

The emergence of genomic psychology

Insights from genomic analyses might allow psychologists to understand, predict and modify human behaviour

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To say that psychology was born out of biology is not a huge overstatement. Many of the founders of modern psychology were trained in medicine, physiology or the natural sciences, and regarded psychology as the physiology of behaviour. Wilhelm Wundt, who founded modern experimental and cognitive psychology, and published the *Principles of Physiological Psychology* in 1874, studied medicine and worked as an assistant to the physicist Hermann von Helmholtz. William James, who is widely regarded as a founder of psychology in the USA, earned a medical degree and, in 1890, published the influential *Principles of Psychology*, which starts with a chapter on brain function. Ivan Pavlov, whose work in the 1890s on the conditioning of reflexes in dogs gave rise to behaviourism, received his doctorate in the natural sciences.

Given its roots in the biological sciences, it is not surprising that psychology

has absorbed many technical innovations from biological research, although their incorporation has been confined largely to the subfield of biological psychology. This has changed notably over the past 15 years, as investigators have begun to use non-invasive functional neuroimaging technologies to study human behaviour and psychological processes. Today, this type of analysis cuts across all domains of psychology—clinical, cognitive, developmental and social/health—and represents the lowest level of the reductionist ladder, as it descends from behaviour to neurons.

Here, I suggest that the field of psychology is about to undergo another transformation that will affect all of its subfields, and that will push analyses further down to the level of the genome. This transformation is inspired by genomics—defined as the molecular study of the entire genome, as opposed to the genetics of single genes—and by the interactions among genes, and

those between genes and the environment. Genomics is more powerful than quantitative genetics—which has produced studies based on twins and adoption that are familiar to many psychologists—because it goes “beyond heritability” (Plomin & Colledge, 2001), and reveals the molecular mechanisms underlying gene function and gene–environment interactions. By linking genomic analysis to behaviour, psychologists can now explain, predict and possibly even alter human behaviour. Indeed, in the future, psychologists will no longer be able to model behaviour without reference to genomic data; the field of psychology will therefore be transformed into genomic psychology.

If psychologists want to understand, predict or possibly alter behaviour, they will need tools that can be applied to individual subjects. Behavioural genetics has already highlighted the importance of both

genetic and environmental factors that are unique to the individual (Plomin *et al*, 2001). Presumably, if one knows a person's genetic make-up and his or her life history, one might better understand that individual's behaviour and devise more effective interventions or treatments for pathological aberrations.

This focus on individual differences is mirrored in genomics. Thanks, in large part, to the Human Genome Project, biologists now understand that many genes have a wide range of common variations within their nucleotide sequence. These polymorphisms can contribute to individual differences in complex traits, and studies are now investigating how they interact with environmental factors to give rise to different behaviours. Taken together, the genomic approach identifies the molecular mechanisms that govern the interaction of both genetic and environmental variables.

Genomic psychology is based, in my opinion, on five breakthrough discoveries made during the past decade. These findings identified genetic variations that were related to personality, then linked these variations to brain function, identified interactions with environmental factors that affect mental health, and identified the neural and molecular correlates of these gene–environment interactions. In 1996, three studies associated gene polymorphisms with specific personality traits. One of these identified a polymorphism in the serotonin transporter gene, and its association with neuroticism and harm-avoidance (Lesch *et al*, 1996). The gene is located on chromosome 17 and contains a polymorphic region that renders it either 'short' ('s') or 'long' ('l'). Because each individual carries one copy of this gene from each parent, a person can have two short variants ('ss') or one short and one long variant ('sl'), or can be a homozygous carrier of the long variant ('ll').

At the molecular level, the two forms differ with respect to the ability of the gene to produce the serotonin transporter protein: the long variant yields larger amounts of messenger RNA and leads to a twofold greater re-uptake of serotonin than the short variant (Heils *et al*, 1996). At the behavioural level, carriers of the short variant exhibited significantly higher scores in self-reported neuroticism than carriers of the long variant (Lesch *et al*, 1996). Since the Lesch *et al* report was published, several replication studies have been conducted, and two meta-analyses of

the literature have concluded that the presence of the short variant is indeed associated with higher levels of neuroticism or harm-avoiding behaviour (Munafò *et al*, 2005; Sen *et al*, 2004).

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Two other studies found a similar, albeit weaker, link between a dopamine D4 receptor gene polymorphism and novelty seeking (Benjamin *et al*, 1996; Ebstein *et al*, 1996). The gene is located on chromosome 11 and contains a nucleotide sequence that is repeated 2–10 times, thereby producing variants of differing lengths. At the molecular level, the polymorphism has been shown to affect receptor function differentially (Asghari *et al*, 1995). At the behavioural level, individuals with at least one copy of the seven-repeat variant had significantly higher levels of novelty seeking than those who had no copies of the seven-repeat variant (Benjamin *et al*, 1996; Ebstein *et al*, 1996). A meta-analysis with subsequent replication studies did not confirm this association (Kluger *et al*, 2002); however, another study found a modest link between novelty seeking and the polymorphism when long alleles, rather than only the seven-repeat variant, were considered (Schinka *et al*, 2002). It now appears that the association between the polymorphism and attention-deficit hyperactivity disorder might be more robust, as several meta-analyses have confirmed such an association (Li *et al*, 2006; Maher *et al*, 2002; Thapar *et al*, 2005; Wohl *et al*, 2005).

Following the demonstration that variations in gene sequences can be associated with complex behaviours, the next milestone in the emerging field of genomic psychology was the identification of brain structures the function of which was associated with these polymorphisms. The authors of the first such study used functional magnetic resonance imaging (fMRI) to show an association between the short variant of the serotonin transporter gene and activation of the amygdala brain region during an emotional face-matching

task: participants who carried a copy of the short variant showed greater activation than non-carriers (Hariri *et al*, 2002). This finding has since been replicated with larger samples, and has been extended by other investigators (Hariri *et al*, 2005; Pezawas *et al*, 2005). For example, Furmark and colleagues analysed social-phobic patients after a public-speaking task and found greater amygdala activation in carriers of the short variant (Furmark *et al*, 2004).

These independent studies imply that the short variant of the serotonin transporter gene is involved in enhancing brain reactivity to negative stimuli, which might be a genetic-susceptibility mechanism for depression (Pezawas *et al*, 2005). Together with Klaus-Peter Lesch from the University of Würzburg in Germany, we proposed an alternative model. In this scenario, the presence of the short variant was not associated with higher brain reactivity to negative stimuli—which would be relatively short-lived—but rather with higher brain activation as the default state (Canli *et al*, 2005, 2006). We explicitly tested this assumption, and confirmed that the presence of the short variant was indeed associated with increased activation of the amygdala during the resting baseline condition (Canli *et al*, 2005, 2006). Individuals who carry one or two copies of the short variant of the serotonin transporter gene are therefore no more reactive to negative stimuli than non-carriers, but instead seem to be in a steady state of heightened activity in brain regions associated with negative emotional arousal or vigilance. These findings have since been replicated by two independent groups (Heinz *et al*, 2007; Rao *et al*, 2007), although the interpretation of these observations continues to be debated.

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Since 2002, several other gene polymorphisms have been identified that are associated with differential brain activation, including the catechol-O-methyl transferase, brain-derived neurotrophic factor and monoamine oxidase-A genes (Bertolino *et al*, 2006; Egan *et al*, 2003; Passamonti *et al*, 2006), and it is likely that scientists will continue to find more. One daunting task

for the future will therefore be to assemble large-scale imaging data sets that will allow investigators to study how interactions among these different gene polymorphisms affect brain function.

Meta-analyses support the link between polymorphisms in the serotonin transporter gene and neuroticism (Munafo *et al.*, 2005; Sen *et al.*, 2004), and neuroticism is a risk factor for depression (Boyce *et al.*, 1991). However, the link between the gene and depression has been more tenuous, implying that it does not have a consistent effect, but might instead be moderated by environmental variables, such as life stress (Schinka *et al.*, 2004). The first report of such a gene–environment interaction for depression came in 2003, when Caspi and colleagues reported a significant effect of stressful life events on depressive symptoms, diagnosed depression and suicidal thoughts, which was much stronger for carriers of the short variant of the serotonin transporter gene (Caspi *et al.*, 2003). Several studies confirmed this effect (Kaufman *et al.*, 2004; Kendler *et al.*, 2005), but others reported an effect only in women (Eley *et al.*, 2004; Grabe *et al.*, 2005) and some failed to find any significant gene–environment interaction (Gillespie *et al.*, 2005; Surtees *et al.*, 2006). It is possible that methodological differences account for some of these inconsistencies or that measures of self-reporting are not sensitive enough to reveal reliably a gene–environment interaction.

In collaboration with Klaus-Peter Lesch, my group recently began to map neural correlates of the interaction between the serotonin transporter genotype and life stress (Canli *et al.*, 2006). Individuals with no history of psychopathology completed a brief questionnaire on their life-stress experiences, including their financial, relationship, legal and health-related problems. My group then used fMRI to measure brain activation during a face-processing task, and measured absolute levels of blood flow at rest. Both methods showed that brain activation, particularly in the amygdala and hippocampus—two regions associated with depression and stress—varied across individuals as a function of both serotonin transporter genotype and life stress. When the absolute blood flow at rest was measured, more life stress was found to be associated with higher resting activation among carriers of the short variant. Conversely, more life stress was associated with lower resting activation for carriers of the

long variant. These neural correlates were mirrored at the behavioural level: for carriers of the short variant, more life stress was associated with more rumination, whereas for carriers of the long allele, more life stress was associated with less rumination. It seems that life stress might have a sensitizing effect on carriers of the short allele, but a de-sensitizing effect on carriers of the long variant.

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This observation raises more questions than it answers. What types of life experience drive this interaction? Does it matter if these experiences occurred early in life or recently? Do the observed effects represent local changes in neural function or changes in cognition in higher-level cortical areas, which then modulate amygdala and hippocampal function? Do the observed interactions generalize to other genes? It is therefore clear that much follow-up work is needed to begin to address these questions.

In 2004, Ian Weaver and colleagues identified a molecular mechanism by which life experience might modulate gene expression in rats (Weaver *et al.*, 2004). They based their work on the effects of maternal behaviour and its impact on the pups' stress reactivity during life: pups who receive more licking and grooming from the mother show less stress reactivity than those who receive less maternal care. Focusing on the hippocampus and the glucocorticoid receptor gene, which are both associated with the stress response, the researchers found that increased maternal pup licking and grooming was associated with DNA methylation of the glucocorticoid receptor gene in the brains of these pups. This epigenetic switch altered the production of the glucocorticoid receptor, which might explain why maternal care affects stress reactivity. To prove that these changes were caused by maternal behaviour, the authors conducted a cross-fostering study, in which pups born to mothers showing high and low levels of licking and grooming were switched to foster mothers of the opposite type within 12 hours of birth; they found that the epigenetic changes were dependent on the rearing mother. Life experiences can therefore alter molecular processes and serve as a mechanism for gene–environment interactions.

It remains to be seen whether this mechanism works for other genes or life experiences, or in humans. Furthermore, there are several epigenetic processes other than DNA methylation that could contribute to gene–environment interactions. This will undoubtedly become a major and exciting area of research, which should be of great interest to developmental biologists, psychologists and clinicians.

Several studies already illustrate how the genomic approach is relevant to all areas within psychology. The bulk of this work has been conducted in the clinical domain, where gene polymorphisms have been related to schizophrenia, Alzheimer disease, attention-deficit hyperactivity disorder, and mood and anxiety disorders. Other work has focused on cognitive processes, such as intelligence (Allen *et al.*, 2005; Gosso *et al.*, 2006a, 2006b; Harlaar *et al.*, 2005; Plomin *et al.*, 2004), and on developmental issues, such as childhood aggression or attention. There has been much interest in the role of genetic variation in social processing related to autism and in complex animal social behaviour, such as monogamy and pair bonding.

Nonetheless, future generations of psychologists will need to receive more training in molecular genetics if they are to reap the benefits of genomic research. They will need a general understanding of the concepts and tools in molecular genetics that are related to gene discovery, gene expression and gene manipulation. They will also need to learn not only about genomic function but also about epigenetic processes, such as imprinting, gene silencing, X-chromosome inactivation, histone modifications and heterochromatin, some of which might act as mechanisms for gene–environment interactions. At a minimum, such training will enable genomic psychologists to follow the specialized literature, and it might also facilitate interactions and collaborations with molecular geneticists. Ideally, such training will empower genomic psychologists to develop their own models of behaviour, and to conduct genetic analyses. Similarly, it will be useful for molecular geneticists to learn more about psychology and behaviour. Molecular geneticists with some background in behavioural analysis could collaborate with psychologists to screen polymorphisms in the human genome that are likely to be of functional relevance in human behaviour.

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Whether they come from psychologists or biologists, these developments will undoubtedly advance genomic psychology and should have three main consequences for society. First, genomic psychologists will have a deeper knowledge of the causes of behaviour and will better understand why people do what they do, because they will comprehend how interactions between genetic and environmental factors influence the brain circuits that generate behaviour. Second, they will have a vastly improved—but by no means perfect—ability to predict behaviour; this could have considerable consequences in many applied settings, such as the judicial system, applicant screening or marketing. Third, there will be the possibility of modifying behaviour, either by removing unwanted traits, such as criminal intentions, or by enhancing desired abilities, such as memory. However, these few examples already illustrate that the potential for abuse is an important concern. Just as neuroscientists have begun to consider the neuroethical implications of their work, so too will genomic psychologists have to be vigilant and vocal in advocating the responsible and ethical use of their science.

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doi:10.1038/sj.embor.7400938