Available online at www.sciencedirect.com
ScienceDirect
Cognition 101 (2006) 247–269
COGNITION
www.elsevier.com/locate/COGNIT

Genes, brain, and cognition: A roadmap for the cognitive scientist

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Abstract

This paper reviews current progress in genetics in relation to the understanding of human cognition. It is argued that genetics occupies a prominent place in the future of cognitive science, and that cognitive scientists should play an active role in the process. Recent research in genetics and developmental neuroscience is reviewed and argued to provide a new perspective on the timeless questions of innateness and modularity. The special case of the genetic bases of language is further discussed, with the study of developmental dyslexia as an exemplary entry point. This Special Issue puts together articles providing different empirical examples and theoretical perspectives on how the integration between the different levels of description (gene, brain, and cognition) is to be achieved.

Keywords: Genetics; Brain development; Developmental disorders; Dyslexia

1. A journey from cognition to gene to brain to cognition

A cognitive scientist's first encounter with behavioural genetics must no doubt come as a shock. As compellingly reviewed by Plomin in the nineties, most developmental cognitive disorders, as well as many cognitive traits within the normal range

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doi:10.1016/j.cognition.2006.04.003

of variation, have been found to be under substantial genetic influence (McGuffin, Riley, & Plomin, 2001; Plomin, 1990; Plomin, Owen, & McGuffin, 1994). Many of these findings were at the time quite unexpected: for instance, the high *heritability*[1] of psychiatric disorders like autism and schizophrenia, which were once thought to be due to inadequate parenting; or the heritability not only of general intelligence and basic cognitive abilities, but also of the main dimensions of personality.[2] The mere evocation of such results inevitably leads to wondering *how* genes could conceivably influence cognitive and behavioural characteristics.

However, heritability studies merely point at genetic influences, but do not by themselves explain anything. The next step is to identify genes whose variations (the *genotype*) correlate with variations in the cognitive domain (the *phenotype*). For complex reasons, this often comes in two steps, first identifying suspect regions of the genome linked with the phenotype (linkage studies), then looking for candidate genes within those regions (association studies) (see *Fisher*).

Yet, even these positional approaches leading to gene identification do not by themselves explain anything. They simply mark the end of the first part of the journey: from cognition down to the gene. The second part of the journey takes the reverse path: starting from the gene, to go back to cognition, i.e., to explain how variation in certain genes *causes* variation in certain cognitive traits. And here the word *explain* takes its full meaning. The matter is to understand the entire chain of events, from molecular variations in DNA to altered protein synthesis to the countless molecular events involved in the construction, development, functioning and disruption of the brain, to brain systems and cognitive functions (at which stage the more familiar problem of mapping brain to cognition is encountered).

At the time of writing, we are near the middle of this journey. For many cognitive traits and disorders, chromosomal regions, and in certain cases particular genes, have been identified. Many more will be identified in the coming years. It is still only the beginning, but the methods are now quite well mastered and improving all the time, so it is only a matter of time before we obtain complete lists of genes involved in most cognitive traits and disorders of interest. The second part of the journey is at a much more preliminary stage, for understandable reasons: whereas the first part, by leaping

[1] Here, I refer to the technical notion of heritability, which broadly quantifies the proportion of phenotypic variance attributable to additive genetic variance rather than to environmental variance. For proper definitions of this and other technical notions, as well as an overview of the methods involved, see the papers by *Fisher, Balaban,* and *Stromswold*.

[2] Needless to say, the notion of heritability is controversial. Since the debate on Sociobiology (Gould & Lewontin, 1979; Wilson, 1975), many people have strongly opposed inferring any genetic influence from twin and adoption studies (Keller, 2000; Lewontin, Rose, & Kamin, 1984). Some aspects of these studies have indeed been widely criticised, like the hypothesis that mono- and dizygotic twins have equally similar environments (Joseph, 2000), or statistical models that leave little room for gene × environment interactions (Schönemann, 1997). Such criticism is valid and thus implies that estimates of genetic influences may be inflated; but whether this makes genetic influences nil remains doubtful. At any rate, the whole point of referring to heritability studies here is that they are *suggestive* of genetic influence, but this is by no means sufficient: they simply point at priority areas for molecular genetic studies. The fact that the latter are (in some cases) beginning to be successful provides a posteriori justification for claims of genetic influence.

wildly from cognition to gene, bypasses most biological complexity, the task of the second part is precisely to unfold this complexity. This implies understanding under which conditions a gene (in its different forms) is expressed, which protein it synthesises, how different parts of this protein bind to various molecules, how this influences cell function, and how such complex cascades of molecular events affect brain development and function in such a way as to influence cognitive functions. This is the vast developing field of *neurogenetics*.

This extraordinary scientific endeavour is not reserved just for molecular biologists. Cognitive scientists have an important part to play. For one thing, genetic analyses can only be as good as the characterisation of the phenotype, and cognitive phenotyping is (or should be) in the hands of cognitive scientists. Measures of the phenotype can either be categorical or quantitative. The typical categorical measure is whether an individual is affected or not by a disorder of interest. This may be straightforward for many diseases (e.g., albinism or haemophilia), but usually is not for cognitive disorders: diagnosis of autism or schizophrenia remains to this day a difficult, partly subjective, and error-prone process, which is bound to evolve with our current understanding. As cognitive models of these disorders and the diagnostic procedures they suggest improve, so will genetic analyses. This is even truer for quantitative genetic analyses, which look for genetic variants that correlate with continuous variables: this may be straightforward when the variable is cholesterol level, but becomes problematic when it is, for instance, a score in a reading test, given the numerous factors that can influence such a score. Of course, current cognitive models of reading and developmental dyslexia suggest more pertinent measures, which have indeed been fruitful for dyslexia genetics (see *Fisher* and *Pennington*). Quantitative genetics, being applicable to any cognitive variable, is not restricted to studying disorders: it lays out the promise of understanding how genetic factors influence normal variation in all aspects of cognition. Again, judicious design of cognitive variables will be crucial. Cognitive scientists are needed in genetics precisely because good cognitive models are needed to design behavioural genetic studies (just like they are needed to design functional brain imaging studies). This remark also highlights the fact that there is no point fearing biological reductionism: there can be no meaningful reduction of cognition to biology, other than in the sense of *connecting* the two levels of description.

Cognitive neuroscientists are also hard-pressed to join in the neurogenetic enterprise. If it were not for its obvious success, one might argue that the behavioural genetic approach is fundamentally flawed: indeed, genes do not code for behaviours, nor do they code for cognitive functions, and not even directly for particular brain areas: they only code for proteins. Linking genes directly with behavioural/cognitive markers is therefore quite a stretch, and indeed the links that have been demonstrated totally elude our intuitive notion of *a gene for* something (see *Fisher*). Obviously there is a need for more brain between genes and cognition. Neurogenetic investigations are trying to fill this gap, but because they start at the gene, they are understandably confined to a very low level of description. Ideally we should put more brain in genetic studies themselves, i.e., by defining *neural phenotypes* that are related to the cognitive phenotypes of interest, and running genetic analyses on the basis of the former. It is in the discovery of such neural phenotypes that cognitive neuroscientists will have an important role to play.

The wide gap between the neural properties described by neurogenetics on the one hand, and the brain functions and areas of interest in cognitive neuroscience on the other hand, must be reduced at both ends.

But the main reason to become interested in genes is that they are intriguing, even challenging. The more we learn about them, the more they seem to confront cognitive scientists with paradoxes: How can there be an innate universal grammar if genes only code for proteins, and are so few, and so broadly shared with other species? How can genetic abnormalities lead to such domain-specific developmental disorders as certain cases of dyslexia, specific language impairment or Asperger syndrome, if genes cannot code specifically for phonology, syntax or mentalising? Such questions can only be answered by tackling the full complexity of cognitive *and* biological phenomena. This Special Issue is a first shot at the biological complexity underlying many questions of interest to cognitive scientists.

2. The many paths from gene to cognition

Progress in biology promises to bear on debates originating in cognitive science, much more directly than used to be the case. When cognitive psychologists postulate a particular cognitive module[3] and attempt to characterise its properties, it is now becoming possible for them (and for skeptics) to look for directly relevant biological evidence, and possibly settle the case on that basis. As we will see, they can put reasonable hopes in the search for genetic mechanisms explaining (partly) the construction of certain cognitive modules. However, if they are to avoid disappointment, they should also become more realistic about what kind of genetic factors to expect. Indeed the paths from gene to cognition are more often than not a long and winding road. This Special Issue is about sharing with the cognitive science community at large both the enthusiasm generated by the new perspectives opened by genetics and neuroscience, and the sobriety imposed by the inevitable complexity of biological mechanisms. Each of the following contributors brings a different perspective on both these issues.

Simon Fisher, after recalling basic notions of genetics for the unfamiliar reader, argues that the popular notion of "a gene for" a cognitive function or even a behaviour, although used by biologists in a technical sense, may be deeply mistaken understood in a more general sense. He illustrates this point with research on the genetics of developmental dyslexia and on the *FOXP2* gene famously involved in a speech

[3] Throughout this paper I use a pretty liberal definition of the word module: a specific information-processing function (a cognitive module), together with its neural substrate, a specialised brain structure (an anatomical module). I consider that the other properties (innateness, domain-specificity, etc.) of so-defined modules are to be determined empirically. For instance, under that definition, the visual word-form area is a module (that processes sequences of letters as part of the reading system), even though it has not evolved to read, and even if it turns out to process other stimuli than sequences of letters. Similarly, this definition does not particularly assume that the neural substrate has to be a single localised Brodmann area, rather than a distributed network. Hopefully, with such a maximally inclusive definition even traditional opponents of modularity can use this word and read this paper. The issue of modularity is discussed further below.

and language disorder, both of which will be of high interest to students of language, as they provide a first glimpse of language genetics. As expected, this glimpse is both highly exciting and sobering.

Evan Balaban goes on with a bird's eye view of the multiple factors that influence brain development, which explain why causal relationships from gene to cognition are highly degraded. His paper covers further discussion of what *FOXP2* may or may not do, biological determinants of critical periods, experience and brain plasticity, and the important but often overlooked role of stochastic factors in brain development. He advocates greater integration between biological data and cognitivist theorising.

Karin Stromswold asks why identical twins don't always have identical linguistic abilities. The question might seem odd at first, given all the non-genetic factors that likely influence a person's linguistic development. Yet, asking this question is an opportunity to explore all the specific processes that interact with genetic information to produce the infinite number of possible endstates compatible with one particular genotype: epigenetic factors, pre- and peri-natal factors, post-natal environment and interactions between these factors. It thus appears that the gene/environment dichotomy is far too simplistic to do justice to developmental processes.

Bruce Pennington, reviewing behavioural genetic research on various developmental disorders, argues that the intuitive notion of single causes producing deterministic effects may well be insufficient to account for the comorbidities typically observed (co-occurrence of several disorders at a frequency higher than expected), yet another illustration that the complexities of biological factors often defy traditional cognitivist logic. The alternative, more complex, multiple deficit model may be the way to go, to the extent that it can be formulated specifically enough to generate suitable explanations and predictions.

James Blair, reviewing extensive data from developmental psychopathy, upgrades his former Violence Inhibition Model to the Integrated Emotions Systems. In so doing, he provides extremely specific hypotheses (and a wealth of data) on how genetic anomalies, affecting a specific part of the emotion system, may alter its development and lead to a relatively specific cognitive disorder. Although the genetics of psychopathy remains to be researched, the neuro-cognitive part of the model is remarkably well specified, so much so that it appears to be the first model of a specific cognitive developmental disorder that is ready for full integration with biological detail at the molecular level.

Finally, *Gary Marcus* invites cognitive scientists to rethink their notion of modularity to make it fit into the general framework of the evolution of biological functions. According to him, asking *how* a module could have evolved inevitably leads to the Darwinian concept of descent with modification, which implies that modules are probably not as modular as is sometimes postulated by psychologists, but may still be modules in a non-trivial sense. This is a challenge both to advocates of strict Fodorian modularity to accept a toned-down but more biologically plausible notion of modularity, and to traditional opponents of modularity to meet them in the middle.

But to begin with, the remainder of the present paper will address two hot issues of broad interest to cognitive scientists. Firstly, what immediate lessons can we draw from current knowledge in genetics and developmental neuroscience? Is it the case, as

is sometimes suggested, that biology prescribes certain answers to questions of innateness, modularity and domain-specificity? If so, which ones? Secondly, we will attempt to go beyond general statements and provide with dyslexia a concrete example of how research on language is getting closer to being connected to data from genetics and molecular neuroscience, and sketch an outline of what the future field of language genetics might look like.

3. Genetic pre-specification of brain structure

3.1. Is there a paradox?

It is a well-known fact that the genome is highly conserved across species. The human genome is unexpectedly small (25000 genes by the latest estimates), highly similar to that of other primates (98.5% similar to that of the chimpanzee), and human genes typically did not arise from vacuum. Rather, their ancestry can most often be traced back to homologue forms with similar functions in other species, including the mouse and even the drosophila. One may therefore wonder what makes humans human.

One way out of this paradox is to assume that human cognition is little neurally prespecified and results from relatively minor tweaks in the primate brain. Basically the human brain may simply be bigger, more flexible, a better all-purpose learner, which might require only a few mutations. And human cognitive functions may result from a few sensory and computational biases requiring minimal architectural constraints before experience-dependent patterning. To mention just one reference work, this was for instance the view espoused in *Rethinking Innateness* (Elman et al., 1996).

This view is definitely a possibility that deserves empirical testing. The good news is that, contrary to earlier claims (Elman et al., 1996; Quartz & Sejnowski, 1997), it is not the *only* possibility allowed by current knowledge in biology. To mention two more recent reference works, *The Birth of the Mind* (Marcus, 2004) and the third edition of the *The Cognitive Neurosciences* (Gazzaniga, 2004) paint a rather different picture (Fossella & Posner, 2004; Garel & Rubenstein, 2004; Preuss, 2004; Rakic, Ang, & Breunig, 2004) (see also Sur & Rubenstein, 2005). Indeed, whereas "neuroscientists have fostered the view that our brains are basically bigger, better versions of a generalized primate or mammalian brain", "it is becoming increasingly clear that this is not the case, and that the brain underwent changes at many levels of organization during the recent evolutionary history of the human lineage" (Preuss, 2004, p. 19). Furthermore, "the cerebral cortex is intrinsically regionalized from very early stages of embryogenesis" (Garel & Rubenstein, 2004, p. 72). Given that this view sharply contrasts with the previous one, let us review some of the details.

3.2. Human genome specificity

So, our genome is 98.5% similar to that of the chimp. But what exactly counts as similar or different? It turns out that this estimate is based only on base substitution

counts – just one way in which genomes may differ, and probably not the most important one. More recent estimates taking into account insertions and deletions are closer to 95% (Britten, 2002; Varki & Altheide, 2005; Watanabe et al., 2004). Furthermore, such insertions and deletions are more likely to modify the amino-acid sequence of a protein than base substitutions. Indeed the recent sequencing of the chimpanzee genome has shown that these 5% sequence changes are sufficient to produce changes in most proteins: only about 30% of proteins are identical between the two species, while 70% of proteins differ by an average of 2 amino-acids (one in each lineage) (Chimpanzee Sequencing & Analysis Consortium, 2005). Furthermore a detailed comparison of human chromosome 21 and its chimpanzee homologue (22) found that 83% of protein coding sequences differed between the two species (Watanabe et al., 2004). Although many of these changes alter the protein's shape too little to be of great functional significance, these authors still found that around 20% of proteins showed gross structural changes. This suggests that human and chimpanzee genomes may well differ by 20%, in terms of functionally significant differences.

On top of these small modifications of DNA sequences, larger-scale duplications of sequences (within or between chromosomes) have occured in *homo* lineages much more frequently than previously thought, and may well be a major vector of our recent evolution (Bailey et al., 2002; Cheng et al., 2005). They typically result in gene expression differences between human and chimpanzee (Cheng et al., 2005), a factor which should not be overlooked as it can produce large phenotypic differences. Occasionally, duplication, shuffling, assembly and modification of stretches of existing coding sequences produce entirely novel and viable sequences, leading to "chimerical" or "mosaic" transcripts. These are, in essence, new, human-specific genes, a concept that once was heretical but is now gaining widespread acceptance (Nahon, 2003). A fine-grained analysis of such mosaic transcripts on human chromosome 21/chimp chromosome 22 has led to an estimate of 150–350 human-specific genes across the entire genome (Bailey et al., 2002). Almost all of these genes remain to be identified and their function studied. They definitely are good candidates as genes implicated in human-specific functions. But note that these are "human-specific" genes in the very narrow sense of having no direct functional homologue in our ancestors. As mentioned above, about 70% of our genes are human-specific in the much broader sense of producing an amino-acid sequence that differs from its evolutionary homologue (and a large proportion are expressed most highly in the brain).

Finally, it is worth remarking that even if our coding sequences were 100% identical to those of the chimp, we might still be very different species. This is because many phenotypic differences may arise from differences in the expression pattern of the same gene. Most of the genome is made of non-coding sequences, which contain sites to which transcription factors may bind to regulate the expression of neighbouring genes. Quantitative gene expression differences between the human and chimp brain have been estimated at about 30% (Enard et al., 2002). Obviously, taking expression patterns into account further increases the genetic distance between the two species.

To sum up, the old saw that human and chimpanzee genomes differ by only 1.5% is not only misleading but wrong. This is not a futile attempt to rescue human "uniqueness". The obviously unique characteristics of the human species (like of

every single species) are in no need of rescue. Rather, the challenge is to understand where these unique characteristics come from. The popular paradox according to which our genome might not be unique enough for that purpose is clearly overrated.

3.3. Brain development and pre-wiring

On the basis of preliminary genomic data, it was once thought that gene expression was largely uniform across the whole cerebral cortex, providing little biological basis for early differentiation of cortical areas. A rapidly growing amount of new data is now showing just the opposite. The three-dimensional structure of grey matter in many areas of the cortex has been shown to be highly heritable (Thompson et al., 2001), and genes responsible for this are being discovered routinely. Asymmetries between left and right hemispheres appear as early as at 12 weeks of gestation in the human embryo, in the form of massive asymmetries in the expression of dozens of genes (Sun et al., 2005). Many genes have also been identified whose early expression is gradient along rostral-caudal or dorsal-ventral axes, while other genes are expressed only in specific anatomical compartments, thereby delimiting broad functional areas (such as visual cortex) early during fetal brain development (Donoghue & Rakic, 1999a, 1999b; Kingsbury & Finlay, 2001). This is true not only for broad anatomical areas but also for much more specific areas: for instance certain genes have been found to have expression patterns strictly matching the boundaries between primary (V1) and secondary visual cortex (V2) (Sestan, Rakic, & Donoghue, 2001). This was shown in rhesus monkeys before birth, thus before any visual input and indeed even before reciprocal connections between cortex and thalamus are established. Similar results have been obtained and generalised in the mouse (Rubenstein et al., 1999), where it has been shown that cortical area-specific gene expression can occur even in the total absence of thalamic innervation (Miyashita-Lin, Hevner, Wassarman, Martinez, & Rubenstein, 1999). Most dramatically, mice's brains can develop normally to a very large extent, even with respect to micro-circuitry and individual synapses, in the total absence of neuro-transmitters (and therefore neural activity) (Verhage et al., 2000). This may be explained by the existence of a large number of transcription factors (genes regulating the expression of other genes) whose restricted expression patterns are sufficient to explain the overall anatomical organisation of the mouse brain (Gray et al., 2004, have identified no less than 349 such genes).

Even with respect to much more fine-grained structure, genetic guidance seems omnipresent. For instance, in the long-standing debate over ocular dominance columns, it seems now clear that their initial patterning is determined by axon-guiding molecular cues and/or self-generated neural activity (Katz & Crowley, 2002) and owes little to visual experience (indeed it occurs before birth in the monkey, Des Rosiers et al., 1978; Rakic, 1976). Such experience-independent patterning has also been demonstrated for orientation preference columns (Gödecke & Bonhoeffer, 1996; Kaschube, Wolf, Geisel, & Lowel, 2002), and in several other sensory systems, including somatosensory representations of whiskers in rodents (Chiaia, Fish, Bauer, Bennett-Clarke, & Rhoades, 1992) and representation of odorant receptors in the olfactory cortex (Lin et al., 2000).

Therefore, there is substantial evidence for genetic pre-wiring of a great deal of brain structure (*Balaban* calls this developmental anticipation), and each week the news brings more. Although this is as yet mere speculation, it is a relatively safe bet that neuroscientists will find intrinsic molecular cues delimiting most (if not all) Brodmann areas. Recall that Brodmann areas were identified by their cytoarchitectonic properties (size, shape, density, and connectivity of various types of neurons in the six layers of the cortex), and that this is the kind of property that is typically driven by the expression of one or several genes in the corresponding areas, so the only risky part of the bet is that the relevant gene expression patterns occur before experience-dependent input.

To be clear, the purpose of this section is not to argue that all brain wiring is genetically determined. "Gene shortage" arguments typically target the hypothesis that every synapse is genetically pre-wired (Ehrlich, 2000), only to point out that 25,000 genes can't code for a trillion synapses. Of course nobody ever suggested that, and indeed no one needs that. There is a sense in which the brain is genetically pre-wired, even down to the level of synapses, but not with total specificity, and with a significant degree of chance involved (see *Balaban*). Synaptic contacts can be specified in a general manner, like "type A neurones should try to connect with type B neurones", which is typically implemented as type A neurones growing axons or dendrites that are chemically attracted by molecules emitted by signalling centres and by molecular cues on the surface of type B neurones (e.g., Sur & Rubenstein, 2005). Such a mechanism may seem far too general to generate any interesting neural architecture, however for that purpose types of neurones can be specified quite narrowly. Indeed whether a neurone will grow dendrites or produce a particular molecular cue at a given time depends on the expression of particular genes, which itself depends on many internal factors like which other genes the neurone currently expresses, as well as external factors like which molecules surround it and in what concentration (which can in particular specify the neurones' position within the brain and within its own neural structure). In that sense almost every neurone is unique, or at least the number of potential types of neurones is very large, sufficiently so that generic genetically encoded connectivity instructions can have relatively specific local effects. Furthermore, as a given connectivity instruction has different effects on different neurones (in different places and/or at different times), it can be used several times for different purposes, further reducing the load on genetic encoding.

Finally, it is of course clear that not all *adult* functional neuro-anatomy is attributable to genetically determined in utero pre-wiring. Indeed it is expected (and observed) that many neuroanatomical modules need considerable input and fine-tuning before acquiring their adult functional capacities. More generally, pre-wiring does not entail hard-wiring (Marcus, 2004). Pre-wiring is perfectly compatible with the fact that certain brain areas can restructure in response to different input regimes, and may owe some of their functional properties to the input they receive. Indeed, there is a lot of evidence that, even where neural structure is largely genetically determined at birth, neural activity is necessary to *maintain* the structure

(Katz & Crowley, 2002; Verhage et al., 2000), and can indeed significantly reshape it. This leads us to the notion of brain plasticity.

3.4. Brain plasticity vs. hard-wiring

Brain plasticity is probably one of the most overrated concepts in contemporary cognitive science. Firstly, the term is being overused as a fashionable synonym of "learning". Second, it is being used to upgrade commonsensical findings to the rank of grand discoveries (e.g., when you learn something, some aspect of your brain changes). Third, it is being inflated as "total" and "absolute", when it is in fact strictly limited in space and time and subject to specific conditions. Fourth, it is being misused to bear on the nature/nurture debate, the argument being that if the environment can reshape some aspect of neural structure, this must imply that this structure was entirely shaped by the environment to begin with. The flaw in this argument is obvious (see Pinker, 2002, for a thorough discussion of plasticity issues).

The development of ocular dominance columns is exemplary in this respect. In a first phase, ocular dominance columns are formed entirely under genetic control, regardless of any visual input (indeed, before birth in macaque monkeys) (Horton & Hocking, 1996; Rakic, 1976). This is followed by a "critical period" during which there is great plasticity: shutting off one eye can make the columns disappear (Des Rosiers et al., 1978; Wiesel & Hubel, 1963). Finally, the critical period closes and the system rigidifies, becoming impervious to changes in the input (Issa, Trachtenberg, Chapman, Zahs, & Stryker, 1999) (see *Balaban* for further explanation of the plasticity window). The development and plasticity of ocular dominance columns therefore exemplifies the typical alliance between genetic pre-wiring, and experience-driven maintenance, fine-tuning, or even dramatic alteration. More generally, the emphasis has been much more on demonstration of plasticity effects than of limitations to plasticity, although such limitations are quite real (e.g., Smirnakis et al., 2005).

Ironically, plasticity is among the properties of the brain that must be under the tightest genetic control. Indeed, the molecular mechanisms that modulate neurons' response to activity and changes thereof are precisely the sort of processes that genes trigger and regulate. For instance, synaptic sprouting and long-term plasticity at the neuromuscular junction following increased neuronal activity is mediated specifically by the down-regulation of a particular cell adhesion molecule at the synapse (Schuster, Davis, Fetter, & Goodman, 1996a, 1996b). More generally, all learning and memory processes seem to be under tight genetic control. Indeed, cell stimulation induces the expression of *immediate early genes*, whose products either directly modify synaptic structure and function, or trigger cascades of expression of other genes involved in learning and plasticity (Clayton, 2000). Genetically mediated effects on brain plasticity have been demonstrated in such a variety of situations as spatial learning (Wisden et al., 1990), motor learning (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996), olfactory learning (Hess, Lynch, & Gall, 1995) or fear conditioning (Campeau et al., 1991)

in rodents, familiarisation with a new song in the zebra finch (Mello, Vicario, & Clayton, 1992), visual imprinting in chickens (Anokhin, Mileusnic, Shamakina, & Rose, 1991), visual learning in macaque monkeys (Okuno & Miyashita, 1996), ocular dominance plasticity in mice (Taha & Stryker, 2002), drug addiction in rats (Hope, Kosofsky, Hyman, & Nestler, 1992), and many more (Chen & Tonegawa, 1997; Davis & Goodman, 1998; Davis, Schuster, & Goodman, 1996; Dubnau & Tully, 1998; Mayford & Kandel, 1999). Genes also influence plasticity consecutive to neurological insult: different genetic strains of mice show different patterns of gene expression after a seizure, which predict different prognoses with respect to cell death (Sandberg et al., 2000). In a nutshell, plasticity is not an alternative to the genome, indeed it is entirely controlled by the genome.

3.5. Genome vs. environment

It has been argued that genetic effects always take place in interaction with the environment, so that pure genetic influences are a fiction. This is correct, although as far as pre-wiring of the brain is concerned, the relevant environment has more to do with in utero biochemical factors than with neurally encoded experience as often assumed (see *Stromswold*). In fact the argument can be turned upside down. All environmental influences, all experience, before impacting on the brain in any way, must first go through genetically designed sensory pathways, which provide a first filter on experience. As soon as they are encoded by our sensory receptors, all external signals are in fact internal, and therefore subject to all the constraints imposed by our neural structure. Any change that these signals may induce on the brain (like changing the firing threshold of a synapse, stimulating dendrite or axon growth in a certain direction) is the product of molecular mechanisms that are under strict genetic control, as explained above. The effects of experience can therefore be viewed as selectively and locally altering the expression pattern of our genes, thereby modulating the execution of our genetic program. Thus there are no pure environmental influences. Instead, experience can only influence an organism through the filter of its own genome. This may be seen as a biological generalisation of the idea that not everything is learnable, an idea dear to many linguists but also important in other fields such as perceptual learning (Goldstone, 1998); instead, the genome defines the envelope of what can be learnt, and more generally the envelope of an organisms' possible responses to external influences.

To sum up, genetics and neuroscience argue in favour of substantial genetic pre-wiring. Of course, this has been demonstrated mainly in sub-cortical and sensory cortical areas, but at least this makes clear that genetic pre-wiring in general is perfectly feasible and consistent with current biological knowledge, no matter how few genes there may seem to be, and no matter how much experience may subsequently alter the wiring. General arguments from gene shortage and from brain plasticity are therefore void. Nevertheless, plasticity shows us that pre-wiring does not amount to hard-wiring. Furthermore, the extent to which pre-wiring amounts to functional pre-specification is an open question. Finally, the extent of pre-wiring, hard-wiring and functional pre-specification may vary from function to function and must be determined empirically for each of them.

Unfortunately, this does not tell us the answer to typical questions dear to cognitive scientists, like whether a given cognitive module is innate or domain-specific. But perhaps the problem is that these are not the right questions to ask.

4. Asking the right questions about modules

To take a specific example, saying that the fusiform face area (FFA) is genetically pre-wired is not necessarily the same thing as saying that the face recognition module is innate. The face recognition module probably owes its ultimate functional properties both to genetic pre-wiring and to experience-dependent tuning and/or alterations. But the interplay between the two must be empirically determined. Furthermore, to what extent genetic pre-wiring constrains the function of the FFA so as to process faces (and only faces?) is also an empirical question.

More generally, biological thinking suggests a number of broad questions to be asked about the genesis of putative modules (while leaving them largely open).

4.1. Four modularity questions

Pre-specification: To what extent does genetic pre-wiring actually take place for a given cognitive module? What kind of structure does it impose, and what does this structure induce in terms of information processing?[4]

Commitment: To what extent does pre-wiring constrain the putative function of the module? Can the wiring be sufficiently altered by experience to take on a different function?

Unicity: How dependent is the module on this specific pre-wiring? Could it be implemented by a different brain area with a different pre-wiring (given adequate input)? How different can the pre-wiring be and still support the same function? Is that function as efficiently supported with the different pre-wiring than with the presumed dedicated one?

Tuning: How much (and what kind of) experience-dependent tuning does the module require to attain its adult functional state? In what way does this alter neural structure and information processing?

Importantly these are not criteria for being a module but questions to be asked about modules. Jerry Fodor (1983) has done a great service to cognitive science by providing a precise definition for the word module and listing nine properties that "peripheral systems" *might* have. This conceptual clarification has fed an immense

[4] At this stage it should be recalled that genetic influences do not reduce to pre-wiring, some genetic influences can last throughout life and have on-line effects (what *Balaban* calls activational effects). Indeed the expression of certain genes is well-known to directly affect certain cognitive functions (for instance, this is typically the case for genes coding for neurotransmitters, their receptors, and other molecules involved in neurotransmission pathways). One might want to extend the notion of pre-specification to such genetic factors as well.

and fruitful field of research. The downside is that people have been too eager to read him literally, either to defend that all modules have those 9 properties, or to use evidence that putative module M does not have property P to conclude that it is not a module (and that there are no modules). But these arguments may be futile.

Understanding cognitive functions requires to precisely assess the properties of putative modules and the origin of these properties, which is not the same thing as deciding modularity on the basis of Fodor's criteria. For that matter a more inclusive definition of a module would seem more useful, like the one proposed in footnote 2: "a specific information-processing function, together with its neural substrate, a specialised brain structure". Then the list of modules becomes much less controversial, and scientists can concentrate on investigating their properties, i.e., trying to answer the questions listed above[5]. Obviously, this view of modules and of how they should be investigated is highly consistent with *Marcus*'s idea that they evolved through descent with modification.

The modularity questions listed above may be seen as alternatives to traditional questions about innateness and domain-specificity, which may have been overrated:

Innateness: By now it should be clear that innateness is too vague a notion to remain useful in the current scientific era. Fully answering the four above questions for a given module would tell us most of what we want to know about it (in terms of genesis), yet this would not necessarily provide a clear answer to the question whether that module is innate. Indeed there may not be a clear answer to that question for any module. What good is the question then? It may well be that innateness, like many other words, refers to a pre-scientific concept understandable in everyday language but not paralleled by a scientifically grounded concept.

Domain-specificity: Can the module process information outside the domain of its putative function? Surely, specifying the input-output function of the module is an important part of its study, and the range of inputs that the module can process is part of it. But where debates lie is typically at the margins of a domain. Then the answer to domain-specificity depends on how strictly the domain is defined. If defined strictly (e.g., a speech module should process all speech and no non-speech sounds), then domain-specificity might never be attained, because a module can only process stimuli on the basis of their surface properties: in the case of speech, plausibly temporo-spectral and other typical speech properties. Then it is inevitable that a speech module can also process stimuli that sufficiently resemble speech, like non-speech formant transitions (e.g., Belin et al., 1998), at least up to a certain level (of course the output of this processing may be uninterpretable by downstream modules, that's another matter). Similarly it is to be expected that even a highly specialised face recognition module should be "fooled" to process face-like

[5] Although the four questions do not parallel all of Fodor's nine properties, it may be fruitful to turn a few more into questions. For instance, it is certainly of interest to ask to what extent a putative module may be informationally encapsulated. But note that the proposed definition is sufficiently liberal to include any cognitive function (whether peripheral or more central), whereas Fodor's nine properties aimed to characterise peripheral systems only.

non-face stimuli like schematic faces (e.g., Johnson, Dziurawiec, Ellis, & Morton, 1991) or "Greebles" (Gauthier & Tarr, 1997), and perhaps that a syntax module could be "fooled" to process musical hierarchical structure and other recursive structures. So if domain-specificity is enforced strictly, it probably never applies to any real-life module. If it is loosened to include "domain-like" stimuli (with fuzzy domain boundaries), then it becomes relatively trivial and applies to all modules.

Evolutionary selection: Another related question that scientists typically have in mind behind innateness and domain-specificity is whether a module[6] has been positively selected by evolution to perform its current function. Intuitively, this amounts to deciphering the "intention" behind the evolutionary process leading to certain genes participating in the construction of a brain area, although of course evolution has no intention. Concretely, answering this question properly would require determining the various stages of the evolution of the relevant genetic factors, assessing the adaptiveness of each stage (compared to other contemporary versions of the genotype), and whether the advantage that these genetic factors conferred at the time was due to that particular function or to something else (e.g., another adaptive function influenced by the same genetic factors, a "spandrel" in the sense of Gould & Lewontin, 1979). Even if such an assessment was positive, one could only conclude that positive selection is plausible, not that it is proven (because it would be impossible to know for sure *why* the individuals with the presumed less adaptive genotype actually transmitted fewer genes – it could be chance rather than maladaptiveness). So the evolutionary selection question is fascinating but it is so difficult to answer that it is of little practical consequence.

The answers to modularity questions will definitely vary according to domain. Right now, vision seems to offer the most compelling illustrations of pre-wiring. But reading is an example of a function that cannot have been pre-wired (although the perceptual pre-requisites may have: Dehaene, Cohen, Sigman, & Vinckier, 2005), yet it looks very much like a module in a non-trivial sense. What matters is that the answers should be determined empirically, and that the technical means to do so are becoming increasingly available.

5. Developmental dyslexia and the future of language genetics

Of course cognitive functions that have direct equivalents in other species like vision are at an advantage. But it would be an error to think that neurogenetics will never be able to teach us much about human-specific cognitive functions because of technical and ethical limitations on human experimentation. The first results that have emerged from the study of developmental language disorders are very

[6] In fact this question only applies to the genetically determined part of the module (its pre-wiring, and the genetically controlled aspects of its functioning).

encouraging and, even if they have not revealed much specific to human language yet, they clearly promise to do so. Here I review the latest findings on developmental dyslexia to illustrate what sort of insights we may expect from the genetic approach.

5.1. A short history of developmental dyslexia

Developmental dyslexia is by definition a disorder of reading acquisition, however it has been well established over the last three decades that most cases of dyslexia can be attributed to a subtle disorder of oral language (the "phonological deficit"), whose symptoms happen to surface most prominently in reading acquisition (Ramus, 2003; Snowling, 2000). Since it has long been known from family and twin studies that there is a strong genetic component to dyslexia (DeFries, Fulker, & LaBuda, 1987), it is one of the developmental language disorders that is expected to ultimately reveal something about genetic factors implicated in language.

In the late seventies, Galaburda and colleagues began to dissect human brains whose medical records indicated a diagnosis of developmental dyslexia (Galaburda & Kemper, 1979). After dissecting four consecutive brains, and finding evidence for abnormalities of neural migration in all four, they hypothesised that this was unlikely to occur by chance, and that such brain development aberrations might provide an explanation to dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Most interestingly, neural migration anomalies were found predominantly in left peri-sylvian areas traditionally associated with language. Humphreys, Kaufmann, and Galaburda (1990) subsequently confirmed these findings in three more brains, as well as the rarity of such abnormalities in control brains (Kaufmann & Galaburda, 1989). Unfortunately, no attempt at an independent replication was ever published, so the dyslexia research community came to consider these findings as intriguing, but inconclusive. Nevertheless, brain imaging studies have largely confirmed structural and functional abnormalities in dyslexics' left perisylvian areas, although at a different level of description (Démonet, Taylor, & Chaix, 2004; Eckert, 2004; Temple, 2002). Quite strikingly, new results from dyslexia genetics now suggest a reappraisal of the old neural migration hypothesis.

Until recently, linkage studies had provided six reliable chromosomal loci suspected to harbour genes associated with dyslexia (Grigorenko, 2003). Now four such genes have been identified in some of these loci: DYX1C1 on 15q21 (Taipale et al., 2003), KIAA0319 on 6p22 (Cope et al., 2005; Francks et al., 2004), DCDC2 just a few markers away on 6p22 (Meng et al., 2005; Schumacher et al., 2005), and ROBO1 on 3p12 (Hannula-Jouppi et al., 2005). If it were not exciting enough to discover four dyslexia genes in two years, functional studies of these genes have provided remarkably converging evidence.

LoTurco and colleagues have used a particularly innovative technique to study the role of three of these genes in brain development (Bai et al., 2003). They have produced "functional knock-out" rats using in vivo RNA interference. This technique allowed them to specifically block the translation of the gene of interest, in vivo, locally, and at a chosen stage of development (indeed, in utero during neural migration). Using this technique, they showed that DYX1C1 is involved in radial neural

migration, and that the part of the protein that is truncated in a Finnish dyslexic family (Taipale et al., 2003) is necessary and sufficient for normal neural migration (Wang et al., submitted for publication). They have further shown that cortical ectopias (like the ones observed in dyslexic brains) sometimes occur as a result of the DYX1C1-induced disruption of neural migration. The same team has been able to conduct similar studies on both DCDC2 (Meng et al., 2005) and KIAA0319 (Paracchini et al., 2006), again concluding that these genes are crucially implicated in neural migration. Finally, ROBO1 is a homologue of a well-known drosophila gene that is involved in inter-hemispheric axon guidance and cortical dendritic guidance (Hannula-Jouppi et al., 2005).

Amusingly, these findings offer a striking parallel with Galaburda's original discovery of the first four brains with neural migration anomalies. Now there are four candidate genes for dyslexia, and all four are involved in neural migration or guidance. How likely is that to occur by chance? Perhaps the hypothesis that dyslexia is a neural migration disorder should be taken seriously at last. Indeed these results offer, for the first time, concrete links between genes, aspects of brain development, brain anomalies, and cognitive deficits conducive to a specific developmental disorder. Nevertheless, these data have no direct relationship with language so far, and raise some puzzling questions.

5.1.1. Are these "language genes"?

Quite obviously, all these "dyslexia genes" are not really *genes for* dyslexia, nor for reading, nor for language (see *Fisher*). Indeed, they are present in other species in very similar forms (although typically not identical). They are also expressed in other organs than the brain, and therefore fulfil several other functions than just neural migration. None of this contradicts the hypothesis that they are directly implicated in a language disorder; simply, it is typical for genes to be implicated in several different functions, by being expressed at different times at different places.

5.1.2. Are these genes for specific brain areas?

None of the current "dyslexia genes" has its expression restricted to, say, a phonology-relevant area (although their expression is not necessarily uniform across the cortex and reveals interesting patterns, Meng et al., 2005). These are general neural migration genes, that are expected to help neurones migrate wherever this is needed. One therefore wonders how a general neural migration disorder could produce such a specific cognitive deficit as dyslexia, rather than mental retardation or general learning disability. One key will probably be to explain how the neural migration disorder can in fact remain confined to specific cortical areas, namely left perisylvian areas involved in speech processing, where most abnormalities of dyslexic brains have been observed. This suggests that other genes remain to be found, whose expression in the cortex is anatomically restricted, and that interact with neural migration genes in such a way as to spatially constrain the effects of risk alleles. As I have mentioned earlier, there are plenty such genes, the latest search yielding 349 (Gray et al., 2004). This would mean that a dyslexic individual who has a mutated version of one of the genes discussed above may be dyslexic not only in virtue of bearing a mutation

of a neural migration gene, but also because of other alleles of other genes interacting with the neural migration gene so as to restrict the disruption to a phonology-relevant area. These alleles on other genes may be frequent within the general population and may not segregate with dyslexia within a given family, thus escaping genetic analyses. At least this would be one way to explain how mutations in very general genes might produce anatomically specific brain disorders. Of course the very same neural migration genes, in combination with other spatially constraining alleles confining the disruption to other brain areas, could be implicated in other developmental disorders than dyslexia (Ramus, 2004).

5.1.3. Why are there so many genes for dyslexia?

Four dyslexia genes, and this is not the end. How many more? At least three more, if the three remaining linkage sites are to be trusted, and probably even more than that. Why? There are at least two reasons: one is that dyslexia is heterogeneous, so that (1) there may be different subtypes of dyslexia (at the cognitive and neural level), and (2) even within a given cognitive subtype, there may be several genotypes compatible with it. For instance, there are many genes involved in neural migration, and the disruption of any of those may hinder migration in very similar ways and produce similar abnormalities when observed a posteriori. This is in the simple case where one mutated gene is sufficient to produce the phenotype (which may be the case at least with DYX1C1 and ROBO1 in certain Finnish families). The second reason is that this simple case may be quite rare, so that most cases of dyslexia, rather than being caused by a single mutation, may in fact involve the combination of several susceptibility alleles, each contributing a small amount to dyslexia susceptibility. There may be a large number of such genes, their susceptibility alleles may be quite frequent in the general population, and there may also be many combinations of such alleles conferring a high susceptibility to dyslexia. Such a scenario is quite similar to that of many diseases (notably some cancers), and the multiple deficit model proposed by *Pennington* is quite well-suited to deal with it.

5.2. But can we really learn something about language?

The scenario of the pre-wiring of a particular brain area is inevitably of great complexity, involving many genes interacting in complex causal pathways. Apart from gene discovery, most of the relevant experimental data described above is obtained on non-human animals (typically mice and rats). How, then, can we expect to learn something specifically about language?

Geneticists are slowly identifying genes associated with language and other cognitive disorders, and neuroscientists are investigating their role in the construction of the human brain. The search for dyslexia genes has been particularly fruitful, and this is only the beginning. Starting from the genes just discovered, database searches and *in vitro* experiments are being conducted to understand which genes operate upstream, which downstream, which are expressed simultaneously, so that by pulling this thread, and studying those new genes, whole physiological pathways involved in neural migration will be uncovered and understood. Such new genes discovered by

molecular studies will provide important new candidates as "dyslexia genes" to be assessed in human populations. In particular, genes that spatially constrain neural migration disorders will also be found. Their molecular interaction with neural migration genes will be studied in mice and rats. Their statistical interaction with neural migration genes will be studied in human dyslexic and control populations. Their spatial pattern of expression will be studied in human embryonic brain tissue, in order to understand why the disorder is restricted to left perisylvian areas. The sequence of each of these genes will be compared across a number of species in order to retrace their recent evolution in the human lineage, and to identify recent modifications in the human form of the protein. Computer simulations and structural studies will predict the shape of the protein, and suggest which new functions it may thus have acquired in humans. Such hypotheses will be tested by incorporating the human form of the gene into transgenic mice. Even if such mice do not start to talk or read (but assuming that they live through gestation), they should provide further insights on human genes. Little by little, we can therefore expect to understand much more about all the genes implicated in the construction of left perisylvian areas, and disorders thereof.[7]

Beyond, it is really the matter of cognitive neuroscience to understand the role of these areas in language acquisition and processing. It is also the matter of linguistics and psycholinguistics to reformulate grammar into computational and representational constraints that can plausibly be implemented in neural networks (the Minimalist Programme and Optimality Theory may be two such attempts), and partly genetically pre-wired (see Smolensky & Legendre, 2006). This does NOT imply simplifying grammar to make it fit the simplest neural network models, to the extent that it loses all explanatory power with respect to language acquisition and (psycho-)linguistic facts.

Although it cannot be excluded that some genes may be entirely specific to language, students of language should not be surprised nor distressed if the gene search turns out to yield none. The necessary genetic pre-wiring of linguistic modules with highly specific computational properties and connectivity could be obtained through the joint effects of (1) genes generally implicated in brain development processes (like the neural migration genes just discussed) (2) genes with specific anatomical expressions that would interact with the former, and (3) transcription factors that would orchestrate the expression of the former two, so that they would be expressed at specific times, in specific combinations and in specific areas so as to produce unique anatomical structures with unique computational and representational properties. Although the third category of genes might include language-specific genes (triggering developmental cascades relevant only to linguistic modules), they might also have other regulating functions elsewhere in the brain or in the rest of the body. As seems to be the case with the FOXP2 gene (see *Fisher*), such functions could be shared with other species, with only one or two recent mutations possibly allowing the protein to

[7] All the above predictions are based only on currently available techniques. Future technological advances could of course significantly push the limits of current possibilities (one can for instance dream of non invasive *in vivo* gene expression imaging).

perform an additional regulatory function without compromising earlier ones[8]. Such may be the reality about the genetics of language.

6. Conclusion

Ten years ago, neuroscience was about to revolutionise cognitive science, or so it was announced. Many cognitive scientists may claim that they haven't felt the difference (apart from much of their funding being diverted to cognitive neuroscience). They are right in that basic neuroscience may have progressed at a staggering pace, but has made little contact with cognitive science. Now genetics is announced to be the next revolution. Should we care? I have argued that we should indeed. In fact genetics may well be overtaking neuroscience in the race to the human mind. Indeed, contrary to basic neuroscience which is largely dedicated to the study of perception and motor control in non-human animals, genetic studies have begun to directly address human cognitive phenotypes. But at the same time genetics is intimately connected to neuroscience, and therefore provides a new opportunity to connect cognition with the brain at the deepest level. This Special Issue is dedicated to raising cognitive scientists' awareness and interest in this new perspective, by putting together articles providing different empirical examples and theoretical perspectives on how the integration between the different levels of description is to be achieved.

Acknowledgements

I thank Anne Christophe, Emilie Gaillard, Evelyn Fox Keller, Gary Marcus, and Sarah White for their feedback on this paper.

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[8] We have noted before that there seem to be quite a few human-specific genes that differ from their evolutionary precursors by much more than one or two amino-acids. Some may turn out to be involved in language, but there is no evidence thereof so far. For all we know they might as well be involved in human-specific aspects of reproduction or digestion.

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