

Exploring the Functional Role of Monoaminergic Neurotransmission *A method for exploring neurotransmitter dysfunction in psychiatric disorders*

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Theories of monoaminergic neurotransmitter dysregulation continue to provide the principal framework for the investigation of the pathophysiology of depression and schizophrenia (Losonczy *et al*, 1987; Willner *et al*, 1992). The availability of techniques enabling quantitative pharmacological measurements, such as receptor number, to be made *in vivo* has heightened expectations for an understanding of the mechanisms underlying these conditions. Dopaminergic receptor systems have been a particular target for *in-vivo* studies. However, the conflicting results from research based upon these approaches have been a source of disappointment (Wong *et al*, 1986; Farde *et al*, 1990). As little is known concerning the functional role of dopamine in higher brain function in humans, findings based upon quantitative pharmacological measurements are in themselves unlikely to provide a sufficient theoretical basis for a mechanistic understanding of psychiatric disease. A fundamental knowledge of normal brain function is almost certainly a prerequisite for the elaboration of theories of psychiatric disease.

Higher brain functions are expressed primarily at a systems level that depend upon an interaction of large populations of neurons organised into complex, often anatomically distributed, systems (Edelman & Mountcastle, 1977). Dynamic interactions between these systems are subject to modifications by a multitude of factors that include neurotransmitter inputs (Edelman, 1987). Therefore a theory of psychiatric illness based upon a putative neurotransmitter dysfunction must address the regulation of neural processes subserving normal psychological functioning. Furthermore, it should explain how neurotransmitter dysregulation leads to the emergence of the psychological symptoms and pathophysiological dysfunctions that characterise psychiatric syndromes. Few, if any, current neurotransmitter theories of psychiatric illness meet these criteria.

Undoubtedly, the limiting factor in relation to the monoaminergic-based theories is the paucity of neuroscientific information regarding their regulatory role on cortical function. Findings based upon work in non-human primates have now begun to establish the role of neurotransmitter systems in the regulation of the neural systems subserving specific psychological

states (Goldman-Rakic, 1988). An important goal in research on humans is to establish similar links. Novel applications of functional imaging techniques can provide the necessary links by specifying the neuroanatomical locus of interactions between neural systems subserving specific psychological processes and neurotransmitter inputs (Friston *et al*, 1991*b*). The theoretical basis of such research, with a particular emphasis on dopamine neurotransmission, and an account of preliminary findings from studies in humans, using positron emission tomography (PET), are the basis of this paper.

Monoaminergic cortical projection systems

Extrathalamic cortical projections include the monoaminergic systems that are implicated in the pathogenesis of major psychiatric illness. Monoaminergic inputs to the cortex have, until recently, been considered diffuse and non-specific. This view is changing with the emergence of evidence that these projection systems display an anatomical specificity characterised by pronounced regional and laminar specialisation (Brown *et al*, 1979; Oades & Halliday, 1987; Gaspar *et al*, 1989; Papadopoulos & Parnavelas, 1991). Within the monoamine systems, dopamine and noradrenaline differ in the cytoarchitectonic areas and cortical laminae that constitute their principal terminal sites (Rakic *et al*, 1988; Goldman-Rakic *et al*, 1990). The high degree of organisation within these systems is exemplified by a consideration of cortical dopamine projections. Dopamine inputs to the cortex have a bilaminar distribution, the highest levels being seen in upper cortical layers I to III and lower layers V and VI, with the principal cortical receptor being of the D₁ type (Lidow *et al*, 1991; Smiley *et al*, 1992). Pyramidal neurons are the principal target of dopamine afferents, which form symmetric or triadic synapses, possibly with cortico-cortical glutaminergic inputs, onto the spines and dendrites of pyramidal cells (Goldman-Rakic *et al*, 1989). The findings of high degrees of anatomical organisation in cortical monoaminergic inputs are consistent with a role in the regulation of processes that involve the cooperative interactions of widespread neuronal networks, particularly those subserving

higher cortical functions (Morrison & Foote, 1986; Mantz *et al*, 1991). The precise mechanisms by which monoaminergic afferents regulate cortical processing is now a subject of extensive investigation.

Physiological functions of cortical monoaminergic systems

The characterisation of the functional properties of monoaminergic systems is best exemplified by an examination of their effects in relation to other neural systems projecting to the same target neurons. Within this framework, complex neurophysiological responses have been described. These responses comprise an alteration in the effectiveness of other excitatory or inhibitory synaptic inputs, rather than a direct effect of the neurotransmitter itself on the firing of postsynaptic neurons. The term 'neuromodulation' has been used to describe a situation whereby a neurotransmitter's actions, among others, alter the responsivity of post-synaptic cells to the effects of other synaptic inputs (Dismukes, 1979). Mesulam (1990) has highlighted the distinction between "anatomically addressed channels for transferring information content and chemically addressed pathways for modulating behavioural tone". Catecholamines such as dopamine or noradrenaline do not convey discrete sensory or motor information but instead appear to have a neuromodulatory role in certain cognitive functions (Foote *et al*, 1975; Brozoski *et al*, 1979; Arnsten & Goldman-Rakic, 1985). At the information processing level, catecholamines enhance signal-to-noise detection (Servan-Schreiber *et al*, 1990). These effects are exemplified by early experiments in which the effects of noradrenaline applied iontophoretically to auditory cortical cells of unanaesthetised squirrel monkeys prior to, and following, acoustic activation by species-specific vocalisations were studied. During auditory activation the effect of applied noradrenaline was to enhance the elicited activity of discrete neural ensembles relative to background spontaneous activity, an effect described as an enhancement of signal-to-noise characteristics of auditory cortical cells (Foote *et al*, 1975).

Dopamine and the regulation of prefrontal cortical function

The functional properties of prefrontal cortical dopaminergic projection systems have been extensively studied and have direct relevance to the theories of dopaminergic dysfunction in neuropsychiatric disorders. The dopaminergic innervation of the cortex seems to be a primate specialisation (Berger

et al, 1991). Among cortical regions, the prefrontal cortex in particular receives a relatively dense dopaminergic input. The effects of dopamine on cortical neuronal resting potentials are complex, though the principal effects in the prefrontal cortex are inhibitory (Bunney & Chiodo, 1984). However, the over-riding effects of dopamine on cortical cells are seen in response to other afferent influences. Stimulation of dopamine cells in the ventral tegmentum blocks the excitatory effects on cortical neurons of thalamic stimulation (Ferron *et al*, 1984). Furthermore, single-cell recordings from the prefrontal cortex of monkeys, studied while performing delayed response tasks, have shown a differential cellular response to the micro-iontophoretic application of dopamine. The application of dopamine causes a further increase in the firing of a subpopulation of prefrontal cells, whose firing rate has already increased during the delay period. Activity in cells not engaged by the delay task is unaltered or inhibited. These effects can be conceived of as altering the state of a network subserving a specific psychological function by increasing the ratio of signal (task-specific firing) to noise (background firing) in specific populations of prefrontal cells (Sawaguchi *et al*, 1990a). The effect of neuroleptics on such patterns of cellular activation has highlighted the receptor-mediated mechanisms that underlie such a differential response. Haloperidol and fluphenazine (non-selective dopaminergic antagonists) antagonised task-related dopamine-induced increases in firing, but not the selective D₂ antagonist sulpiride. These findings imply that a D₁ effect is responsible for the task-related increased activity of prefrontal neurons (Sawaguchi *et al*, 1990b).

In terms of neurophysiological effects, it seems that activation of dopamine D₁ receptors, in particular, may be related to the performance of delayed response tasks where the underlying processes involve the temporal organisation of behaviour guided by short-term memory (Sawaguchi *et al*, 1990b). Local injections of selective D₁ antagonists, such as SCH23390 and SCH39166, into the prefrontal cortex of rhesus monkeys induce errors and increased latencies on an oculomotor task that requires memory-guided saccades (Sawaguchi & Goldman-Rakic, 1991). The drugs had no effect on performance in a task that required visually guided saccades, indicating that sensory and motor functions were unaltered. Thus D₁ receptors have a permissive role in the mnemonic or predictive functions of the primate prefrontal cortex (Sawaguchi & Goldman-Rakic, 1991). Finally, loss of dopamine inputs into this region impairs

these aspects of prefrontal function (Brozoski *et al.*, 1979).

Monoaminergic neurotransmission and neuropsychological function in humans

The neurotransmitter regulation of higher cognitive function in humans is largely unknown. Links between a specific neurotransmitter and a neuropsychological function have been made by relating drug-induced changes in neuropsychological performance to the neurotransmitter system targeted by the drug, for example clonidine-induced impairment of paired associate learning and noradrenergic neurotransmission (Frith *et al.*, 1985). A less direct approach has been to determine the neuropsychological deficits associated with distinct neuropathology/neurochemistry, for example verbal fluency and Parkinson's disease (Gurd & Ward, 1989; Wolfe *et al.*, 1990). The limitations to these approaches include the fact that drug-induced changes in neuropsychological performance lack neuroanatomical specificity, whilst neuropsychological deficits in patients with specific diseases do not necessarily identify the neurotransmitter system involved.

The *in vivo* study of the functional role of monoaminergic neurotransmission in humans

Positron emission tomography (PET) has provided a powerful tool for the mapping of the functional anatomy of cognitive processes such as language, attention, and willed action (Petersen *et al.*, 1988; Posner *et al.*, 1988; Frith *et al.*, 1991; Friston *et al.*, 1991a; Wise *et al.*, 1991). Recent methodological developments enable the neuromodulatory role of monoaminergic neurotransmitters in such higher functions to be investigated. With PET, the measurement of a neuromodulatory effect requires the conjoint stimulation of a large set of neurons (to be modulated) with the simultaneous manipulation of a neuromodulatory neurotransmitter system. In functional imaging experiments, combined pharmacological and neurocognitive challenges are used in conjunction with simultaneous measurements of regional cerebral blood flow (rCBF). Regional cerebral blood flow in this context provides a sensitive index of neuronal activity (Raichle, 1987). The pharmacological challenge specifies the neurotransmitter system under investigation while neurocognitive-induced patterns of rCBF identify the anatomical substrate of the psychological function under investigation (Friston *et al.*, 1991b). The basic design of such experiments is illustrated in Fig. 1.

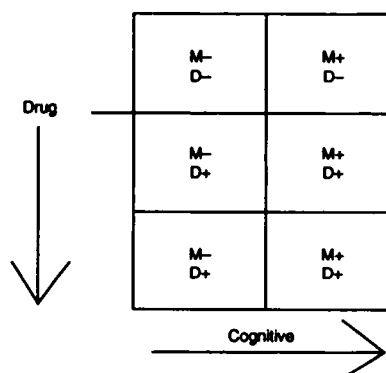


Fig. 1 Experimental design for a combined psychopharmacological activation study. Each box refers to a single PET measurement of regional cerebral blood flow (rCBF). Active drug or placebo was given after the second measurement. D- refers to pre-drug, D+ to post-drug scans. M- refers to subspan task, M+ refers to supraspan task. The main effects of drug, supraspan-subspan task and interactions can be specified by the appropriate contrasts. For example, the averaged main effect of the memory task (supraspan-subspan) is given by the contrast of scans $[2-1] + [4-3] + [6-5]$. The interaction effect of drug-induced attenuations of supraspan-induced increases in rCBF is given by the contrast $[2-1] - ([4-3] + [6-5])/2$.

Using such an approach, the neuromodulatory effects of manipulation of dopaminergic and serotonergic (5-HT) neurotransmission on changes in rCBF induced by memory tasks has been studied in groups of normal subjects. Auditory-verbal memory challenges, consisting of subspan and supraspan word lists, provided the neuropsychological challenge. The choice of drug challenge was dictated by the fact that dopaminergic and serotonergic neurotransmitters both have neuromodulatory effects on cerebral function, and are implicated in memory processes (Foote *et al.*, 1975; Arnsten & Goldman-Rakic, 1985; Altman & Normile, 1988; McEntee & Crook, 1990; Sawaguchi *et al.*, 1990a; Coop & McNaughton, 1991). The specific drugs used were apomorphine, a non-selective dopamine agonist, and buspirone, a 5-HT_{1A} partial agonist (Peroutka, 1985; Traber & Glaser, 1987). The experimental hypothesis was that these compounds would have regionally distinct effects on memory-task-induced alterations of rCBF. Given the role of prefrontal dopamine function in mnemonic tasks in monkeys, a specific prediction was that apomorphine would modulate memory-induced activations in the prefrontal cortex (Goldman-Rakic, 1987; Sawaguchi *et al.*, 1990a). In contrast, as hippocampal neuronal activity is sensitive to 5-HT_{1A} partial agonists, and 5-HT_{1A} receptors are in high concentration in hippocampal structures, the prediction was that buspirone would modulate

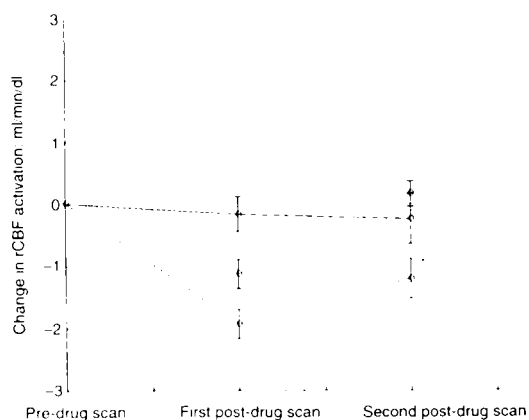


Fig. 2 Memory–apomorphine interactions. The effect of two doses of apomorphine on memory-task-induced increases of regional cerebral blood flow (rCBF) in the left dorsolateral prefrontal cortex. Data represent rCBF equivalents in a (weighted) spherical domain of about 20 mm diameter. In the left dorsolateral prefrontal cortex the memory activation shows no time effect in the placebo group (○—○), maintaining an average activation of ≈ 2 ml/min/dl (equivalents) over the three memory activations (this activation has been set to 0 on the y axis for comparison with active drugs). Conversely, apomorphine (□—□, 5 µg/kg; △—△, 10 µg/kg) attenuates the memory activation in the first post-drug condition. There is a more normal activation in the second post-drug condition. The attenuation of the activation in the first post-drug condition was significant ($P < 0.05$) for both doses of apomorphine.

memory-induced alterations of rCBF in medial temporal structures, including the hippocampus (Wree *et al.*, 1987; Pazos *et al.*, 1987; Kelly *et al.*, 1988; Sprouse & Aghajanian, 1988; Grasby *et al.*, 1992a).

The findings of these experiments confirmed that regional activations of rCBF during the performance of a verbal memory task were selectively influenced by drug manipulation of dopaminergic and serotonergic neurotransmission. Apomorphine attenuated memory-induced increases of rCBF in the right prefrontal cortex (BA, 10,46) and in the left prefrontal region (BA 45/46). Unlike apomorphine, buspirone attenuated memory-induced increases of rCBF in the retrosplenial area (BA 30) and adjacent parahippocampal gyrus (BA 27/29/30). In keeping with the attenuation of these neurophysiological responses, a decrease in memory performance was seen under all active drug conditions (Friston *et al.*, 1992b; Grasby *et al.*, 1992b). It would seem therefore that the worsening of memory performance was a direct effect of the modulation, in these studies, of the neurophysiological response of a distributed brain system subserving auditory verbal memory. The different sites of attenuation of memory-induced activations with buspirone and apomorphine suggest an anatomical dissociation in the effects of

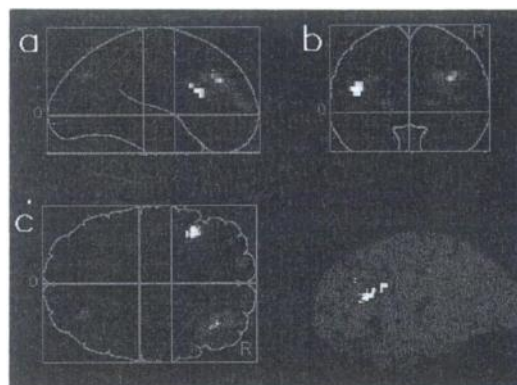


Fig. 3 Site of apomorphine-induced attenuations of regional cerebral blood flow increases with memory task. Volume images of the brain viewed from the right (a), from the back (b) and from the top (c). The brightest voxel along any line of view is displayed. These statistical maps are of the *t*-statistic computed for all voxels assessing the attenuation of rCBF memory increases on comparing the pre-drug sub/supraspan pair with both post-drug pairs. Only *t* values corresponding to $P < 0.05$ are displayed. The site of maximal attenuation is located in the left dorsolateral prefrontal cortex.

manipulation of serotonergic and dopaminergic neurotransmission during a memory task. Although the exact pharmacological site of action of the drugs used is difficult to specify, certainly the sites of functional interaction between manipulation of dopaminergic/serotonergic neurotransmission and a cognitive function can be specified. Indeed, these sites of functional interaction may well be ‘downstream’ of the drug’s pharmacological site of action through which the effects on function are mediated. Despite these difficulties, the findings show that it is possible to link neurotransmission to neuropsychological functioning and to specify the neuroanatomical sites of such interactions *in vivo* (Figs 2, 3).

Conclusions

Neuromodulatory neurotransmitters act, not by directly affecting neuronal firing, but by modifying neuronal excitability so that responses to other neurotransmitters are altered (Kaczmarek & Levitan, 1987). These effects can be conceptualised as biasing the intrinsic response properties of neuronal systems. The selective interaction between dopamine and memory function in the prefrontal cortex seen *in vivo* in human experiments is consistent with such neuromodulatory effects. These studies provide direct evidence that monoaminergic projection systems have a high degree of regional functional specificity in humans and also constitute a framework for studying

links between neurotransmitter systems and specific psychological processes. Cortical functions are the result of convergence of diverse afferent systems upon intrinsic neuronal elements. How these diverse synaptic inputs are integrated to produce a coherent output is central for an understanding of neuronal function (Friston *et al*, 1992a). In view of their relatively discrete architecture, monoaminergic cortical afferent systems are likely to act at a level that influences processes of cortical integration. A dysfunction, due to either an increase or a decrease in monoaminergic inputs, could have profound effects on neuronal integration. In this respect the application of methodologies, similar to those described, which can examine these effects have a powerful theoretical potential in the study of psychiatric disease. A possible neuromodulatory role for dopamine in prefrontal function in disease states has now been demonstrated in schizophrenic patients (Daniel *et al*, 1991). Linking neurotransmitter systems to the neural correlates of psychological processes provides a strong theoretical and mechanistic basis for the study of pathophysiological mechanisms in the major psychoses.

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