D1 and D2 and D3

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Annotation

D_1 and D_2 and D_3

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Good scientific hypotheses rarely succumb to a lack of confirmatory evidence; they may sometimes even be resistant to apparent outright refutation (Kuhn, 1970; Lakatos, 1970). Considering this, Kuhn (1970) suggested that the dominant hypotheses in a field are often replaced not on grounds of greater theoretical coherence but rather on grounds of strategic necessity.

The succession of dominant views about schizophrenia illustrate these points well. Kraepelin's initial formulation of 'dementia praecox' was a clinical one, based in the main on a combination of clinical features and the course of the illness, without much recourse to a supposed pathogenetic mechanism. This was succeeded by Bleuler's 'schizophrenia', which was more clearly psychopathological. However, Bleuler's central concept of a fundamental loosening of associations was itself loose enough to claim and be claimed by the emerging psychodynamic models of mental disorder. The concept of schizophrenia that developed, as a consequence, broadened by the 1950s to encompass much of what had previously been hysteria (Healy, 1991).

The emergence of the neuroleptics and antidepressants in the 1950s laid the basis for a further succession of dominant hypotheses in the 1960s. The advent of the catecholamine hypothesis of depression and dopamine hypothesis of schizophrenia illustrates clearly the strategic elements of a change in paradigm, in that these neurochemical hypotheses were, overall, clearly less adequate accounts of depression or schizophrenia than the dynamic or social models they displaced, but they possessed the strategic virtue of potentially being able to account for the effects of drug treatment in a way that these latter models could not plausibly do (Healy, 1987).

If matters of strategy influence the direction of research as much as does the theoretical coherence of relevant hypotheses, are there any grounds for thinking we may soon be faced with an abandonment of the dopamine hypothesis of schizophrenia?

The internal history of dopamine and schizophrenia

With time, Kuhn (1970) argued, any newly dominant model develops in complexity in an attempt to account for the many aspects of the problem it initially fails to account for. In the case of schizophrenia, this has involved a progression of foci from catecholamine functioning (Carlsson & Lindquist, 1963), to dopamine neurotransmission (Van Rossum, 1966; Anden *et al*, 1970), to a focus on dopamine receptors (Snyder, 1976), and finally to a homing in on the D_2 receptor (Seeman, 1980).

At the same time, there have been developments in the functional anatomy of dopamine systems and a shift in emphasis from the nigrostriatal system to a mesolimbic dopamine system (Stevens, 1973) and more recently to a mesocortical system (Bannon & Roth, 1983; Robbins, 1990). In each case the proposed site of pathology has become more plausible. Allied to these developments have been attempts to account for how disturbances of neurotransmission in dopamine systems might give rise to the clinical features of schizophrenia. The best known of these has been Crow's (1980) influential proposal that disturbances of dopaminergic systems account for the features of type-I schizophrenia. There have also been others (Joseph *et al*, 1979; McKenna, 1987).

There are two ways to view these developments. One is in terms of the pursuit of the neurobiological substrates of schizophrenia, laying the basis for a set of solid developments in our understanding of brain function – developments that might not otherwise have taken place. The most recent such development has been the discovery of a D_3 receptor (Sokoloff *et al*, 1990). The other view is that these developments have been generated by a need to 'save' the hypothesis.

The difficulties in saving the dopamine hypothesis of schizophrenia have never been more marked than recently. The development of positron emission tomography (PET) has enabled a direct testing of D_2 receptor functioning. While an initial study suggested that there were abnormalities in the dopamine system of individuals with schizophrenia (Wong *et al*, 1986), more recent studies have suggested that there are no apparent abnormalities in the dopamine system, or of the D_2 receptor in particular, in schizophrenia (Farde *et al*, 1987, 1990). These findings led one of the principal advocates of the dopamine hypothesis, Arvid Carlsson, to conclude that the dopamine hypothesis of schizophrenia is no longer tenable (Carlsson, 1990).

However, the recent isolation of a D_3 receptor with similarities to the D_2 receptor and a preferential,

although not selective, localisation to limbic areas of the brain (Sokoloff *et al*, 1990) suggests that all previous work on neuroleptics and schizophrenia may need to be reviewed. Given the early state of work on the D_3 receptor and the lack of pharmacological tools to characterise its function, it could be several years before we can decide conclusively whether there is a malfunction in some part of what we now know of the dopamine system in schizophrenia – at which point there is no guarantee that there will not be a D_4 receptor to take into account. Can the issue of whether there is an abnormality of dopamine neurotransmission in schizophrenia ever be resolved, or are we doomed to a lengthy endgame?

Dopamine hypothesis of neuroleptic action

A consideration of the history of hypotheses on schizophrenia suggests both that it might be profitable to pay heed to factors external to research on dopamine rather than simply to developments internal to the field, and that a dominant hypothesis may be struck down in its prime without ever suffering conclusive rebuttal.

However, before attempting to assess the most significant external influences in the case of research on dopaminergic systems, it is worth noting that abandoning the dopamine hypothesis of schizophrenia need not mean abandoning the very real developments there have been in our understanding of dopamine systems in the brain. This follows as all of the above developments also support a dopamine hypothesis of neuroleptic action. The difference between this and the dopamine hypothesis of schizophrenia lies in not making the claim that because the neuroleptics are helpful in schizophrenia, they must somehow be acting on the core psychophysiological disturbance in the disorder (Snyder, 1982; Healy, 1989, 1990*a*).

In favour of a dopamine hypothesis of neuroleptic action are a number of observations. One is that neuroleptics do not cure schizophrenia. Another is that their use clinically is not specific to schizophrenia – they are also used for mania (Silverstone, 1985) and for impulsive and suicidal behaviour of diverse origin (Montgomery & Montgomery, 1982) as well as for agitation generally (Baldessarini, 1980). Finally, in contrast to the latency between giving neuroleptics and clinical improvement, which is typically of the order of several weeks, there is a close congruence between the length of time taken to block D_2 receptors and the induction of states of either 'psychic indifference' or dysphoria – something of the order of 30–60 minutes (May *et al*, 1976).

An almost exclusive focus on the dopamine hypothesis of schizophrenia in recent years has led to a situation in which we can only with difficulty say what neuroleptics actually do clinically. When first introduced in the 1950s there were attempts to characterise their effects, which resulted in Laborit's description of an ataractic state and a variety of other comparable descriptions either of a non-sedating calming effect or a mildly stimulant clarifying effect (Swazey, 1974).

More recently May, Van Putten and colleagues have drawn attention to the variability in individual responses to the acute effects of different neuroleptics and the role that this response may have in shaping the outcome of treatment (May *et al*, 1976; Van Putten *et al*, 1974, 1981, 1990). In the light of this, the recent isolation of a D_3 receptor may be of considerable significance. It remains the case for all currently available neuroleptics that the correlation between clinical potency and receptor affinity is closest for the D_2 receptor. But the fact that most neuroleptics bind with variably high affinity to both D_3 (Sokoloff *et al*, 1990) and 5-HT_2 receptors (Glennon, 1990), in addition to the effects of many of these drugs on D_1 (Waddington, 1989) as well as on adrenergic and cholinergic receptors (Baldessarini, 1980), may help account for such individual variability and may enable a more rational planning of combination therapies to help manage clinical problems – until such time as we truly have an agent which cures schizophrenia.

Indeed, at present, while there is little confirmed evidence of a dopaminergic abnormality in schizophrenia, there is evidence that individual variability in response may correlate with markers of dopamine functioning. In a series of studies of cerebral dopamine turnover and neuroleptic-induced side-effects, including dysphoria, Bowers & Heninger (1981), Bowers (1985) and Bowers & Swigar (1988) found that individuals who do poorly on neuroleptics appear more susceptible than others to profound blockade of the dopamine system – a result that would not be predicted by a dopamine hypothesis of schizophrenia.

The external history of dopamine and schizophrenia

The psychodynamic hypotheses of schizophrenia in the 1950s and 1960s paid little heed to the possible psycho-physiological substrates of the disorder. Equally, however, the dopamine hypothesis of schizophrenia has been a radically neurochemical one, with little heed being paid to the intermediate psycho-physiological level of functioning.

Both psychodynamic and dopamine hypotheses have also had in common a relatively uncritical attitude to the question of what constitutes schizophrenia.

The neuropsychological level of functioning, between receptor dynamics on the one hand and psychodynamics on the other, has in the past few years been a focus of growing interest in schizophrenia and neuroleptic research, as has the question of what constitutes schizophrenia.

(a) Neuropsychology and pharmacopsychology

Starting from the neuropsychological level, there have been a number of hypotheses put forward locating the pathophysiology of schizophrenia in the temporal lobe (Trimble, 1990) or the frontal lobe (Frith, 1987; Frith & Done, 1988; Healy, 1990*a*). In favour of a temporal lobe disorder are an increasing number of findings of pathological abnormalities in the medial temporal lobe of individuals with schizophrenia (Crow, 1990; Roberts, 1991). In favour of a frontal lobe disorder are repeated findings that individuals with schizophrenia have difficulties on a variety of tests of frontal lobe functioning (Cohen *et al*, 1987; Goldberg *et al*, 1987; Bellack, 1990; see also Healy, 1990*a*; Robbins, 1990, for review).

However, the primary rationale for these differing proposals appears to lie other than in such evidence. A conspicuous feature of the Trimble (1990) model and that of Frith & Done (1988) and Healy (1990) has been their efforts to account for the symptoms of the disorder, and in particular first-rank symptoms, in terms of what is known about temporal or frontal lobe functioning.

These models have been made possible by a number of different developments. One has been the emergence of neuropsychology in recent years as a discipline of central importance to psychiatry (Healy, 1990*b*). This has in turn legitimised a return to phenomenological investigations of psychological functioning in a way that was not possible during an era when statements of personal functioning were invariably liable to be interpreted in terms of latent content. The neglect of phenomenology has been no less with the rise of the dopamine hypothesis, under the influence of which phenomenology has been seen simply as an aid to diagnosis, given some indication of which, drug treatment could be expected to put things right.

Allied to an emerging subjective phenomenology of neuroleptic effects as outlined above, there has also been a developing pharmacopsychology of neuroleptics based on investigations of the effects of neuroleptics on neuropsychological functioning (Medalia *et al*, 1988; Berger *et al*, 1989; Spohn & Strauss, 1989; King 1990; Cassens *et al*, 1990). In contrast to the neurobiological emphasis of 'psychopharmacology', by 'pharmacopsychology' I mean an attempt to analyse the constitution of psychological functions by manipulating those functions through the administration of drugs. The recognition of a D_3 receptor, to which neuroleptic drugs may bind variably and which has a somewhat different regional distribution to that of the D_2 receptor (Sokoloff *et al*, 1990), taken in conjunction with the variable binding of all neuroleptics to 5-HT_2 receptors (Glennon, 1990) and that of many neuroleptics to D_1 receptors (Waddington, 1989), will potentially permit a more subtle pharmacopsychological dissection of psychological functions and functioning.

(b) Cognitive-behavioural strategies

A further element in the analysis of the clinical features of schizophrenia has been the development of cognitive-behavioural strategies for a range of 'psychotic' features, such as hallucinations (Falloon & Talbot, 1981) and most recently delusions (Chadwick & Lowe, 1990; Lowe & Chadwick, 1990). These therapies make it imperative to distinguish between core neuropsychological deficits in schizophrenia and cognitive reactions to underlying disorders, both from the point of view of diagnosis but also for the purposes of management (Healy, 1990*a*).

A similar proposal and research agenda was first put in place by Chapman and McGhie in the 1960s before the dopamine hypothesis of schizophrenia was formulated (McGhie & Chapman, 1961; Chapman & McGhie, 1963, 1964; Chapman, 1966, 1967). The dopamine hypothesis, however, effectively led to an eclipse of this research programme. Allied to the current difficulties of the dopamine hypothesis of schizophrenia, however, the increasing vigour of the cognitive research programme, drawing on successes in the case of depression and anxiety, suggests that a switch in research emphasis may be of strategic value.

(c) Schizophrenia: diagnosis and aetiology

There is, in addition, a quite different set of developments that are likely to shape research strategies for schizophrenia. Ever since the International Pilot Study on Schizophrenia, it has been clear that there is wide variability in the diagnosis of this illness (Cooper *et al*, 1972). This variation has been an important stimulus to the development of current research and diagnostic criteria for psychological disorders.

Despite this increased critical concern, it remains clear that there is substantial variability in diagnosis – particularly when diagnosis is based on phenomenological data (Taylor & Abrams, 1978). Nowhere is this more clear than in the case of Schneider's first-rank symptoms (Koehler, 1979).

Since the development of the category of post-traumatic stress disorder in 1980 (American Psychiatric Association, 1980), there has been increasing concern about the effects of physical and sexual abuse on children as well as the effects of witnessing violence or the effects of mental cruelty (Healy, 1991). This concern has led to a number of studies and findings that many psychiatric patients, and in particular up to 50% of those labelled as having schizophrenia, have been subject to significant trauma in childhood (Carmen *et al*, 1984).

An even higher proportion of patients who meet criteria for diagnoses of borderline or multiple-personality disorders (American Psychiatric Association, 1980), many of whom would have been diagnosed as having schizophrenia during the 1950s, '60s, '70s and early '80s (Healy, 1991), are liable to have been traumatised in childhood – current estimates suggest over 80% (Herman *et al*, 1989).

These findings intersect with the question of the aetiology of schizophrenia in a set of recent studies that indicate that 'first-rank symptoms' are even more common in patients with multiple-personality disorder than in schizophrenia (Kluft, 1987; Ross *et al*, 1990). Are these Schneider's first-rank symptoms? Do they originate in temporal or frontal lobe disorder?

Koehler (1979), in discussing the variability in understanding of first-rank symptoms that can be found even in the work of the most-eminent researchers, distinguished broadly between experiences of influenced thinking, feeling and bodily processes, and experiences of alienation from thinking, feeling and bodily processes. The recognition of prominent dissociative symptoms in many psychiatric patients who have been traumatised in childhood (Chu & Dill, 1990) points to a third possibility, which is one of experiencing actions that are not happening under direct conscious control but from which the subject does not feel alienated in a rigorous Schneiderian sense. The experience is rather one of being on automatic pilot, in the same way that we sometimes may be when driving a car or in response to questions at an interview, when we may wonder "where are these answers coming from?".

In favour of a temporal lobe hypothesis for the origin of the symptoms described by patients with borderline and multiple-personality disorders, which may seem like Schneiderian first-rank symptoms, is a long-standing recognition that temporal lobe disorders may give rise to multiple-personality pictures – a recognition that antedates the current fashion for this diagnosis (Mesulam, 1981). Temporal lobe dysfunction may also produce illusions of possession and the trance-like states characteristic of borderline disorders which, given differences in understanding and usage of the first-rank symptoms, are all too likely to have led in many instances to a diagnosis of schizophrenia (Mesulam, 1981).

Against this, there has been a proposal from Williams (1991) that Frith's (1987) and Frith & Don's (1988) model, applied initially to schizophrenia and implicating frontal lobe dysfunction, applies equally well if not somewhat better to the clinical features of borderline personality disorders.

While the notions of borderline and multiple-personality disorder do not meet with general acceptance, the close association between trauma in childhood and conditions that meet criteria for these disorders suggests that there are conditions here that should be distinguished from classic schizophrenia (Kroll, 1988). Failure to differentiate these states would seem liable to compromise genetic and neuropathological studies of classic schizophrenia.

To avoid this confusion, it would seem that an attempt to refine our phenomenological criteria is needed. In contrast to the state of affairs hitherto, future attempts to make such phenomenological distinctions will be able to call upon the resources of neuropsychological – and most probably pharmacopsychological – testing in an effort to distinguish the particular experiences of schizophrenia and of the borderline disorders and also to pin each of them down to specific neuropsychological functions. The need to undertake such differentiations will in turn be likely to lead to a change of research emphasis from a largely neurochemical to a more general psycho-physiological strategy.

Schizophrenia: a switch of research strategies?

The internal history of research on the neurobiology of dopamine systems has been, in the best scientific tradition, one of steady methodical progress leading to substantial advances. This progress has been inspired by a concern to unravel the enigma of schizophrenia. The progress in identifying different dopamine receptors and systems and the functions subserved by dopamine systems in the brain does not seem open to drastic refutation, at least in the imminent future.

Despite this, there are considerable grounds for wagering that the dopamine hypothesis of

schizophrenia will fall by the wayside in the near future. The basis for this claim lies in the conjunction of internal difficulties with the dopamine hypothesis of schizophrenia and a variety of external factors that are likely to affect any strategic calculation of where the next research developments are most likely to come from.

If there is a change of strategy, however, it seems unlikely that there will be the imbalance between current research on schizophrenia, dominated as it has been by the dopamine hypothesis, and that on new developments in other areas, as there was between the psychodynamic and dopamine hypotheses. This is because the developments that there have been in our understanding of dopamine systems and receptor pharmacology are almost certain to underpin at least one set of future research tools – those that will be derived from pharmacopsychology. From this perspective the recognition of a D_3 receptor can only be good news, as indeed the recognition of a D_4 receptor would also be – provided we can also find compounds that would permit an analysis of the neurophysiological functions of these receptors and the behavioural functions of systems in which they feature.

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