ARTICLE

Applying neuroscience to mental disorder

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The neuroscience of personality is becoming increasingly sophisticated, both in terms of theoretical models and methodological approaches, and research in Britain is at the forefront of these developments. The combination of theory and method is especially important in understanding mental disorders (e.g. anxiety and schizophrenia). This article surveys some achievements in this area, existing challenges, and the promise of future developments.

question

How do genes influence people's reactions to the environment, and how can these influences be experimentally tested?

resources

Munafò, M.R. & Flint, J. (2011). Dissecting the genetic architecture of human personality. *Trends in Cognitive Science, 15*, 395–400.

British Society for the Psychology of Individual Differences (BSPID): www.bspid.org.uk

There is a long tradition in British psychology and psychiatry of viewing mental illnesses as the extreme ends of normal personality continua. If we define personality as long-term stability in cognition, emotion and behaviour, then we can view such illnesses as expressions of dysfunction in the systems that regulate these stabilities. This allows us to talk of a 'personality–psychopathology continuum'. This perspective is important because it throws light on the nature of mental illness through the study of underlying systems in non-clinical, healthy populations, which, unlike patient groups, are not confounded by illness chronicity and medication. In this article we showcase some of the successes of the British individual differences perspective in this increasingly important field.

Molecules of life – genetics

We have known for some time, from twin, family and adoption studies, that individual differences in personality traits are under a degree of genetic influence (Munafò & Flint, 2011). Heritability estimates indicate that around 50 per cent of the variation in the trait of interest can be attributed to genetic differences. However, it is only relatively recently that we have been able to investigate which genetic variants (polymorphisms) are associated with which traits, and how. These molecular techniques, which directly measure genetic variation, generally take one of two forms: candidate gene association studies and genome-wide association studies.

Candidate gene studies take as their starting point what is already known about the neurobiology of the trait of interest. This is used to identify genetic 'candidates', in other words, genes that encode products involved in relevant neurotransmitter pathways. So, for example, when studying anxiety-related traits, such as neuroticism, genes involved in the serotonin pathway are the likely candidate, while for approach-related traits, such as extraversion or novelty seeking, genes involved in the dopamine pathway are the focus. As well as identifying a candidate gene in this way, it is necessary to identify a polymorphism within this gene – that is, a region that can exist in multiple forms (alleles). This should ideally be functional, so that different alleles confer corresponding differences in biological function. Genetic variation at this locus should, therefore, confer biological individual differences, which in turn should result in behavioural (phenotype) differences between people (e.g. anxiety). It is then a matter of comparing the phenotype of interest across distinct genetic groups defined by the specific combination of alleles possessed (genotype).

In contrast to the candidate gene approach, genome-wide association studies are agnostic to the underlying neurobiology of a phenotype. This approach scans the genome for a very large number (500,000+) of genetic markers to see if any are related to the phenotype of interest (e.g. anxiety) and, if so, to what extent. Then, once the associated genetic markers are reliably identified, the process of exploration of the function of the related genes can start in earnest. This 'needle in a haystack' approach is far from easy due to the likely small effects of individual genes. However, beyond this technological difference, the statistical approach is very similar to candidate gene studies – we look for a correlation between genetic variation and phenotypic variation. As a result of this situation, and especially

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because of the very large number of statistical tests conducted, there is a clear risk of false positive findings. For this reason, an extremely stringent alpha level is employed – typically a p value of 10^{-8} is required for a result to have achieved 'genome-wide significance'. This, in turn, requires very large sample sizes in order to achieve the statistical power necessary to observe what are likely to be very small genetic effects (which are likely to equate to less than 1 per cent of phenotypic variance) at this level of statistical significance. Perhaps of more concern is the likelihood of false negatives, that is, of not identifying genes that exist. Nonetheless, interesting findings are beginning to emerge.

As genotyping costs decrease year-on-year, it is becoming easier to incorporate genetic information into ongoing research. Gene-by-environment interaction studies, which attempt to explore the interplay between genetic and environmental risk factors, have proliferated, as have intermediate (or endophenotype) studies, which focus on cognitive, neural and biological correlates of behaviour in an attempt to characterise the causal pathway between genetic variation and individual differences in behaviour. For example, studies have shown that functional Val158Met COMT polymorphism, a putative susceptibility gene for schizophrenia (Harrison & Weinberger, 2005), contributes to the variance in certain aspects of the self-reported schizotypal personality dimension (Avramopoulos et al., 2002; Schürhoff et al., 2007).

The proliferation of genetic research is not without its risks; the candidate gene literature concerning personality dimensions, for example, is mixed and characterised by a pattern of early excitement followed by disappointment (Ebstein, 2006) as results have failed to replicate. Subgroup effects (in gene-by-environment and gene-by-gene interaction) or small sample sizes (in intermediate phenotype studies) may exacerbate these problems. On the other hand, combining genetic tools with the experimental paradigm's proxy for environmental effects (e.g. stress induction) may provide more statistical power and permit a clearer interpretation of any associations observed.

'A window on the mind' – electrophysiology

Before the advent of advanced neuroimaging techniques (e.g. PET and MRI), the only way to measure activity in the brain was to use electroencephalograms (EEGs) and event-related potentials (ERPs). Together with these, electromyography (EMG) and oculography techniques have formed a series of electrophysiology methods for studying mental disorders. In this section we highlight two areas: affective and anxiety disorders, and schizotypy.

Affective and anxiety disorders: In the blink of an eye

Notable in this context are the contributions made by EMG and oculography techniques. EMG quantification of the eyeblink has been utilised extensively to examine affective and cognitive modulation of the startle reflex by environmental stimuli, both in relation to individual differences and psychopathology. Affective modulation of the startle reflex has proved particularly informative in the study of harm avoidance, a personality dimension known to modulate the risk of affective disorders (e.g. Cloninger et al., 2006). Confirming theoretical predictions of the personality models of Jeffrey Gray and Robert Cloninger, and in line with the clinical presentations of some anxiety disorders, there is clear evidence from British laboratories that high harm avoidance scorers exhibit greater startle potentiation during exposure to unpleasant stimuli (e.g. Corr et al., 1995, 1997).

Cognitive modulation of the eyeblink startle reflex, in particular prepulse inhibition (PPI), has been widely used to index attention and information processing deficits in schizophrenia and in

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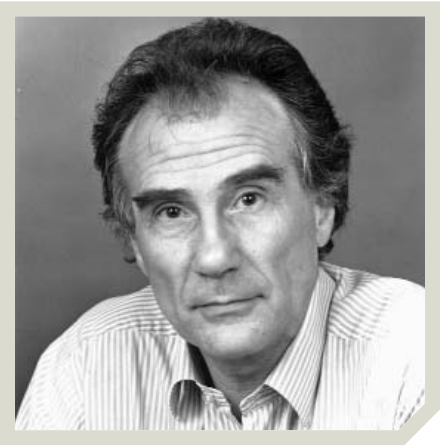
animal-to-human translational research. PPI refers to a reliable reduction in startle amplitude to a strong sensory stimulus (the pulse) when it is preceded, 30–150 ms earlier, by a weak stimulus (the prepulse). It is considered to provide an operational index of sensorimotor gating. PPI is reliably reduced in people with schizophrenia, as demonstrated by many studies in Britain and other parts of the world (e.g. Kumari, Peters et al., 2008; Kumari, Soni et al., 2000). A number of studies have also revealed a negative association between PPI and the level of schizotypy in healthy groups (e.g. Kumari, Toone et al., 1997), providing empirical support for a personality-psychopathology association.

Schizotypy and EEG/ERP and eye movements

Some recent studies linked to British laboratories have used EEG to differentiate individuals affected by mental illness (primarily schizophrenia) from those with a schizophrenia-spectrum phenotype (i.e. schizotypy). For example, Vernon et al. (2005) used EEG to highlight possible information-processing deficits linked to schizophrenia. They showed that, following repeated presentation of an auditory stimulus, healthy participants who had been classified as high on the unreality scale of the Schizotypal Personality Questionnaire (SPQ) showed less habituation in terms of both gamma and beta 1 when attending to stimuli after a short interval, compared with those who had been classified as low on the unreality scale. Such data point to fundamental processing deficits in normal individuals who score highly for schizotypy, which is a weaker form of the full-blown schizophrenia phenotype. This is another example of the personality–psychopathology spectrum.

ERPs have also been used to research the schizotypy–schizophrenia continuum. For example, one ERP is P300, a wave that indexes attention, memory and contextual updating. It is the most widely studied of all ERP components and found to be aberrant in schizophrenia (Gruzelier, 2003). P300 amplitude also correlates with various aspects of schizotypy in healthy relatives of patients with schizophrenia (Sumich et al., 2008a) and healthy controls (Sumich et al., 2008b).



Jeffrey Gray characterised the neuropsychological nature of anxiety

Oculography has been used to obtain objective and reliable measurement of eye movements during a range of experimental tasks. For example, the antisaccade, which requires the participant to inhibit a reflexive saccade towards the target and instead initiate a saccadic eye movement in the direction opposite to the target, measures the processes involved in resolving the conflict between volitional and reflexive responses (Hutton & Ettinger, 2006). Research carried out in Britain and elsewhere has shown a higher percentage of errors, indicative of inhibitory failures, in people with schizophrenia relative to healthy controls (for a review, see Hutton & Ettinger, 2006) and a positive association between the level of schizotypy and the antisaccade error rate in healthy participants (Ettinger et al., 2005).

Functional patterns of activation – neuroimaging

It is now possible to observe the brain in action when performing a task; this functional magnetic resonance imaging (fMRI) is distinct from structural MRI which measures only structural properties of the brain. fMRI provides important insights into the brain processes related to mental states. Sophisticated techniques are being developed that can trace fibre pathways in the brain, via diffusion tensor imaging (DTI), which promises a new vista on brain processing. Early researchers of personality and brain function could only dream of such technology; they had to rely on lesions sustained through accidents or disease (or experimentally induced in laboratory animals).

Recent fMRI studies from British laboratories have demonstrated remarkably powerful and expected associations between personality traits, measured by a simple questionnaire, and brain activity during a number of cognitive and affective tasks (e.g. Kumari, ffytche et al., 2004, 2007; Mobbs et al., 2005). For example, a series of studies have shown that neuroticism (N) and extraversion (E) are associated with altered brain activation in response to affective stimuli (Kumari, ffytche et al., 2007). E and N, as well as emotional states, are implicated in a very wide range of psychological disorders. This is what Hans Eysenck predicted many years ago.

Although the majority of existing fMRI studies are exploratory and not designed to test specific predictions from biologically based theories of personality, their potential contribution to this area has been demonstrated. For example, Eysenck's model (1967) proposes that the personality dimension of introversion–extraversion (E) reflects individual differences in a cortical arousal system that influences cognitive performance. A circuit that apparently corresponds to this system, including the dorsolateral prefrontal (DLPFC) and anterior cingulate (AC) cortices, has been identified in studies applying fMRI to a broad range of cognitive tasks (Duncan &

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Owen, 2000). Given this correspondence, Eysenck's model would predict that, the greater the increase in DLPFC and AC activity as a function of working memory load, the higher the E score; this is exactly what was observed by Kumari, ffytche et al. (2004).

Drugs as research tools

Running through all the above research has been the use of drugs to probe and characterise neural systems underlying normal and abnormal behaviour. It was famously used by Jeffrey Gray to characterise the neuropsychological nature of anxiety by asking: What are the behavioural profiles of the different classes of drugs used to treat anxiety in human beings? Recently, a reformulation of the reinforcement sensitivity theory of personality by Gray and McNaughton (2000; see also McNaughton & Corr, 2008) was based on the effects of panic reducing and anxiety-reducing drugs on rodent defensive behaviour (on such behavioural paradigms as the startle reflex, discussed above). This has given rise to a fundamental distinction between fear and anxiety, which has been discussed by Pickering and colleagues in their article in this special issue.

Summary

With the use of timely technical and statistical advances, exploration has begun into the mechanisms underlying the personality–psychopathology continuum and the impact of individual differences on life outcomes, including mental health. There is, however, still a long way to go before we fully understand why some people are more vulnerable than others to the negative effects of adversity and manifest related mental disorders, while others may show resilience in the face of adversity or are more susceptible to the beneficial effects of supportive and enriching experiences. We look forward to future studies from laboratories in Britain and other parts of the world that will combine valid and psychometrically sound measures of individual differences with genetics, multimodal imaging (i.e. imaging using electrophysiological indices to add temporal information), and sophisticated experimental paradigms to advance the neuroscience of personality and explain its role in life outcomes including manifestation, treatment, and possibly prevention of common mental disorders. British individual differences research was at the forefront of these developments and may be expected to play a similarly significant role in the future.

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