Article 3: Applying Neuroscience Methods to Understanding 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 the UK is at the forefront of these developments. The combination of theory and method are especially important in understanding mental disorders (e.g., anxiety and schizophrenia). This article surveys achievements in this area, existing challenges, and the promise of future developments. We show how neuroscientific tools are opening up whole new areas of research with important clinical applications. Our survey will consider the following tools: (a) structural and functional neuroimaging; (b) EEG/ERP; (c) statistical and molecular genetics; and (d) psychopharmacology. The importance of rigorous experimental research designs is emphasised, as well as the integrative, multi-level, nature of much of this research, including consideration of the more obscure corners of the human mind (e.g., conscious awareness).

Applying Neuroscience Methods to Understanding Mental Disorder

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There has been a long tradition in British psychology and psychiatry of viewing mental illnesses as the extreme end of normal personality continuua. If we define personality as long-term stabilities in cognition, emotion and behaviour, then we can view mental illness as the expressions of dysfunctions 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 by the study of underlying systems in non-clinical, healthy, populations which, unlike patient groups, are not confounded by illness chronicity and medication. The aim of this article is to showcase some of the successes of the British individual differences perspectives in this important field.

Recent years have borne witness to the remarkable developments in technology, and this has lead to the emergence of a highly visible cognitive neuroscience that has been applied to a very wide range of phenomena, from education to mental illness. At the same time, there has been the realisation of a neuroscience of personality – something that was long predicted by Hans Eysenck as was the essential continuity between personality and psychopathology. Eysenck's latest (and highly critical) biographer (Buchanan, 2011, p. 319) notes, 'With the dominance of sophisticated biogenetic techniques in the neurosciences and beyond, Eysenck's conservative nativism – so against the grain in the 1960 and 1970s – now looks both cruder and more prescient." The now dominant view of defining mental illness in terms of normal dimensions of personality is *par excellence* Eysenckian.

Few people now doubt the importance of genetics, brain processes, experimental measures (nowdays, 'endophenotypes') and individual differences in vulnerability to stress, etc. But in the 1940s to 1970s, Eysenck was condemned for suggesting such like. A misconception was that Eysenck was purely 'biological'; more accurately, he was 'biosocial': social (and environmental) factors are important, but importantly they interact with personality trait predispositions that, themselves, are instantiated in the brain.

Neuroscience cometh

The neuroscience of personality is sophisticated both in terms of theoretical models and methodological approaches, and research in Britain has been at the forefront of these developments. The combination of theory and method are especially important in understanding mental disorders (e.g., anxiety and schizophrenia). Neuroscientific tools are opening up whole new areas of research with important clinical applications, as discussed below.

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. Heritability estimates consistently indicate that around 50% of the variation in the trait of interest can be attributed to genes. However, it was not until 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 which 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 which can exist in multiple forms (known as 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. 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 underlying neurobiology of a phenotype. This approach scans the genome for a very large number (500,000+) of genetic markers to see if any, and to what extent, they are related to the phenotype of interest (e.g., anxiety). Then once associated genetic markers are identified reliably can the process of exploration of the function of the related genes start in earnest. This 'needle in a haystack' approach is far from easy, especially as the genetic needle resembles the other hay sticks and due to its small effect does not lend itself to immediate detection. However, beyond this technological difference, the statistical approach is very similar to candidate gene studies – we simply look for a correlation between genetic variation and phenotypic variation. As a result of this situation, and especially 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 <1% of phenotypic variance) at this level of statistical significance. Perhaps more of 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 becomes easier to incorporate genetic information into ongoing research. Gene-by-environment interaction studies, which attempt

to explore the interplay of 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 genes for schizophrenia (Harrison and Weinberger, 2005), contributes to the variance in certain aspects of self-reported schizotypal personality dimension (Avramopoulos et al., 2002; Stefanis et al., 2004, Schürhoff et al., 2007).

The proliferation of genetic research is not without 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 fail to replicate. Sub-group effects (in gene-by-environment, gene-by-gene interaction) or small sample sizes (in intermediate phenotype studies) may exacerbate these problems. On the other hand, combing genetic tools with experimental paradigms proxy of environmental effects (e.g. stress-induction) may provide more power and permit a clearer interpretation of any associations observed.

A Window on the Mind: Electrophysiology

Before brain imaging techniques, the only way to measure activity in the brain was by the electroencephalogram (EEG) and event-related potentials (ERPs). As its pioneer, Hans Berger often noted, EEG was a 'window on the mind' – although one that was rather opaque. In relation to personality, in Britain, from the late 1960s, Anthony Gale was at the forefront of much of this work, which focussed on Eysenck's (1967) arousal/activation-based biological theory of personality. For instance, when eyes open and eyes closed resting EEG were recorded from high and low extraversion groups, Gale, Coles and Blaydon (1969)

reported increased EEG alpha, theta and beta in high extraverts. Since the prevailing assumption was (and still is) that EEG alpha has an inverse relation to activation or arousal, these data were considered supportive of Eysenck's (1967) claim that extraverts have low cortical arousal. Later, in a study examining relations between EEG, personality and emotional empathy, Gale, Morris, Edwards, Moore and Forrester (2001) confirmed this trend.

Later, there was a shift in Gale's theoretical focus to Jeffrey Gray's Reinforcement Sensitivity Theory (RST). Moore, Gale, Morris and Forrester (2006) reported increased EEG theta activity during task stages linked to the experience of goal-conflicts in a cognitive task. In relation to RST, Gray and McNaughton (2000) postulated that goal-conflict processing is experienced as anxious rumination. The link with theta was recently confirmed by Andersen, Moore, Venables and Corr (2009) on task stages in which participants were actively engaged in anxious rumination. Though preliminary, these data provide evidence of a link between EEG theta and individual differences in a predisposition towards anxiety experiences.

EEG.ERP and schizotypy

Some recent studies linked to British laboratories have also used EEG to differentiate individuals affected by mental illness (primarily schizophrenia) and those with a schizophrenia-spectrum phenotype (i.e., schizotypy). For example, Vernon, Haenschel, Dwivedi and Gruzelier (2005) used EEG to highlight possible information processing deficits linked to schizophrenia. They showed that, following repeated presentation of an auditory stimulus, healthy participants 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 to those classified as low on the unreality scale. Such data point to fundamental processing deficits in normal individuals who

score high on schizotypy, which is a weaker form of the full-blown schizophrenia phenotype).

Event related potentials (ERPs) have also been used to research schizotypy-schizophrenia continuum. For example, in Croft, Lee, Bertolot and Gruzelier (2001), the P50 ERP component - an index of pre-attentive sensory gating - differentiated normal controls and participants showing schizotypy symptoms. When a second stimulus was presented 500 ms after an initial stimulus, the second P50 was attenuated in normal controls but this attenuation reduced in participants with schizophrenic symptoms suggesting impairment in sensory filtering.

Another relevant ERP is P300. P300 indexes attention, memory and contextual updating and 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, Kumari, Gordon, et al., 2008) and healthy controls (Sumich, Kumari, Dodd, et al., 2008). Meta-analysis of the P300 and P50 waveforms in schizophrenia confirms that these ERP components are disturbed in schizophrenia patients (Brammon et al. 2004) and in their realatves (Brammon et al. 2005; Thaker, 2008).

Event-related potentials and reward sensitivity

The ERP known as Feedback Related Negativity (FRN) has also proved an important phenomenon for study in personality and psychopathology. The neural source of FRN appears to be the anterior cingulate cortex (ACC; (Holroyd & Coles, 2002; Potts, Martin, Kamp, & Donchin, 2011), an evolutionarily recent specialization of the neocortex that is involved in the integration of emotion and cognition processes (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). Recent work suggests that the FRN may provide a signature of

reward-prediction-error signalling by dopamine neurons (Schultz, Dayan, & Montague, 1997), which fits well with the close connectivity between the ACC and brain structures implicated in motivation and reward-processing (e.g., ventral tegmentum and orbitofrontal cortex). Variation in the FRN (recorded during an associative learning paradigm in which reward and non-reward events were presented) has been associated with variation in both EPQ Extraversion and the Taq1A polymorphism of the dopamine DRD2 gene (Smillie, Cooper, & Pickering, 2010). These findings built upon separate research by the same team, demonstrating a link between Extraversion and DRD2 variation (Luke D. Smillie, Cooper, Proitsi, Powell, & Pickering, 2010). These findings may contribute to our understanding of individual differences in reward-processing and approach motivation as well as deficits in such processes such as is seen in motivational anhedonia (Treadway & Zald, 2011).

In the blink of an eye

Also notable in this context are the contributions made by electromyography (EMG) and oculography techniques. EMG quantification of the eyeblink has been extensively utilised 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 (Vrana, 1988) 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 Gray and Cloninger, and in line with clinical presentation of some anxiety disorders, there is clear evidence from the British laboratories that high harm avoidance scorers exhibit greater startle potentiation during exposure to unpleasant stimuli (Corr et al., 1995, 1997). Cognitive modulation of the eyeblink startle reflex response, in particular prepulse inhibition (PPI), has been widely used to index attention and information processing deficits in schizophrenia and in animal-to-human translational research. PPI refers to a reliable reduction in startle

amplitude to a strong sensory stimulus, the pulse, if this is preceded by 30-150 ms by a weak stimulus, the prepulse (Graham, 1975). 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 the UK and other parts of the world (e.g. Braff et al., 1978; Kumari et al., 2000; 2008, Swerdlow et al., 2006). A number of studies have also revealed a negative association between PPI and the level of schizotypy in healthy groups (e.g. Kumari et al., 1997, Evans et al., 2005), providing empirical support for a personality-psychopathology association.

Eye movements

Oculography has been utilised to obtain objective and reliable measurement of eye movements during a range of experimental tasks, for example the antisaccade. The anti-saccade task 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: it measures the processes involved in resolving the conflict between volitional and reflexive responses (Hutton and Ettinger, 2006). Research carried out in the UK and elsewhere has shown a higher percentage of errors, indicative of inhibitory failures, in people with schizophrenia relative to healthy controls (review, Hutton and Ettinger, 2006) and a positive association between the level of schizotypy and anti-saccade error rate in healthy participants (Ettinger et al., 2005).

Pharmacological Dissection of Behaviour: Drugs

The use of drugs to probe and characterise neural systems underlying normal and abnormal behaviour has a long tradition. It has been 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? His now

world-famous behavioural inhibition system (BIS) is a direct outcome of this approach. More recently, reformulations of the reinforcement theory of personality (RST) by Gray and McNaughton (2000; see McNaughton & Corr, 2008, 2008), was based on the effects of panic-reducing and anxiety-reducing drugs on rodent defensive behaviour. This has given rise to a fundamental distinction between fear and anxiety (which can be measured by one-way and two-way avoidance, respectively), which hold important implications for understanding internalising clinical disorders. As an example of this work, Perkins et al (2011) has shown that anxiety-related two-way avoidance behaviour is improved by the anxiolytic drug lorazepam. Human analogues of one-way and two-way avoidance behaviour now affords the opportunity to explore the brain basis of these behaviours via functional MRI.

Functional Patterns of Activation: Neuroimaging

It is now possible to observe the brain in action when performing a task; this is *functional* magnetic resonance imaging (fMRI), as distinct from *structural* MRI which measures structural properties of the brain. Functional MRI gives important insights into the brain processes related to mental states. Increasingly, sophisticated techniques are being developed which can trace fibre pathways in the brain, via diffusion tensor imaging (DTI), which is promising 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 accident or disease (or experimentally in laboratory animals).

Recent fMRI studies have demonstrated remarkably powerful and expected associations between personality traits, measured by simple questionnaire, and brain activity during a number of cognitive and affective tasks (e.g. Canli et al., 2001, 2002; Canli 2004; Kumari et al., 2004, 2007, 2008; Mobbs et al., 2005). For example, a series of studies have shown that Neuroticism (N) and Extraversion (E) are associated with altered brain activation

to affective stimuli (Canli et al., 2001, 2002; Canli 2004, Kumari 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 before, and for which he was unduly criticised.

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, 1981) 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 and Owen, 2000). Given this correspondence, Eysenck's model would predict, the greater the increase in DLPFC and AC activity as a function of working memory load, the higher the Extraversion score; this is exactly what was observed by Kumari et al. (2004).

An emerging topic deserving systematic attention in relation to individual differences is the activity and functional connectivity of resting-state neural networks, related to various processes such as the visual, auditory, motor, sensory, attention as well as the so-called default-mode action. The findings of earlier mentioned Kumari et al. (2004) study had indicated strong negative relationships with activity at rest in distinct brain regions: Extraversion, with Wernicke's and Broca's areas, and the thalamus (most likely related to self-talk in introverts in highly confined fMRI environment); Psychoticism, with the globus pallidus and putamen (dopamine-linked areas); and Neuroticism, with left orbitofrontal cortex (suggestive of relatively low positive affect in high N scorers). Another study (O'Gorman et al. 2006) provided evidence of personality influences in regional resting cerebral perfusion. Given these findings, and other recent evidence of altered activity in

brain's default mode of action across a range of psychiatric disorders, including anxiety and depression (review, Broyd et al., 2009), future studies may benefit from probing resting brain activity along side task-related neural activity changes (experimental conditions *minus* control/rest condition) as a function of individual differences.

Functional imaging methods such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) also enable the assessment of neural activity during a particular task but, as they are based on detecting photons emitted by radioactive substances injected into the body, they are less desirable than fMRI for this purpose. However, PET and SPECT methods are required and proven useful in investigations of possible association between personality traits and functioning of certain receptor systems (e.g. Gray et al., 1994; Farde et al., 1997; Soliman et al., 2011).

More recently, diffusion tensor imaging (DTI) technique has added a new dimension to personality research. DTI is a non-invasive technique that allows for in vivo inference of white-matter tract strength on the basis of diffusion-weighted MRI and can be utilised to test white matter circuitry connecting the functional network regions of interest. Cohen and colleagues (2008) have recently shown that personality traits are linked to dissociable connectivity streams in the human brain. Specifically, they demonstrated that fibre tracts between a subcortical network (including the hippocampus and amygdala) and the ventral striatum predict individual differences in novelty seeking, whereas tracts between the prefrontal cortex and the striatum predict individual differences in reward dependence.

Summary

With the use of timely technical and statistical advances, we have begun to explore the mechanisms the underlying personality-psychopthology continuum and the impact of individual differences in life outcomes, including mental health, in greater detail. 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 be 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, multi-modal imaging (i.e. imaging, which has excellent spatial resolution but poor temporal resolution, with online 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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