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Monoamines and Abnormal Behaviour
A Multi-Aminergic Perspective

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Classical nosology has been the cornerstone of biological psychiatric research; finding biological markers and eventually causes of disease entities has been the major goal. Another approach, designated as 'functional', is advanced here, attempting to correlate biological variables with psychological dysfunctions, the latter being considered to be the basic units of classification in psychopathology. Signs of diminished DA, 5-HT and NA metabolism, as have been found in psychiatric disorders, are not disorder-specific, but rather are related to psychopathological dimensions (hypoactivity/inertia, increased aggression/anxiety, and anhedonia) independent of the nosological framework in which these dysfunctions occur. Implications of the functional approach for psychiatry include a shift from nosological to functional application of psychotropic drugs. Functional psychopharmacology will be dysfunction-orientated and therefore geared towards utilising drug combinations. This prospect is hailed as progress, both practically and scientifically.

Functional psychopathology: a look backward

From the very beginning, biological psychiatry has orientated itself towards nosology, a way of looking at behavioural disorders as distinct, separable entities, each with their own symptoms, causation, outcome and treatment. Finding a marker and, eventually, the cause of, for instance, schizophrenia, depression or panic disorder has always been the major goal of biological psychiatric research. The introduction of DSM–III (American Psychiatric Association, 1980) powerfully reinforced this approach.

For many years now we have advocated and pursued another route, termed the functional approach to psychopathology (van Praag & Leijnse, 1965; van Praag *et al*, 1975, 1987*c*). Essentially, this approach has three tenets.

(a) The basic units of classification in psychopathology are not syndromes or nosological entities, but psychological dysfunctions, such as disturbances in perception, cognition, memory and information processing. *They* are the elementary constituents of psychiatric syndromes.

(b) Nosological classification of a given psychiatric disorder is the first step in diagnosis. The next step is the dissection of the syndrome into its component parts (i.e. the psychological dysfunctions and their subsequent measurement). Analogies of two-tier diagnosing are provided by medicine. Myocardial infarction, for example, is a nosological diagnosis which will be routinely complemented by an analysis of its functional sequelae, in terms of, for instance, heart beat frequency and rhythm, conductance and output. Treatment is predicated on the functional analysis, not on the nosological diagnosis.

(c) In biological psychiatric research, correlations between biological and psychological dysfunctions should be sought.

Functional psychopathology is dimensional in orientation, viewing a given psychiatric disorder as a conglomerate of psychological dysfunctions, most of them nosologically non-specific and occurring in different severities and in different combinations in the various psychiatric syndromes. The nosological approach is categorical, viewing psychiatric disorders as discrete entities, each with its own causation, symptoms and course.

The term 'functional' is not identical with 'symptomatological'. Psychiatric symptoms are the behavioural expression of a psychological dysfunction, not the dysfunction itself. A visual hallucination for example is a symptom, a particular perceptual disturbance the underlying dysfunction. Within the functional framework, the latter is the target of biological research.

The following exposition is meant to illustrate our belief that the functional approach is a productive one.

The role of dopamine in abnormal behaviour

In the late 1960s we reported the occurrence of dopamine (DA) disturbances in depression, most notably in vital depression (major depression melancholic type, called melancholic depression here)

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(van Praag & Korf, 1971*a*). In some patients, the probenecid-induced accumulation of the major DA metabolite homovanillic acid (HVA) in cerebrospinal fluid (CSF) was decreased, indicating a lowered DA metabolism in the central nervous system (CNS), particularly in the nigro-striatal DA system, the region that is predominantly represented by CSF HVA. Guided by Parkinson's disease with its severe disturbances in motor functioning and profound DA depletion, we searched for correlations between lowered CSF HVA and motor retardation. Comparing groups of depressed patients with and without pronounced motor retardation and lack of initiative, the HVA accumulation after probenecid was twice as low in the retarded patients as in the non-retarded depressives and in a control group. Similar findings were reported by other investigators (Papeshi & McClure, 1971; Banki, 1977*a*; Banki *et al*, 1981).

If lowered DA metabolism in the nigro-striatal system underlies retardation and inertia, increasing DA availability could be expected to exert an activating and energising effect. The drug *l*-dihydroxyphenylaline (*l*-DOPA) was chosen to boost DA metabolism, since it increases this substantially, while having little impact on noradrenaline (NA) metabolism. Moreover, the increase in DA metabolism persists over time (van Praag & Lemus, 1986).

No overall therapeutic effects were found when *l*-DOPA (average dose, 260 mg/day) in combination with a peripheral decarboxylase inhibitor was first studied in a group of melancholically depressed patients who were biochemically undifferentiated. Subsequently, we compared the effect of *l*-DOPA (290 mg/day) and a peripheral decarboxylase inhibitor in melancholic patients with lowered post-probenecid CSF HVA and in such patients with normal HVA response. Motor retardation and inertia were significantly more pronounced in the former group. *l*-DOPA improved motor functioning and level of initiative in the low-HVA group and normalised the HVA level. Mood and hedonic functioning were not significantly influenced. Anxiety levels rose slightly, but significantly. In the group with normal HVA response, *l*-DOPA failed to exhibit therapeutic effects (van Praag & Korf, 1975).

The latter experiment was repeated in a different group of patients using *l*-tyrosine instead of *l*-DOPA (van Praag, 1986*b*). In contrast to *l*-DOPA, *l*-tyrosine, the precursor of the catecholamines (CA) DA and NA, significantly increases CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) in humans, indicating increased NA metabolism. CSF HVA, on the other hand, rises only slightly, suggesting that tyrosine's impact on DA metabolism (in the nigro-striatal system) is less pronounced than that of *l*-DOPA. Again, studying melancholic patients with and without lowered CSF HVA accumulation after probenecid, we observed no therapeutic effect of tyrosine on motor retardation and inertia in either group. Anhedonia improved, but anxiety worsened (see later), so that total ratings did not change significantly. Normalisation of CSF HVA did not occur.

Based on these findings we hypothesised that diminished DA metabolism in the nigro-striatal system underlies decreased motor activity and lowered level of initiative, irrespective of nosological diagnosis (van Praag *et al*, 1975). In accordance with this is Lindstrom's (1985) observation that low CSF HVA occurs in schizophrenics with pronounced lassitude and slowness of movement.

When attempting to link the DA system to the ability to carry out goal-directed behaviour, it is necessary to take into account that such behaviour consists of different components. First, an initial stimulus is needed. This can be an instinctual drive, such as hunger, thirst or sex, an emotion, such as anger or a cognitive set (e.g. the realisation of having to prepare for a test). Next, the goals to respond appropriately to the stimulus have to be selected (e.g. to find food to satisfy hunger; to display aggressive behaviour to reduce anger or to move to a library and study in the case of an upcoming test). Then, the behaviour to attain these goals has to be initiated and sustained. Finally, signals should be set in operation when the mission has been accomplished so that the behaviour can be terminated. The term 'drive' is used to indicate an initial stimulus of an instinctual nature. It is also used for the entire process of initiation and completion of goal-directed behaviour. For the sake of brevity we use the term in the latter sense in this paper.

The sequence leading to goal-directed behaviour can be disturbed at any junction. The human data suggest that DA is involved in the mobilisation, facilitation and sustenance of goal-directed behaviour (see Fig. 1). The large pool of animal data accord with this conclusion (Crow & Deakin, 1985; Freed & Yamamoto, 1985; Ashton, 1987).

The role of serotonin in abnormal behaviour

Whither '5-HT depression'

Disturbances in central serotonin (5-hydroxtryptamine; 5-HT) metabolism were first reported in individuals with depression. The lowered post-probenecid minus baseline levels of 5-hydroxyindole acetic acid (5-HIAA, the major degradation product of 5-HT) in the CSF of such individuals indicated diminished 5-HT metabolism in the CNS (van Praag *et al*, 1970).

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Subsequently, disturbances in other systems indicative of central 5-HT-ergic functioning were observed. First, disturbances in platelet 5-HT, such as deviations in 5-HT content and uptake and in the density of imipramine receptors, were reported. Blood platelets have been considered as a model of central 5-HT-ergic nerve endings. Furthermore, disturbances in the ratio of the plasma concentration of tryptophan and the so-called competing amino acids were found. This ratio determines the influx of tryptophan into the CNS, and CNS availability of tryptophan, in its turn, is an important determinant of 5-HT synthesis rate. Moreover, several hormonal challenge tests indicated disturbances in 5-HT-ergic functioning. Finally, psychopharmacological experiments with indirect 5-HT agonists such as the 5-HT precursor 5-hydroxytryptophan (5-HTP), the selective 5-HT uptake inhibitors, and 5-HT antagonists, such as parachlorophenylalanine (PCPA), a 5-HT synthesis inhibitor, suggested that manipulation of central 5-HT can effect mood changes (Brown *et al*, 1990).

The data most directly related to central 5-HT metabolism are derived from CSF studies, although these studies are the most cumbersome to conduct. The inter-relation between the various 5-HT indicators is insufficiently known. (For review on 5-HT and depression see: van Praag, 1982; Goodwin & Post, 1983; Brown *et al*, 1990).

Initially, depressed patients with and without demonstrable disturbances in central 5-HT seemed indistinguishable in psychopathological terms. Therefore, in 1971, based on the data available at that time, the concept of biochemical heterogeneity of depression was introduced (van Praag & Korf, 1971*a*) which suggested that some forms of depression are linked to disturbances in 5-HT functions; others are not or are to a lesser extent only. The same syndrome, then, could be the ultimate outcome of various pathophysiological processes. As an analogy the anaemia syndrome was mentioned: anaemia patients present by and large the same symptoms, but the pathogenesis of the syndrome is heterogeneous, as is the treatment.

Subsequent studies, however, made the postulate of a separate category of '5-HT depressions' untenable (van Praag & Lemus, 1986). They indicated that increasing 5-HT availability *alone* is not a sufficient antidepressant measure. This argues against the concept of a depression type that is generated predominantly by central 5-HT disturbances, leading to decreased 5-HT availability.

Contra '5-HT depression'

In a double-blind, placebo-controlled, comparative study it was demonstrated that 5-HTP is an active antidepressant in patients admitted to hospital with rather severe forms of melancholic depression, while tryptophan is no better than placebo (van Praag, 1984). Both 5-HT precursors increase central 5-HT metabolism to an equal extent, as reflected in the probenecid-induced accumulation of 5-HIAA in CSF. They appeared to differ, however, in their effect on catecholamine (CA) metabolites in CSF (reflecting intracerebral metabolism of the mother amines). 5-HTP increases the metabolism of DA as well as of NA, while tryptophan does not (van Praag, 1983). In high doses (> 5 g intravenously) trytophan even lowers DA and NA metabolism, possibly by interfering with the influx of tyrosine, the precursor substance of the CAs, in the CNS (van Praag *et al*, 1987*a*).

The ability of 5-HTP to stimulate CA metabolism is thought to be due to the presence of aromatic amino acid decarboxylase in CA-ergic nerve cells. Hence, 5-HTP is converted to 5-HT not only in 5-HT-ergic but also in CA-ergic neurons. In the latter, 5-HT functions as a false transmitter, as a consequence of which the synthesis rate of CA increases. The net functional effect of the two opposing processes (i.e. false transmitter formation leading to decreased function and increased CA production leading to augmented function) is probably heightened CA-ergic activity.

If 5-HTP's therapeutic superiority to tryptophan is related to its combined effects on 5-HT and CA systems, tryptophan's antidepressant efficacy would be expected to increase above the significance level by combining it with a compound capable of selectively increasing CA availability. In humans tyrosine increases CA metabolism, while 5-HT metabolism is not measurably changed. Combining tryptophan with tyrosine indeed led to significant antidepressant activity (van Praag, 1986*b*).

A second observation supports the hypothesis of 5-HTP deriving its therapeutic potential from its dual influence on 5-HT-ergic and CA-ergic systems. In about 25% of patients initially treated successfully with 5-HTP, the response subsided in the second month of treatment (van Praag, 1983). This phenomenon was paralleled by the normalisation of CA metabolism (again, as reflected in the CSF concentration of CA metabolites) while the metabolism of 5-HT remained increased. It was hypothesised that if clinical relapse and normalisation of CA metabolism were related, re-activating CA metabolism should restore clinical remission. This was indeed so: adding tyrosine to the 5-HTP regime in the group of relapsers once again led to subsidence of the depression and to a rise of CA metabolism (van Praag & Lemus, 1986).

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These data suggest that *combined* augmentation of 5-HT and CA availability in the CNS provides the best conditions for antidepressant activity, and they argue against the existence of a separate diagnostic entity called '5-HT depression'. The behavioural effects of 5-HTP in monkeys have also been shown to be a function of its influence on 5-HT and CA systems (Raleigh, 1987).

If 5-HT disturbances are not linked to a particular syndromal subtype of depression, could they relate to particular psychopathological dimensions that may occur in depression, but might be lacking as well, explaining the occurrence of 5-HT disturbances in some, but not other, depressions (van Praag *et al*, 1987*c*)? This hypothesis seems plausible in the light of recent observations, the dimensions in question being disregulation of aggression and heightened anxiety. The relevant data are now briefly summarised.

5-HT and disturbed aggression regulation

In 1976 Asberg *et al* confirmed our findings of a subgroup of depressed individuals with low CSF 5-hydroxyindoleacetic acid (5-HIAA), and added that individuals who had attempted suicide accumulate in that subgroup. This finding was confirmed by many, although not all, investigators. Subsequent studies revealed moreover that low CSF 5-HIAA was not only observed in depressed individuals who attempted suicide but also in such individuals who were non-depressed and non-psychotic (e.g. personality disturbed) and in schizophrenic patients who had made suicide attempts because 'voices' had ordered them to do so, but who were not suffering from depression as defined by DSM–III (see van Praag, 1986*a*).

Lowered concentration of CSF 5-HIAA has also been reported in individuals with increased outward-directed aggression, but belonging to different diagnostic categories (Brown *et al*, 1979, 1982; Bioulac *et al*, 1980; Linnoila *et al*, 1983; Lidberg *et al*, 1984, 1985; Virkkunen *et al*, 1987). The biological study of aggression in humans is fraught with methodological difficulties such as the usually short duration of aggressive outbursts and the fact that these explosions are often associated with a host of social or toxicological (drugs, alcohol) factors which it is hard to control for. However, the fact that all seven studies published so far have reported low CSF 5-HIAA indicates that the finding is robust.

Dysregulation of aggression can be a major feature of depression, as evidenced by the greatly increased incidence of both suicidal behaviour and outward-directed aggression in depressed individuals (Plutchik *et al*, 1989). Depressed patients with low CSF 5-HIAA show not only an increased rate of suicide attempts but also an increased frequency of outward-directed aggression (van Praag *et al*, 1986).

The facts, then, seem to support the hypothesis that the signs of diminished 5-HT metabolism in the CNS, as originally observed in depression, are related to dysregulated aggression (see Fig. 1), irrespective of the direction it takes and of the nosological context in which it occurs.

5-HT and heightened anxiety

Anxiety is a second psychopathological dimension occurring in depression (although being by no means specific to that disorder) and several pieces of evidence indicate that it is related to 5-HT.

Therapeutic effects in panic disorders have been reported with 5-HT potentiating drugs, in particular 5-HTP, increasing 5-HT synthesis and the 5-HT uptake inhibitors such as clomipramine, trazadone, fluvoxamine and fluoxetine (Evans & Moore, 1981; Koczkas *et al*, 1981; Evans *et al*, 1986; Kahn *et al*, 1984, 1987; Den Boer *et al*, 1987). Even more interestingly, the effect of those indirect 5-HT agonists seems to be biphasic, at least in some patients (Kahn & Westenberg, 1985). An initial phase of increased anxiety, lasting 2–3 weeks, is followed by a phase of amelioration in which anxiety and panic attacks diminish. This biphasic effect was explained by postulating: (a) the hypersensitivity of post-synaptic 5-HT receptors; and (b) the relatedness of this phenomenon to the anxiety attacks. Under these circumstances, increasing 5-HT availability would first lead to additional stimulation of an already hyperactive 5-HT system and, hence, to clinical deterioration. Down-regulation of the receptor system due to increased 5-HT availability would eventually lead to amelioration of the anxiety disorder (Kahn *et al*, 1988*c*).

Recently, additional evidence favouring this hypothesis was acquired. Panic disorder patients were challenged with m-chlorophenylpiperazine (MCPP), a relatively selective 5-HT1 and 5-HT2 receptor agonist. Normals and patients suffering from major depression served as controls. The major findings were two-fold. Patients with panic disorder who were given MCPP showed a substantial increase in anxiety during the test, in comparison with those given placebo. In the control groups no significant response occurred, on either MCPP or placebo (Kahn *et al*, 1988*a*). Moreover, the cortisol response to MCPP was augmented in panic disorder patients; again, as compared with both the response to placebo and the MCPP response in the two control groups (Kahn *et al*, 1988*b*).

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Another piece of confirmatory evidence is found in the development of drugs that diminish central 5-HT activity, and possess anxiolytic potential. Buspirone is an established anxiolytic. It has a high affinity for pre-synaptically located 5-HT1A receptors, and probably decreases 5-HT-ergic activity (Taylor *et al*, 1985). Ritanserin is a selective antagonist of post-synaptically located 5-HT2 receptors, for which anxiolytic actions have been reported (Ceulemans *et al*, 1985). Both drugs seem to be effective in generalised anxiety disorder; their effect in panic disorder has not yet been well studied. Recently, Jones *et al* (1988) reported animal data indicating that GR38032F, a selective antagonist of 5-HT3 receptors, appears to be a potential anxiolytic agent. In humans, the various 5-HT receptor systems cannot yet be studied separately.

If, indeed, in (certain) states of increased anxiety (certain) post-synaptic 5-HT receptors are hypersensitive, one would expect a compensatory diminution of central 5-HT synthesis, reflected by a drop of 5-HIAA concentration in CSF. No data are available on CSF 5-HIAA in anxiety disordered patients. In depressed patients, a negative correlation between CSF 5-HIAA and anxiety levels has indeed been observed (Banki, 1977*b*; Rydin *et al*, 1982).

The present data do not permit extending the 5-HT hypersensitivity hypothesis beyond panic disorder, but some preliminary data indicate 5-HT receptor hypersensitivity may be related to increased anxiety in general rather than to panic disorder alone. First, a correlation was found between cortisol response to MCPP and anxiety level as measured one week before the test in both panic disorder and major depression (Kahn *et al*, 1988*b*), suggesting a relationship between the general state of anxiety and 5-HT receptor hypersensitivity. Second, the relationship between CSF 5-HIAA and anxiety in depression, mentioned above, points in the same direction, and so does the finding that suppressors of 5-HT activity like ritanserin and buspirone are effective in generalised anxiety disorder.

A dimensional 5-HT hypothesis

Signs of decreased central 5-HT metabolism, then, seem to correlate not with a particular syndromal depression type but with particular affective disturbances – increased aggression and augmented anxiety (see Fig. 1). If these psychopathological dimensions are both related to disordered 5-HT metabolism, they would be expected to intercorrelate, and indeed this is so. In a recent series of studies on predictors of suicide and violence in groups of psychiatric patients with a range of diagnoses, we found trait anxiety to be strongly correlated with both suicide risk and violence risk (Apter *et al*, 1990).

The data favouring a dimensional 5-HT hypothesis, linking 5-HT disturbances to disordered regulation of aggression and anxiety across diagnoses, seem fairly convincing.

The role of noradrenaline in abnormal behaviour

Inside the pleasure principle

So far we have discussed MA-ergic involvement in the regulation of drive and affect. Both domains are frequently disturbed in depression (in particular in major depression, melancholic type) but such disturbances are by no means specific to that disorder.

A third major sphere of dysfunction in melancholic depression relates to the ability to experience pleasure. Normally much of what we do, or think, is not emotionally neutral but provided with a charge; globally speaking, a positive or a negative one. It generates pleasure or displeasure, in whatever way that may be defined. Anhedonia, the inability to experience pleasure, is a typical symptom of melancholic depression. It is one of the few almost pathognomonic symptoms in psychiatry.

Anhedonia is unlike flat affect or emotional blunting as may be observed in schizophrenia. Flat affect pertains to a global inability to experience, or at least to express, emotions; anhedonia indicates the inability to link a particular mental or motor activity with gratification, a quality that has been 'stamped in' when similar activities were carried out in the past. In melancholic depression, the emotional defect is 'localised' and there is no global defect in experiencing or expressing emotions. On the contrary, particularly negative emotions such as sadness, guilt, and shame are felt with profound intensity. In very severe cases of melancholic depression the ability to experience discomfort is also impaired. Mental and physical activities that usually would be experienced as aversive have less capacity to produce this effect.

Behaviour is strongly motivated by the attainment of pleasure and the avoidance of discomfort. The decreased ability to experience such modalities will reinforce the state of drive reduction, characteristic in melancholic depression.

In animals, brain systems have been found that code for rewarding and aversive experiences that occur naturally. The so-called reward and punishment systems (Olds & Milner, 1954) are, at least in part, MA-ergically innervated, the former by CA, the latter by 5-HT. DA is thought to be particularly

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involved in mobilising and orientating goal-directed behaviours. DA neurons constitute a 'go-system' or 'incentive-system' guiding the organism to areas in the environment associated with reward (Crow, 1973). In addition, DA neurons have been implicated as a substrate for intracranial self-stimulation (Wise, 1982; Mason, 1984). Although a role for NA in self-stimulation is less well supported than for DA, NA-ergic neurons seem to be active in 'emotional memory' (van Praag *et al*, 1988), the consolidation and retrieval of the emotional arousal induced by particular behaviours. Alternatively, NA-ergic tracts may constitute the connections between the neural representations of rewards anticipated from behaviours and the DA-ergic incentive system (Crow, 1973, 1977). NA-ergic mechanisms have also been implicated in selecting among a choice of possible behaviours to attain a particular goal, based on the experiences of reward or punishment that those behaviours elicited on prior occasions (Robbins *et al*, 1985; Ashton, 1987). A reward-related role of NA-ergic mechanisms in self-stimulation is supported by experiments with clonidine, an α_2-adrenergic agonist. This substance disrupts the rewarding component of brain stimulation in a selective manner, probably via activation of pre-synaptic α_2-receptors, and by doing so it curtails NA-ergic impulse flow (Franklin, 1978; Hunt *et al*, 1976). The catecholamine synthesis inhibitor α-methyl-*p*-tyrosine magnifies this effect (Hunt *et al*, 1976).

A noradrenaline hypothesis of anhedonia

NA-ergic mechanisms seem to enable the animal to couple the experience of reward or anticipated reward to a particular activity. The hedonic component of the melancholic syndrome can be conceived as a dysfunction of exactly that coupling mechanism. Situations that used to create pleasure are perceived as usual, but are now devoid of an emotional charge. Stein (1978) was the first to suggest depression to be "a disorder of positive reinforcement or reward function". We do not subscribe to this generalisation, but would suggest a more focused version of it. The hedonic disturbance in depression is, we submit, related to NA-ergic insufficiency, a transmission defect resulting in the inability to couple the reward component to mental or physical activities that used to carry such a charge (see Fig. 1).

The NA hypothesis of anhedonia fits into the classic information-processing theory of human cognition, in which two sets of structures are postulated, one for storing information, and the other for transferring it from one structure to another. In this model – and here we follow Kihlstrom's (1987) description – information from the environment is transduced into a pattern of neural impulses by the sensory receptors. This pattern is briefly held in the sensory registers, one for each modality, where it is then analysed by processes known as feature detection and pattern recognition. Information that has been identified as meaningful and relevant to current goals is then transferred to a structure known as primary or short-term memory. Here, the information is subject to further analysis, whereby the perceptual information is combined with information retrieved from secondary or long-term memory. In the primary memory, processes such as judgement, inference and problem solving take place. On the basis of an analysis of the meaning of the stimulus input, a response is generated. Finally, a trace of the event is permanently encoded in the secondary memory. It is in the short-term memory, one might assume, that the percepts (i.e. the perceptual information) is linked with the appropriate emotion (i.e. the emotion that was aroused in similar circumstances on previous occasions).

NA metabolism and NA-ergic functions have been studied in depression and in anxiety disorders. In the former, NA-ergic hypofunction has been postulated (Siever, 1988); in the latter, NA-ergic hyperfunction (Redmond & Huang, 1979). The concept of the NA-ergic nature of anhedonia, conceived as a psychopathological dimension, has not been systematically studied and, hence, is largely hypothetical. Some scattered data however, although tentative in nature, are sufficiently intriguing to prompt further investigation.

Preliminary studies of the noradrenaline hypothesis of anhedonia

Clozapine

Anhedonia can be pharmacologically induced by neuroleptics. With anticholinergic phenomena and extrapyramidal symptoms, it is one of the more common side-effects. The motor symptoms are thought to be related to nigro-striatal DA-ergic blockade. Most neuroleptics also block variably NA-ergic transmission. Conceivably, the latter effect could underlie the hedonic disturbances. Drugs that deplete NA stores such as reserpine, and drugs which reduce NA-ergic function via pre-synaptic inhibition, such as clonidine, can cause depression and anhedonia.

Clozapine is an 'atypical' neuroleptic, one of a group of compounds with more selective effects on meso-limbic and meso-cortical DA systems than their 'typical' counterparts. This could explain why their propensity to elicit motor side-effects

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is lower and their therapeutic potential is probably greater. In addition, clozapine has a profound blocking effect on NA receptors, particularly after acute administration (Burki *et al*, 1974; Bartholini *et al*, 1972; Buus Lassen, 1974).

The effects of clozapine (100 mg/day) administered for two weeks to six normal volunteers were studied in a placebo-controlled, double-blind, two-group design. Mood, drive and hedonic functions were assessed via a structured interview and recorded by a (blind) interviewer on a five-point scale. Effects occurred more or less sequentially. First, listlessness was reported (after 2–3 days); subsequently, there was lack of energy; and finally, in the second week, lowering of mood was noted (van Praag *et al*, 1990). The 'clozapine-syndrome' resembled that of mild vital depression (major depression, melancholic type). The hedonic decifit elicited by clozapine was significant and in the first few days was 'pure'; that is, not combined with other psychological disturbances.

Moreover, clozapine was compared with perphenazine (trilafon) in acutely psychotic patients without evidence of brain damage. Clozapine augmented the concentration of the NA metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF, while perphenazine did not (van Praag *et al*, 1976). The reverse proved to be true for the DA metabolite HVA; its concentration rose during perphenazine, but not after clozapine. These data suggest that clozapine, in contrast to perphenazine, has a blocking effect on post-synaptic NA receptors, conceivably accounting for the hedonic defects observed in the 'clozapine-syndrome'.

Tyrosine

In depressed patients, tyrosine, the precursor of DA and NA, increases the CSF concentration of HVA and MHPG (van Praag & Lemus, 1986), indicating that tyrosine furthers CA synthesis and metabolism. It has no overall therapeutic effect in depression, but is not devoid of pharmacological activity. In a preliminary experiment, discrete components of the depressive syndrome did change significantly. This was particularly true for anxiety which increased and for hedonic functioning, which improved (van Praag *et al*, 1990). These preliminary findings suggest that tyrosine exerts a measurable effect on NA availability while also significantly reducing anhedonia.

Clonidine

Clonidine, in low doses, stimulates pre-synaptic α_2-adrenergic receptors, leading to diminished NA release. Administered to normal individuals, it reduced paired-associate learning (Frith *et al*, 1985). Sedation is an unlikely explanation because clonidine did not affect other memory functions. It decreased blood pressure, suggesting diminished NA-ergic impulse flow, but this effect could of course be totally peripheral.

This finding suggests that NA neurons are involved in the coupling of the neural representation of associated stimuli. This is as far as one can go; it does not imply that these neurons are involved in linking an emotional memory trace ('pleasure') with a particular behaviour.

Hormonal studies

The growth-hormone response to clonidine (supposedly mediated by post-synaptic α_2-adrenergic receptors in the hypothalamus) has been shown to be blunted in endogenous depression compared with neurotic depression (Checkley *et al*, 1984). The most important distinction between the two syndromes with regard to symptoms is the presence or absence of anhedonia (van Praag 1962, 1989). Conceivably, the NA-ergic deficit and the hedonic disturbances correlate, but data to this effect are not available.

Another hormonal disturbance observed in major depression is blunting of the plasma cortisol response to desmethylimipramine (DMI), a tricyclic antidepressant and a selective inhibitor of NA uptake (Asnis *et al*, 1985). Correlating blunted DMI response with items of the SADS (Schedule for Affective Disorders and Schizophrenia; Endicott & Spitzer, 1978) related to anhedonia, a significant correlation was found with 'lack of reactivity', but not with 'loss of interest' or 'social withdrawal' (van Praag *et al*, 1990). The study was a retrospective one, and no specific attempts had been made to delineate the symptom of anhedonia from those that are somewhat similar but basically different.

A dimensional monoamine hypothesis

In this paper, we have discussed evidence of MA-ergic dysfunctions underlying the major domains of psychological dysfunctioning in melancholic depression: drive, affects and hedonic functioning. Sufficient evidence is available to implicate DA in drive reduction and 5-HT in disturbed aggression regulation and heightened anxiety. Tentatively, a link has been proposed between NA-ergic dysfunction and anhedonia (Fig. 1).

Both 5-HT-ergic and DA-ergic systems (Green & Deakin, 1980; Williams & Davis, 1983; Fuenmayor & Bermudez, 1985; Curzon *et al*, 1985) and 5-HT-ergic and NA-ergic systems (Ferron *et al*, 1982;

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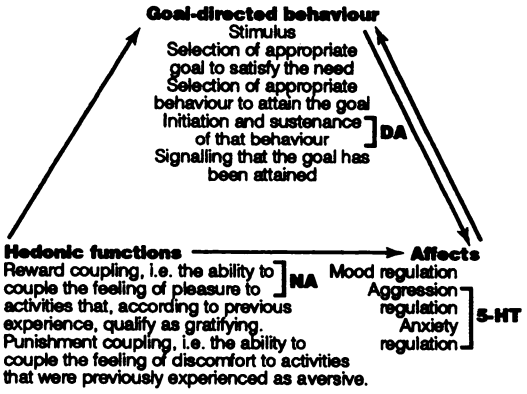


FIG. 1 Summary of major domains of psychological dysfunction in melancholic depression, and hypothesised MA-ergic dysfunctions (NA = noradrenaline, DA = dopamine, 5-HT = 5-hydroxytryptamine) underlying these (e.g. 5-HT is implicated in disturbance of the affective components of anxiety and aggression).

Reinhard *et al*, 1983; Manier *et al*, 1984; Feuerstein & Hertting, 1986; Heal *et al*, 1986; Asakura *et al*, 1987; Devau *et al*, 1987) are strongly mutually intertwined. If the psychological dysfunctions under discussion are linked to MA-ergic dysfunctions, the psychological dysfunctions would be expected: (a) to often go in concert; and (b) to influence each other's severity. Disorders of drive, mood and hedonic functioning meet in the melancholic syndrome, but no systematic data are available about their quantitative interaction. Clinical experience, however, suggests that such interactions do occur. Anhedonia reinforces lack of drive and tends to aggravate mood lowering. Mood lowering in its turn has a negative impact on drive, while drive reduction itself probably acts as a mood-lowering force.

Disturbances in drive and in regulation of anxiety and aggression are by no means specific for melancholic depression, but also occur in other behavioural and in certain neurological disorders. This could explain the nosological non-specificity of MA disturbances. Signs of decreased DA metabolism have, for example, been found in retarded depression and in Parkinson's disease; 5-HT disturbances have been reported in depressed individuals who have attempted suicide but also in subjects with other diagnoses who have tried to kill themselves and in patients with outward-directed aggression irrespective of diagnosis. 5-HT disturbances have, moreover, been implicated in panic disorder, but the odds are that they relate rather to increased anxiety across diagnoses. Anhedonia, on the contrary, seems to be relatively characteristic for melancholic depression. The same would therefore be expected to be true for the alleged signs of NA-ergic hypofunction, but no data are as yet available.

So far, no data implicate particular MA-ergic disturbances in the mood component of melancholic depression. It is true that this issue has hardly been studied, but such a lack of data could also be explained by hypothesising mood disturbances to be secondary to other depressive dysfunctions, possibly lack of drive and anhedonia. A few observations support this. Katz *et al* (1987) demonstrated that the therapeutic effects of amitriptyline in depression are manifest already in the first week of treatment. The first symptoms to decrease are anxiety and hostility, and they do so in correlation with plasma amitriptyline levels. Mood improvement follows later in the second and third week (Katz *et al*, 1990). We found that in 100 patients admitted for first or second episodes of melancholic depression, anhedonia was the single most frequent initial symptom (42%), with drive reduction second most frequent (31%). Mood lowering was indicated as a first symptom by only 11% of the sample. Also, it should be noted that electroconvulsive therapy (ECT) works initially to increase motor behaviour and only subsequently to change mood (Fink, 1979).

Recently, Cloninger (1986, 1987) advocated the dimensional approach for the biological study of personality disorders. He introduced a system of personality variants based on three dimensions: novelty seeking, harm avoidance, and reward dependence – traits he additionally linked to particular MA-ergic systems. The scheme is elegant but lacks empirical foundation and to define and measure such distinctions in personality make-up will be very difficult. To view biological variables occurring in psychiatric disorders from the vantage point of psychopathological dimensions is feasible. Whether the same is true when personality dimensions are substituted for psychopathological dimensions remains to be seen. Considering the present state of diagnostic methodology, we predict that Cloninger went one step too far.

Functional psychopathology: a look forward

MA disturbances found in psychiatric disorders look chaotic if viewed from a nosological vantage point, being demonstrable in so many different diagnostic entities. Interpreting them from the functional viewpoint brings order to the apparent chaos. Thus, MA research clearly demonstrates the usefulness of the functional approach in psychopathology. The implications of this approach, however, reach beyond the boundaries of biological psychiatry in several important ways.

First, they reach into the realm of clinical psychopharmacology. Several psychotropic drugs

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have turned out to be diagnostically non-specific. Tricyclic antidepressants are efficacious in certain forms of depression *and* in certain anxiety states. Clomipramine is an effective antidepressant *and* a useful treatment in obsessive–compulsive disorder. Carbamazepine is an established antiepileptic agent *as well as* an asset in the prophylaxis of episodic mood disorders. These observations are puzzling from a nosological but not from a functional point of view. A particular drug could influence a particular functional system in the brain, and thus, a particular set of psychological dysfunctions, irrespective of diagnosis. The greater the biochemical specificity of a drug then, the greater the chance it will be nosologically non-specific, but effective against certain (clusters of) psychological dysfunctions, across diagnoses.

Once correlations between psychological and biological dysfunctions have been established, the next step will be the search for drugs that can selectively correct the biological dysfunctions. Such drugs would be expected to ameliorate the corresponding psychological dysfunctions, irrespective of nosological diagnosis. Within a nosological frame of reference treatment is directed towards a particular disorder, and within a functional framework towards the underlying or resulting dysfunctions. In the former approach treatment is preferably restricted to one drug; in the latter approach combinations of drugs will be used, contingent on the existing spectrum of dysfunctions. Functional psychopathology will lead to functional psychopharmacology and this will tend to use drugs in combination. Elsewhere, we have given an (hypothetical) example of transnosological indications of a group of psychotropic drugs – the selective 5-HT reuptake inhibitors, the first group that seems to possess a high degree of selectivity, at least as far as MAs are concerned (van Praag *et al*, 1987*b*). The objection could be raised that neuronal systems do not act in isolation, but interact with numerous others. That does not mean, however, that selectivity is illusory and that limiting a drug's primary actions is meaningless. Fluoxetine, for example, is a selective inhibitor of 5-HT uptake with little effect on NA reuptake. Its impact on NA-ergic functioning is not negligible, but certainly much less than that of a drug that primarily inhibits the uptake of both MAs, such as amitriptyline. Indeed, perfect selectivity is unattainable, but that goal can certainly be advanced.

Goal-directed, dysfunction-orientated polypharmacy is not a chimera, but a strategy legitimately employed in other medical disciplines. For example, once a myocardial infarction has been diagnosed and the cardiac condition functionally analysed, drugs will be administered to regulate the discrete disturbances in, for instance, rhythm, conduction, frequency and output. These drugs are often prescribed simultaneously. Thus, this represents goal-directed, dysfunction-orientated multipharmacy. It is in this direction that we expect to see clinical psychopharmacology develop. It is *the* scientific approach to drug treatment, at least as long as we cannot address the cause(s) of the disease directly.

A second field that will benefit from a functionally orientated psychopathology is that of measurement of abnormal human behaviour. So far, the presence of a psychiatric syndrome or symptom is expressed as a rough estimate; that is, as mildly, moderately or severely present, or anywhere in between. Many psychological functions and dysfunctions, however, are measurable in real quantitative terms and with considerable precision and reliability. Functional psychopathology will lay the groundwork for a scientifically based psychopathology.

Finally, the psychotherapies would benefit from the functional approach, because it would allow, much more precisely than is possible today, the delineation of mental domains that are dysfunctional from those that are still relatively normal. This would permit a rather precise definition of treatment goals and a more rational choice of treatment method. Treatment planning would thus be furthered and provided with a rationale.

Thus, functional psychopathology is not only a productive framework for biological research in psychiatry, but could, in addition, be evolving into a forceful catalyst for psychiatry's ongoing scientific orientation.

We introduced the functional/dimensional approach in psychopathology as a complement of and not as an alternative to the nosological/categorical approach. We still fully subscribe to this standpoint, as much as we do to the view that the exclusive adherence to nosology has not served biological psychiatry well. In fact, it has been a factor stunting its growth.

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