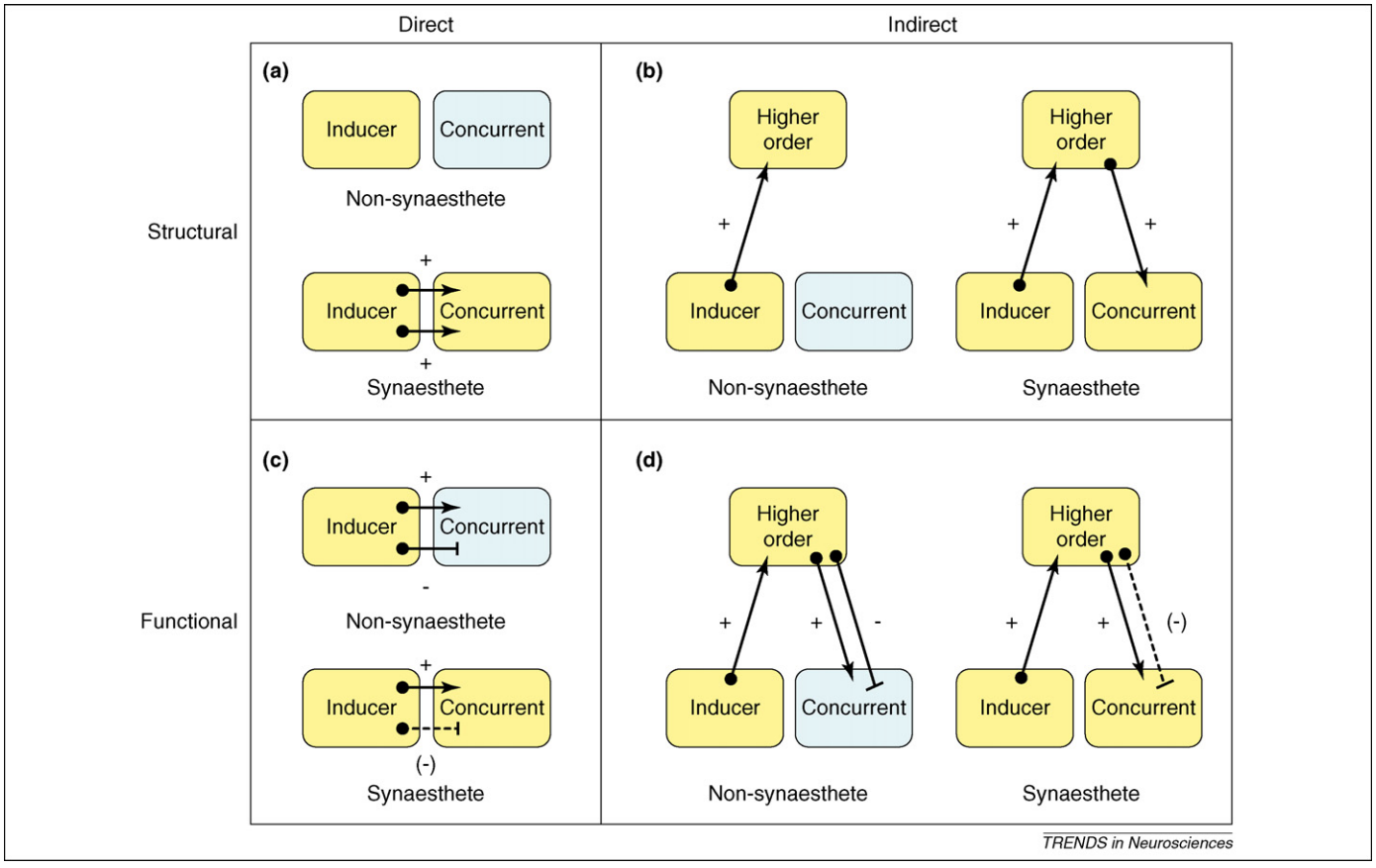

Figure 2. Models of synaesthesia. Models differ in the proposed route of cross-activation (direct [1,19,21] or indirect [17,18]) between the inducer area and the concurrent area and the proposed underlying difference in synaesthetes (structural [1,19,21] or functional [18,20]). Yellow areas are active (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. (A variation on the disinhibition model would posit a structural *decrease* of inhibitory connections as the reason for excess cross-activation.) Connections from the concurrent area to the higher-order area in **(b)** and **(d)** are not shown for simplicity, but note that such connections pose a problem for indirect models as they would lead to a recurrent excitatory loop [32]. Note also that indirect, driving connectivity via the thalamus as opposed to a higher-order cortical area is also possible [34].

The defining characteristics of the cross-activation in synaesthesia are that it is driving, usually unidirectional (but see Ref. [38]) and comprises a set of stable associations from specific inducers to specific concurrents (e.g. specific tastes with words or specific colours with numbers). These properties are most consistent with feedforward connections. They are also consistent with a topographic (map-to-map) arrangement of connections from an inducer area to a concurrent area which would tend to produce stable pairings of associations. This again implicates feedforward-type projections, which tend to maintain tighter topography than feedback projections [39]. Topography is a ubiquitous property of connections between cortical areas [40–42], even in cases where no obvious external parameters (such as visual space or sound frequency) are mapped by that topography. This reflects the developmental and evolutionary processes involved in connecting additional cortical areas [40,43], and might also be a fundamentally important computational property [41].

Another striking principle of cortical connectivity is its 'small-world' properties. The vast majority of inter-areal connections are between adjacent or nearest-neighbour-plus-one areas [44], with a small number of long-range connections providing important links between more distant regions. This has been shown to be an optimally efficient arrangement in terms of both information transfer and minimization of wiring [45–47]. It also again presumably reflects constraints imposed by developmental and evolutionary processes [40]. Given that the areas involved in one of the most common forms of synaesthesia, grapheme–colour, are adjacent to each other [48], it seems a parsimonious prediction that this will be the case for other types. This seems plausible based on the locations of areas thought to be involved in various other forms of synaesthesia, such as taste–shape, word–taste, number forms or linguistic personification [15,49–51] (as represented in Figure 1), but adjacency has certainly not been shown to be an essential characteristic of synaesthetic cross-activation.

Even if direct, feedforward connections from the inducer area to the concurrent area are responsible for synaesthetic cross-activation, this still leaves the question of whether these are atypical connections that are not normally present in non-synaesthetes or are normal connections that are usually inhibited. (In fact, this distinction need not be all or none; a change in the ratio of feedforward versus feedback connections from one area to another can determine hierarchical relationship [29].) The disinhibition model makes an untested assumption, however: that adjacent areas of the cortex are always connected with each other, that is, that there are some connections there to 'disinhibit.' In fact, several studies using optical imaging

and other techniques have demonstrated the existence of distinct borders in the cortex across which very little activity is propagated [36,37]. In some cases, activation is propagated across this border when inhibition is suppressed (which we term 'soft' borders), but in many cases it is not because no axons cross the border ('hard' borders) [52,53]. Importantly, such borders are usually not detectable by differences in cytoarchitecture but might correspond to sharp boundaries of gene expression at earlier stages of development (e.g. [54]). It will thus be important to address whether areas such as the grapheme area and V4 are normally separated by a soft or hard border.

Alternative routes of feedforward connectivity include longer-range, direct corticocortical connections (e.g. [55]) and indirect connectivity via the thalamus [34]. The possibility of subcortical cross-activation as the origin of the synaesthetic experience [3] has generally been rejected on the basis of the high-level nature of many synaesthetic inducers, but this does not necessarily exclude the thalamus as an intermediate in driving cross-activation from one cortical area to another.

Direct evidence for structural differences in the brains of synaesthetes

A recent diffusion tensor imaging (DTI) study provides direct support for the model of altered structural connectivity in synaesthetes [10]. DTI uses magnetic resonance imaging to track the diffusion of water molecules, which is generally isotropic (equal in all directions) in grey matter but highly anisotropic in white matter, owing to the preferential diffusion along axonal tracts [56]. The fractional anisotropy (FA) in a given area has been taken as a measure of the 'structural integrity' of white matter tracts, although the microstructural correlates are poorly understood [56]. FA in a given imaging voxel can be influenced by the number or diameter of axons in a tract, the percentage of axons aligned in a specific direction, the degree of bundling, the amount of myelination and possibly other cellular parameters. This study found greater FA in several clusters in temporal, parietal and frontal regions comparing a group of synaesthetes to controls. One such area in the right inferior temporal cortex is near V4 and also near, but does not overlap with, an area of increased functional (BOLD) response in these synaesthetes to grapheme stimuli that induce colour percepts [10]. The degree of FA in this area correlated with subjective reports of the nature of the synaesthetic experience (projected into space or experienced in the mind's eye [57]), with FA being greater for 'projectors.' (Interestingly, this study found no structural or functional differences on the left side, which would be expected if the grapheme area were directly involved, although this reflects the variability of lateralisation seen in previous functional imaging studies, e.g. [5,48,58]). These data were interpreted as evidence for 'greater structural connectivity' *within* this general region which could underlie the synaesthetic experience. Tractography in this region did not reveal any differences in specific tracts, however, nor did it directly show increased connectivity *between* any two defined areas. Thus, although the study provides strong evidence for structural differences in the brains of synaesthetes, the microstructural correlates of such differences are not yet clear.

The hypothesis that developmental synaesthesia is caused by altered structural connectivity between cortical areas raises the question of whether there are specific developmental mechanisms that could mediate it. In fact, the processes controlling connectivity between cortical areas are only beginning to be elucidated, but several important principles have emerged.

Connecting cortical areas

The definition of cortical areas during development is intimately related to the establishment of areal connectivity. Primary cortical areas are thought to emerge from the patterning of the neocortex by secreted molecules, which is translated into regional expression profiles of transcription factors [59]. This leads to visible differences in local characteristics such as cytoarchitecture and myelination profiles (reviewed in Ref. [60]), or gene expression patterns [59,61] that distinguish areas. It also leads to the area-specific attraction of appropriate thalamocortical (e.g. [62,63]) or corticocortical axonal connections [64–66], although the specific molecules mediating these guidance processes remain unknown. This linear perspective (from patterning to connectivity) is misleading, however, as the elaboration or maintenance of many aspects of the subsequent development of cortical areas (e.g. rates of proliferation and cell migration [67], patterns of gene expression [68,69], connectivity [70]) depends on correct afferent connectivity [43,71]. This interplay between patterning and connectivity has been well documented in the thalamocortical system, but it seems likely that it will also apply to corticocortical connections. In this way, connectivity from earlier-maturing areas could help to specify the 'identity' of later-maturing areas in a hierarchical fashion [40,61,72].

Many later-developing areas cannot be distinguished readily by cytoarchitectonic criteria but can nonetheless be recognized by functional selectivity. These include, for example, areas in the ventral visual stream that are highly selectively responsive to words, faces, scenes or objects [73,74]. Recent studies have demonstrated that these areas or functional clusters of neurons emerge over time through experience-dependent processes [75,76]. Remarkably, however, they tend to emerge in roughly the same regions in different individuals [74], suggesting that their development reflects the refinement and consolidation of visual or multisensory responses that are biased by underlying circuitry [73].

Possible molecular mechanisms

There are three obvious processes that, when disrupted, could specifically result in excess connectivity between cortical areas (Figure 3).

Axon guidance

The establishment of connectivity between cortical areas is remarkably specific from the outset, much more so than previously thought. Several studies have shown that axons from one cortical area show preference for their correct target areas, both *in vivo* and *in vitro* ([64–66]

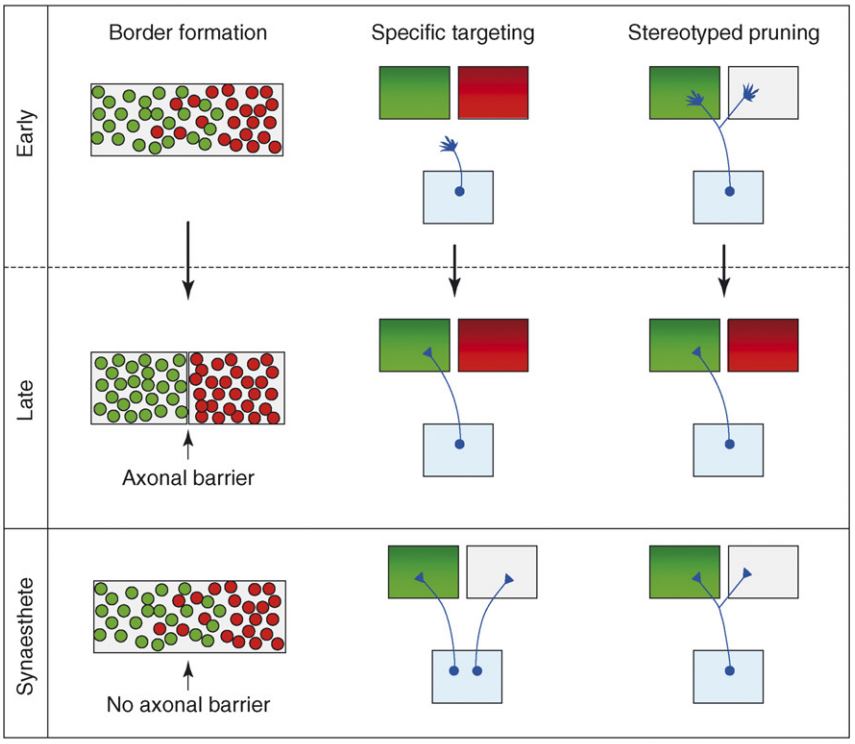

Figure 3. Cellular mechanisms of areal formation and connectivity. Three example mechanisms are shown that, if defective, could plausibly underlie synaesthesia. 'Early' and 'late' do not refer to specific time points but reflect the serial stages of each process. Left panel: formation of borders between at least some cortical areas relies on differential expression of proteins (green and red) on the surface of cells that mediate segregation of cell types (e.g. Cadherins, Ephrins). Failure to form distinct compartments in synaesthetes (bottom panels) might lead to subsequent invasion of axons across what should be a hard border. Middle panel: specific targeting of axons is mediated by the expression of attractive (green) and repulsive (red) molecules (e.g. Ephrins). Right panel: many connections in the developing brain are specifically pruned in a stereotyped and programmed manner that is dependent on upregulation of specific repulsive molecules (red) (e.g., Semaphorins, Plexins). The hypothetical effects of mutations in genes encoding these types of proteins in synaesthetes are shown in the bottom panels.

and references therein). Although the identity of the molecules that specify these preferences is unknown, genes involved in axon guidance are obvious candidates. One class of molecules that is known to regulate the guidance of thalamocortical connections to specific cortical target areas is the Ephrins [77], which also control the establishment of intra-areal circuitry. Based on their expression patterns [78], genes such as these are good candidates to also control corticocortical connectivity and to mediate both inter- and intra-areal differences in synaesthesia.

Border formation

Ephrins and their Eph receptors are also well known to be involved in the formation of borders between tissue regions. In the cortex, they have been shown to be involved in the sorting of cells into distinct areal compartments [79]. Similar functions have been associated with another class of proteins, cadherins (reviewed in Ref. [80]), which are also expressed in distinct cortical areas [81]. The formation of borders between cortical areas (and possibly the concomitant establishment of barriers to axonal invasion) might therefore be affected by mutations in genes with these types of functions.

Pruning

Eventual patterns of inter-areal connectivity are also determined by regressive events (reviewed in Ref. [82]). Failure to prune normally transient cross-modal connections (e.g. [55]) is thus another plausible developmental mechanism that could be affected in synaesthesia [19,83]. Importantly, this pruning happens in a highly stereotyped fashion as a normal part of the developmental programme [55,82,84]. This might be mediated by molecules such as semaphorins and plexins, mutations in which result in the persistence of normally transient connections in several areas of the brain (reviewed in Ref. [85]).

The examples listed above are not meant to suggest specific candidate genes so much as to illustrate that there are known classes of neurodevelopmental genes which, when mutated (in mice at least), cause wiring differences that fit well with the phenomenology of synaesthesia. These types of genes are expressed in quite specific patterns, defining areas and borders in many cases, and their disruption affects some systems and not others. These characteristics contrast with genes encoding neurotransmitter pathway components, mutations in which have been proposed to mediate disinhibition, but which might actually be expected to have more general effects on brain function.

The emergence of the phenotype

Two important outstanding questions for any genetic model of synaesthesia are: (i) how can mutation of a given gene cause different types of synaesthesia, and (ii) why are some types so much more common than others? The fact

that different types of synaesthesia can co-occur in individuals or families argues strongly that mutation of a single gene can result in quite different phenotypic outcomes, apparently involving very different parts of the brain. One possible way in which this could occur is if the miswiring were initially quite broad (see below) and subject to intrinsic developmental variation [16,86] or subsequently refined through experience-dependent mechanisms to generate a discrete phenotype in each individual.

Evidence for a broader phenotype in synaesthesia

In the DTI study referred to above [10], structural differences in the brains of synaesthetes were not confined to regions of fusiform and inferior temporal cortex, where the grapheme area and V4 are located, but were also present in parietal and frontal regions. Whereas the extent of hyperconnectivity in the fusiform area correlated with the subjective strength of synaesthesia, this was not true for the parietal and frontal areas.

Additional evidence suggesting broader dysconnectivity in synaesthesia comes from two studies using electroencephalograhy to map the time course of synaesthesia. Beeli *et al.* [11] found that synaesthetes showed differences compared to controls in auditory event-related potentials in response to letters, words or pseudowords. These differences included activity in areas consistent with the location of V4, based on current source density maps, but interestingly also included differences in sensory processing in the auditory cortex itself as early as 122 ms after stimulus onset. We have recently obtained similar evidence of very early processing differences in synaesthetes to very simple visual stimuli that, crucially, do *not* induce synaesthesia (unpublished). These differences in early sensory processing are suggestive of wiring differences within primary sensory cortices that might be unrelated to the synaesthetic experience *per se*. The model of more widespread differences in connectivity is consistent with reports of other phenotypic manifestations in synaesthetes including possible differences in creativity [87] and mental imagery [88] and higher incidence of *mitempfindung* (referred tactile sensation) [89].

Trends across types of synaesthesia

This model still leaves the question of why some types of synaesthesia are so much more common than others and why there are certain trends in the nature of inducers and concurrents. Broadly speaking, many inducers tend to belong to learned, categorical classes of stimuli such as letters, numbers, musical notes and days of the week. By contrast, concurrents are generally simpler sensory percepts involving colour, taste, shape and spatial position, for example. This difference is reflected in different rates of maturation and modes of development of the cortical areas representing these two types of information. Primary sensory and motor areas mature earlier than secondary areas, which in turn mature earlier than association areas [61,72,90,91]. Still later maturing functional areas such as the visual word form area develop through experience-dependent mechanisms and consolidate over many years [51,73]. Initially broad excess connectivity might thus be expected to be resolved differently between early- and late-maturing areas, which might bias the maintenance of certain cross-activations over others. This could be especially true if afferent corticocortical connectivity can in part determine the functional 'identity' of a cortical area, either molecularly or through experience-dependent processes [40,43,73,92]. In addition, there might be a functional bias to consolidation depending on the compatibility of the computational profile of certain neuronal circuits [93,94].

Conclusions

We have reviewed evidence in favour of a structural difference as the primary cause of developmental synaesthesia and presented arguments that it is most likely mediated by direct, feedforward connections between adjacent areas. We have also discussed several plausible developmental mechanisms that could link a genetic variant to altered cortical connectivity. Finally, we have considered some convergent evidence that the experience of synaesthesia might be just one manifestation of broader connectivity differences in the brain. These discussions highlight some important outstanding questions in this field. First, does synaesthesia always involve adjacent areas? This seems parsimonious but will have to be investigated by neuroimaging of rarer types of synaesthesia. Any model of the underlying mechanisms must clearly be able to explain all types. Second, are there really more direct connections between inducer and concurrent areas in the brains of synaesthetes? The DTI study referred to above provides suggestive evidence that there could be, but more discrete tractography between specifically delineated areas will be necessary to answer this question. Third, the results of the EEG studies suggest that synaesthetes might have differences in early sensory processing in both the auditory and visual domains. It will be interesting to address whether this extends to other sensory domains and what the behavioural or perceptual consequences are. These types of studies should greatly inform cognitive and neurophysiological models of synaesthesia and its relationship to normal sensory processing and multisensory integration. Ultimately, identification of a gene or genes that predispose to synaesthesia should reveal whether functional or structural models are correct and, in either case, illuminate fundamental molecular processes controlling cortical connectivity.

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