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Curiouser and curiouser: genetic disorders of cortical specialization

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The processes by which cortical areas become specialized for high-level cognitive functions may be revealed by the study of familial developmental disorders such as dyslexia, dyscalculia, prosopagnosia, color agnosia and amusia. These disorders are characterised by the inability to integrate information across multiple areas and the consequent failure to develop representations of the knowledge of some category based on its associated attributes. In contrast, synesthesia may be seen as a hyper-associative condition, possibly due to a failure to properly segregate areas into distinct networks. Here, I consider recent advances in our understanding of the genetic and neurobiological bases of these conditions and the developmental mechanisms underlying the specialization of cortical areas and networks.

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Introduction

Certain areas of the cortex in humans seem to be dedicated to processing or representing very high-level properties of particular stimuli, even to the level of cognitive concepts. The existence of such 'knowledge areas' is dramatically illustrated by their highly selective patterns of activity in functional magnetic resonance imaging experiments and even more so by the symptoms that arise when they are lesioned, which can be astonishingly specific [1]. These symptoms are described as 'agnosias'-literally the lack of knowledge of something. Most famous, thanks to Oliver Sacks, is prosopagnosia, which is characterised by an inability to recognise faces, despite normal visual acuity and the ability to see individual features perfectly normally. Other examples include color agnosia, the inability to name colors or associate them with particular objects, despite normal color perception, and amusia, the inability to detect incongruous notes within a melody despite normal pitch discrimination.

Remarkably, in addition to acquired forms, these conditions can also be both congenital and strongly familial. This is somewhat surprising, given that the full specialization of these areas emerges in an experience-dependent fashion [2,3••]. However, even if an area is not genetically specified from birth, that does not mean its development does not rely on genetic mechanisms. These may be involved, first, in patterning the underlying circuitry which is the substrate for specialization and, second, in encoding the mechanisms and rules by which specialization occurs.

Below, I consider several examples of developmental disorders, including prosopagnosia, color agnosia, dyslexia, dyscalculia, and congenital amusia (Box 1). All of these are, at some level, characterised by the failure to make the consistent associations between modalities that constitute the idealized representation, or schema, of some category of object. I contrast these with the even more curious condition of synesthesia, which can be thought of as the opposite situation, where additional, sometimes arbitrary attributes are incorporated into the schemata of some class of objects. Rather than a detailed look at each disorder, this review gives a conceptual overview of the neurobiological bases of these conditions and examines them in the context of our current knowledge of the developmental and genetic mechanisms underlying the specialization of cortical areas and networks.

Disorders of cortical specialization

The disorders referred to in Box 1 comprise an apparently diverse set of conditions affecting distinct cognitive functions. Even within each disorder there may be distinct subtypes affecting these functions at different levels. However, a unifying theme is that all seem to reflect in some way a failure of higher-level areas to link information into a coherent schema, despite intact sensory processing at lower levels. These disorders can thus all be thought of as associative agnosias, 'the inability to associate a well-discriminated percept with its semantic attributes, which are stored in separate cortical areas' [1].

Synesthesia presents an interesting counter-example. This condition is often described as a cross-sensory phenomenon, where, for example, particular sounds (such as words or musical notes) will induce a secondary percept

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Box 1

Agnosias: Typically involve intact sensory processing and discrimination abilities but inability to combine multiple aspects of a stimulus into a coherent and stable schema, often in terms of higher-order contextual information. They can be thought of as the inability to attach appropriate *meaning* to sensory data — often manifest as the inability to recognize objects of a certain category. Developmental forms of such conditions are far more prevalent than commonly appreciated.

Color agnosia: Lack of color knowledge, as shown by inability to name colors or to know the typical colors of objects, despite normal color detection and discrimination. Prevalence unknown.

Congenital amusia: Better known as 'tone deafness' but more accurately described as 'tune deafness'. Amusia is characterised by a lack of conceptual knowledge of melodic contours and patterns and an inability to detect discordant notes within that context. This is despite normal ability to discriminate individual tones. Prevalence: ~4%.

Dyscalculia: A specific difficulty in mathematics that cannot be explained by general intelligence or educational opportunity. Can occur in 'pure' forms, but may also be co-morbid with dyslexia and ADHD. May be considered a 'number' agnosia-lack of the knowledge of the meaning or context of numbers. May relate to either a defect in the core numerosity system or in the association of concepts of numerosity with symbolic representations. (Indeed, defects in either domain may reinforce the other.) Prevalence: 5–6%.

Dyslexia: A specific and significant impairment in reading ability that cannot be explained by deficits in intelligence, learning opportunity, motivation or sensory acuity. As with all these disorders, there may be multiple subtypes, including difficulty in word recognition or in making letter–phoneme associations. Whether the primary defect is in associating letters with sounds or more fundamentally in encoding speech sounds is debated. Prevalence: 5–10% (English-speakers).

Prosopagnosia: The inability to recognize people's faces. Despite ability to see individual features, holistic impressions are not linked to schemas of individuals. Can, not surprisingly, have a profound impact on social interactions. Covert recognition and processing of facial emotion can, in some cases, be demonstrated by galvanic skin responses. Can occur with other object agnosias. Prevalence: 1–2%.

Synesthesia: The odd one out on this list. Characterised by some extra percept or association induced by a particular category of stimulus. Over 60 quite diverse manifestations have been reported to date. Whatever the form, the particular associations are stable and idiosyncratic. Many pairings seem arbitrary, but they can be biased by regularities in the early environment. It has been argued that synesthetic effects are common to all individuals but usually below the level of consciousness. This is particularly appealing for manifestations such as mirror-touch and visualized speech, which do not involve arbitrary pairings across modalities. An intriguing model, with growing support, proposes that savant abilities in mathematical or calendar calculations may arise due to the conjunction of synesthetic number or calendar forms and narrow, obsessive interests associated with autism. Prevalence: 2–4%.

(such as a color or taste), which is specific for each stimulus [4,5]. Although these florid types of synesthesia involve very vivid perceptual experiences, the more common manifestation is associative [6]. These cases involve the certain knowledge that some object, such as a letter or number, has, in addition to its normal attributes (shape, sound, value, etc.), some extra traits associated with it, such as spatial position, color, texture, even gender and personality. These associated characteristics are stable, idiosyncratic and have typically comprised as an intrinsic part of the person's schema of that object for as long as they can remember.

Some of these disorders have been described at a psychological level for over a century but it is only recently, with the advent of neuroimaging techniques, that it has been possible to assess the underlying mechanisms at a neurobiological level. Given the similarities of the associative agnosias with the symptoms of lesions to specific cortical locations, one might expect that the primary defect underlying the congenital forms would be the failure of these cortical areas to respond to their normal category of stimulus. Neuroimaging experiments have indeed provided strong evidence for just such an effect [7–9].

However, this explanation does not seem sufficient to explain all cases. It is clear, in fact, that in many individuals with these disorders, the defect lies not in the specialized responses of the 'knowledge areas', which can occur normally, but in the communication of these responses to higher-order areas, preventing conscious access to these multimodal representations. For example, in congenital amusia, despite behavioral deficits in the detection of notes that are out of tune or key, event-related potentials clearly show that some brain regions respond to the discordance of these notes. Particular waveforms or fMRI signals associated with conscious awareness of these differences are not observed, however [10•,11•,12•]. Similarly, in prosopagnosia, a clever fMRI adaptation paradigm demonstrates that the core face area is responsive to facial identity in prosopagnosics [13•]. The deficit seems to be in the communication of this response to an extended network of higher-order areas responsible for conscious face recognition [14]. Psychophysical experiments have similarly demonstrated implicit effects of color knowledge in a patient with color agnosia [15].

These disorders may best be explained by connectivity defects in a network, rather than dysfunction of isolated areas, and thus may be considered disconnection syndromes [16]. One recent study in dyslexia provides a telling example of such a defect: van der Mark and colleagues [17•] analysed the functional connectivity of the visual word form area (VWFA), an area that is highly specialized for processing letters [18]. The activity of the VWFA during a reading task is strongly temporally coupled with that of several frontal and parietal areas in controls but this functional coupling was absent in people with dyslexia [17•]. The VWFA thus seems to act as a central node in this network, the activity of which is crucially required, but not sufficient for automatic recognition of letters and words.

These differences in functional coupling in dyslexia are correlated with differences in structural connectivity [19],

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ascertained by powerful diffusion-weighted imaging techniques that enable detailed tractography in the living brain [20]. Similar studies have found defects in structural connectivity of areas involved in numerical cognition in developmental dyscalculia [21•], in processing music in congenital amusia [22•] and in the face network in prosopagnosia [23•].

Conversely, in synesthesia, functional and structural neuroimaging experiments provide support for a model of hyperconnectivity between cortical areas that are not normally connected in adults. A number of studies of synesthetes with grapheme-color or sound-color synesthesia have observed activation of additional cortical areas, such as the color area V4, in response to the auditory or visual presentation of sounds or letters (e.g. [24–26]). Similar cross-activation between different brain areas may give rise to other forms of synesthesia [5]. The level at which such cross-activation occurs may also determine whether the experience is more perceptual or associative [4]. Structural hyperconnectivity is also suggested by some imaging studies [27] (our unpublished observations) though it has not been seen by all [26].

The defects in these congenital disorders thus seem to involve not just the specialization of individual areas, but their incorporation into extended networks. Below, I consider what is known of the developmental mechanisms that mediate these processes and the limited amount we currently know of the genetic bases of these disorders.

Developmental mechanisms

There has been considerable debate as to whether cortical areas that are specialized for one function or another are specified by genetic mechanisms and are thus innate or come 'on-line' on a predefined maturational schedule, or whether their emergence is driven by experience [2]. In fact, a combination of all these processes seems likely and this interaction is appealingly encapsulated in the model of 'interactive specialization' [3].

This model proposes that cortical areas become specialized in a competitive process of strengthening or weakening connections within a network. It argues, crucially, that regressive events are as important to this process as the formation or strengthening of connections. Loss of responsiveness of an area to a non-preferred category may reflect pruning of synapses carrying that information or, alternatively, the development of active inhibitory processes that mediate cross-category lateral inhibition [28,29]. As networks respond to statistical regularities and contingencies in sensory inputs, schemata will come to be represented as patterns of weighted synaptic connections within and between particular brain regions.

Several recent imaging studies looking specifically at children support this general framework and provide details of the developmental processes that accompany specialization. Joseph *et al.* found both progressive and regressive changes in the network of areas responsive to faces across children of different ages, with increased tuning of some areas for faces and loss of responsiveness of other areas to faces [30••]. Similarly, Cantlon *et al.* found that areas that are somewhat selective for either faces or symbols (including letters and numbers) are already present in the visual system of 4-year old children [31••]. Importantly, greater behavioral category-specific recognition was associated not with higher responsiveness in these areas to the preferred category, but with lower responsiveness to the non-preferred category.

Learning letters seems to be an essentially multisensory, associative phenomenon: emergence of sensitivity to print is mediated not merely by visual expertise with particular shapes but specifically by mapping them to their associated phonemes [32••]. This tuning for print is greatly reduced in dyslexic children [33], consistent with a fundamental defect in making grapheme–phoneme associations [34•]. Learning to read seems to improve both tuning of these visual systems and phonological processing [35], suggesting that observed defects in processing of speech sounds in dyslexics may be secondary to reading difficulties, rather than the converse [7]. A similar situation may apply in dyscalculia, where a defect in learning symbolic numbers could feed back on to a non-symbolic numerosity system [36•].

Both progressive and regressive changes are also observed in developmental studies of brain-wide functional connectivity [37••,38••]. These have consistently found a steady transition from local to distributed brain networks over time as the strength of local connections decreases while that of longer-range connections increases. This leads to a greater functional segregation of distinct networks, which is paralleled by similar changes in measures of structural connectivity [39].

It seems plausible, therefore, that the associative agnosias are caused by reduced connectivity within cortical networks (see below for one possible cause), while synesthesia could arise due to failure of the regressive processes that normally prune inappropriate connections or a defect in cross-inhibitory processes (Figure 1). Ultimately, identification of the genes affected may be the clearest way to test these hypotheses.

Familiality and genetic architecture

Twin and family studies have shown moderate to high heritability for dyslexia [40] and dyscalculia [41] and high rates of affected first-degree relatives for synesthesia [42,43,44•], amusia [45] and prosopagnosia [46•]. Each of these disorders has examples of multiplex pedigrees where segregation patterns are most consistent with Mendelian, dominant inheritance [42,43,44•,45,46•,47,48].

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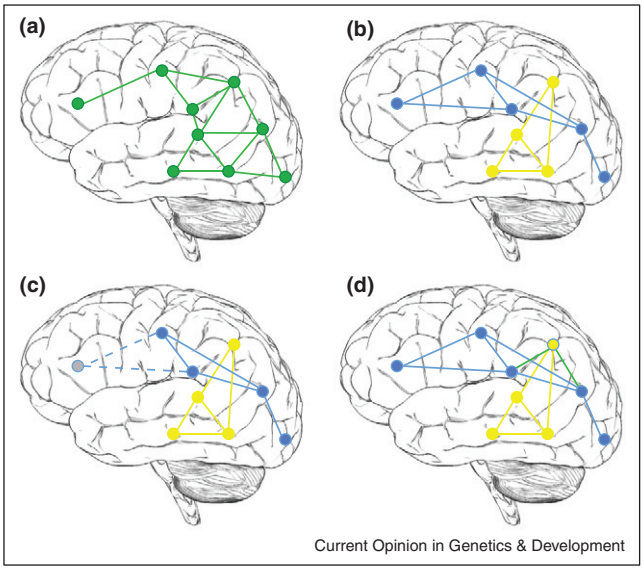
Figure 1



A highly schematized view of the specialization of cortical areas and networks. Panel **(a)** represents cortical networks in a young child and shows areas broadly responsive to several stimuli, but not yet selective for a specific category. Functional connectivity is denoted by lines. In adults **(b)**, these areas have segregated into two distinct networks (blue and yellow), through strengthening of some, mainly long-range connections and pruning of other, mainly local connections. **(c)** A disconnection syndrome, caused by a failure to form or strengthen long-range connections (dotted lines), resulting in an associative agnosia. **(d)** Local hyper-connectivity, caused by failure to prune connections (or to develop cross-inhibitory systems, not illustrated here), results in cross-activation of an additional cortical area and could explain synesthesia.

The generality of this interpretation is complicated, however, by a number of factors. Recruitment methods may bias towards individuals with multiple affected family members and also towards those with the most severe and discrete forms. The disorders are generally defined by the presence of a specific defect in the absence of more general cognitive or sensory defects. Similar symptoms can, however, also arise in the context of more general phenotypes. In addition, some of these disorders may be co-morbid with each other or with other conditions — for example, dyslexia, dyscalculia and attention-deficit hyperactivity disorder (ADHD) share high rates of co-morbidity [49]. Only considering the mode of inheritance of the most 'pure' forms of the disorder may give an incomplete picture of the genetic architecture of the disability.

Variability in phenotypic expression suggests that, in some cases, the same mutation(s) may result in disconnection of different circuits in different carriers. A similar situation is observed in synesthesia, where very different types (e.g. colored music vs. tasting words) can co-occur in different members of the same family [44•], or even in the same individual [43,50]. Correctly defining the phenotype(s) of interest is thus crucial for any genetic study.

A more fundamental question is whether these disorders should be considered as the tail end of the normal distribution of a generally heritable trait (such as reading ability or face recognition), or seen as discrete from that distribution. If the disorder is defined as including all those people below some arbitrary cut-off on this distribution, the implication is that the genetics of the trait and the genetics of the disorder are one and the same (i.e., polygenic). On the other hand, it is obviously possible to have a normally distributed trait (like height for example), where there are also exceptional cases at either end caused by mutations in single genes.

Finding the culprits

With the exception of dyslexia, no specific genes have yet been identified for any of these disorders. Indeed, linkage studies for most have not yet been reported. A single linkage study of synesthesia, which combined numerous multiplex families, yielded several suggestive peaks but no major locus [50]. This suggests that the disorder is either polygenic or genetically heterogeneous, the latter appearing more likely given the inheritance patterns observed.

For dyslexia, in contrast, numerous candidate genes have now been identified. These remain very much candidates however, as the evidence implicating them is circumstantial. As this topic has been reviewed in detail recently [51,52], I will only sketch the highlights here. Linkage studies across samples of dyslexia families have identified nine distinct loci, four of which are well replicated. Association studies of candidate genes within these regions have identified polymorphisms that are statistically associated with an increased risk of dyslexia (i.e., they occur at higher frequency in cases than controls). While these association results are statistically robust, their effect sizes are fairly small and their replication has been inconsistent.

Arguing against the possibility that these findings are false positives, however, is a remarkable convergence of the biological functions of the implicated genes. The three best-associated genes (*DYX1C1*, *KIAA0319* and *DCDC2*) are all involved in cell migration. Knockdown of any of these genes by RNA interference in the developing rat cortex disrupts cell migration and leads to ectopic cells in both the ventricular zone and layer 1 [52,53]. *ROBO1*, which has been implicated by translocation breakpoints and association findings [54], is also involved in cell migration and axon guidance.

The reason this convergence is so compelling is that an increased incidence of cellular ectopia is a consistent finding in post mortem studies of the brains of individuals

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with dyslexia [53]. In addition, periventricular nodular heterotopia, a disorder caused by mutations in the *Filamin-A* gene, and a concomitant defect in cell migration, is associated specifically with reading deficits, despite normal intelligence. In these patients, groups of ectopic cells within the white matter disrupt long-range cortical connectivity, correlating with defects in reading fluency [55]. Studies in rodents where similar ectopia have been induced further suggest that the secondary effects on connectivity may be especially severe in males, possibly providing an explanation for the greater incidence of dyslexia in males [53].

There are presumably many ways to disrupt brain connectivity, which may predispose to different disorders, depending on where the relevant genes are expressed. What is not at all clear, however, is why a phenotype as specific as dyslexia should result from defects in a process that affects large regions of the brain. Selectivity of the reading defect is a diagnostic criterion for dyslexia but perhaps the disorder is not really, or not always that specific. In addition to co-morbidity with dyscalculia and ADHD, dyslexia is also associated with a range of motor and sensory deficits [56]. Similarly, prosopagnosia is often associated with other visual agnosias [56], while congenital amusia is associated with visuospatial deficits [57]. In synesthesia, there are also broader phenotypic effects, including differences in very early sensory evoked potentials [58•,59•] and a reported increase in scores on a scale of schizotypy (V. Walsh, pers. comm.). This suggests that whatever miswiring results in the manifestation of these conditions may affect additional brain areas and functions.

Whole-genome sequencing approaches will likely identify genes for many of these disorders in the near future. Whatever the precise mechanisms, the key to understanding these disorders will be to consider them from a developmental perspective [60]. The eventual phenotype that emerges in any individual will be determined not just by their starting genotype (the mutations they carry and any modifying effects of genetic background), but also by stochastic events during development and by the interplay between the resultant circuitry and the activity- and experience-dependent processes of cortical specialization.

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