Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia

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DOPAMINERGIC dysregulation remains an empirical cornerstone for theories concerning the causation of schizophrenia. Evidence for a dopamine system dysfunction in schizophrenia includes the psychosis-inducing effects of dopaminergic agonists and the antipsychotic potency of dopaminergic antagonists. Here we use positron emission tomography (PET) to examine the regulatory role of dopamine on cortical function in normal subjects and unmedicated schizophrenic patients. Using a factorial experimental design, we compared the effect of dopaminergic manipulation with apomorphine on a neural response to a cognitive task. In the schizophrenic patients, relative to controls, an impaired cognitive activation of the anterior cingulate cortex was significantly modulated by a manipulation of dopaminergic neurotransmission. Thus, after apomorphine, the schizophrenic subjects displayed a significantly enhanced cognitive activation of the anterior cingulate cortex relative to the controls. These data provide in vivo evidence that an impaired cognitive-task-induced activation of the anterior cingulate cortex in schizophrenic patients can be significantly modulated by a dopaminergic manipulation.

We measured brain activity, indexed by regional cerebral blood flow (rCBF), in 12 normal male volunteer subjects and 12 unmedicated male schizophrenic patients under two conditions. We scanned all subjects while they performed a paced verbal fluency task and a baseline paced verbal repetition task using an established protocol. Under the same conditions, we scanned the subjects before (scans 1 and 2) and after (scans 3–6) an injection of either the non-selective dopaminergic agonist apomorphine or a placebo. Six separate rCBF measurements, with an interscan interval of 10 minutes, were thus recorded from each subject. The overall experimental design is summarized in Fig. 1. This factorial design enabled us to determine from the interaction term the effect of one treatment (the administration of the dopaminergic agonist apomorphine) on the effect of the other (the neuronal response to a cognitive activation). In this particular experiment, the effect of interest is the differential effect across groups of dopamine perturbation on the pattern of neuronal activation induced by the cognitive activation.

The cognitive activation defined the neural system to be modulated by apomorphine administration. In normal subjects the cognitive activation, derived from the subtraction of the neuronal response in the repetition condition from the fluency condition, showed the expected pattern of activation that included the left dorsolateral prefrontal cortex, the thalamus and the anterior cingulate cortex. The same cognitive activation in schizophrenic patients indicated a failure of activation that was localized to the anterior cingulate cortex (P<0.05, corrected for multiple comparisons). After dopaminergic manipulation with apomorphine, this relative failure of task-induced cingulate activation in schizophrenic patients was reversed. In the post-apomorphine state, schizophrenic patients displayed a significant augmentation of the neuronal response to cognitive activation in the anterior cingulate cortex relative to control subjects (P<0.0001, uncorrected) (Fig. 2b). This effect was specific for verbal fluency-induced activation as no differential effect of apomorphine on patterns of activation was evident under the repetition condition alone (P>0.05 uncorrected). The changes in rCBF at a selected pixel, pre- and post-apomorphine, during cognitive activation for controls and schizophrenic patients are shown in Fig. 3. A restriction of the analysis to the nine medication-naive subjects provided findings identical to those of the whole group.

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**FIG. 1** Experimental design. Each square refers to a single measurement of rCBF. The cognitive task consisted of a paced orthographic verbal fluency (scans 1, 3 and 5) or a verbal word-repetition control task (scans 2, 4 and 6). The tasks required a verbal response every 5 s, so equality of response rate was ensured across trials and groups. The cognitive activation, defined by the subtraction of the repetition control from the fluency conditions, activates a prefrontal network that includes the dorsolateral prefrontal cortex and the anterior cingulate cortex. The drug manipulation consisted of apomorphine, given subcutaneously in a dosage of 10 μg kg, or placebo administered before scan 3. This dosage has a significant effect on neural activity in the prefrontal and anterior cingulate cortex. Control subjects and schizophrenic patients were therefore studied under a condition of verbal fluency and verbal repetition both before and after a subcutaneous injection of either apomorphine or placebo. Thus 6 of the 12 controls and 6 of the 12 schizophrenics received placebo, and the remaining 6 controls and 6 schizophrenics received apomorphine, before scan 3. The cognitive activation within a group is specified by the contrast of scans (1−2)+(3−4)+(5−6). The drug-induced augmentation of the cognitive activation, within a group, is specified by the contrast [(3−4)+(5−6)]/2−(1−2). Between-group comparison is the difference in the magnitude of this effect across groups. We studied 24 subjects, all of whom were right-handed as determined by the Edinburgh Handedness Inventory. These comprised 12 unmedicated patients who met DSM III-R criteria for schizophrenia. The mean age of the patients was 26 years (s.d., 7), and the mean duration of illness was 4.3 years (s.d. 6). Nine of the patients were neuroleptic and psychotropic-medication-naive, while the remaining three were free of psychotropic medication for a minimum of six months. The 12 control subjects, with a mean age of 25 years (s.d., 4), were volunteers recruited through advertisement. None of the controls had any past psychiatric or medical illness.

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These observations can be considered in the context of the neuromodulatory functions of dopamine, which has a critical regulatory role on prefrontal neurophysiology. A disorder of this regulatory function is thought to account for a range of human pathologies including the psychoses. The effects of dopamine on cortical function are complex, although the net effect is inhibitory. However, its critical effects are neuromodulatory, as exemplified by observations that the electrophysiological responses of populations of task-activated prefrontal neurons are further enhanced by dopamine. We found a significant neuromodulatory effect of dopamine manipulation on the neuronal response to cognitive activation in the anterior cingulate cortex of unmedicated schizophrenic patients. A significant effect of apomorphine on glucose metabolism in the striatum in drug-naive schizophrenics under non-activation conditions has previously been reported. We found a modulatory effect of dopamine which was activation-task specific, and was not seen under the repetition condition. These findings suggest that dopaminergic inputs, either direct or indirect, have a differential regulatory effect on anterior cingulate activity in schizophrenics compared to controls.

One model of dopamine dysfunction in schizophrenia has suggested diminished tonic dopamine release, upregulation of postsynaptic dopamine receptors, and a resulting increase in postsynaptic responsiveness to phasic dopamine activation. As apomorphine at the dose administered has significant postsynaptic actions, the observed impairment of pre-drug task activation and the augmented post-drug task activation are consistent with this model. The apparent regional specificity of our finding is also in accord with evidence from functional imaging and other investigative modalities which indicate cingulate pathology in schizophrenia.

The anterior cingulate cortex has multiple functional specializations, including a role in attentional mechanisms, which are core abnormalities in schizophrenia. The predominant dopaminergic inputs to the cingulate are to layer II and III pyramidal cells, which are the primary cortico-cortical output layers. A disorder of cortico-cortical integration in schizophrenia has been suggested by PET findings of abnormal functional connectivity between the frontal and temporal cortices. The anterior cingulate may participate, directly or indirectly, in cortico-cortical integration. A direct modulatory effect of cingulate...
FIG. 3 Relative changes in adjusted rCBF response (adjusted to an arbitrary mean of 50 ml dL⁻¹ min⁻¹) in the anterior cingulate under cognitive activation (verbal fluency and repetition), pre-drug or post-drug times 1 (t₁ = 15 min) or times 2 (t₂ = 30 min). A pixel, at coordinates x = -4, y = -6, z = 32, was chosen on the basis of the focus of maximal difference between controls and schizophrenics under cognitive activation in the non-drug-treated state. This pixel is within a subset of the pixels that define the region where there is a significant difference between controls and schizophrenics post-apomorphine. The data depict responses in the control (a) and schizophrenic (b) groups under cognitive activation at each time point. A relative failure of activation in the schizophrenic patients (averaged response for schizophrenic and control groups) pre-drug is evident. Post-drug, at times t₁ and t₂, there is a significant augmentation of circulatory activation (P < 0.001) in the schizophrenic apomorphine-treated group relative to both control groups and the non-apomorphine-treated schizophrenic group. Error bars were computed on the basis of +1 s.e. for the mean effect, and the comparisons are based upon the interaction term from the SPM. A time-related decrease in the magnitude of activation is evident in both control groups (for extended discussion, see ref. 30). A comparison of the relative decreases post-drug and post-placebo in controls was not statistically significant.

activation on the temporal cortex has been demonstrated in primates23. A similar effect in humans is implied by a finding that cingulate activation is associated with modulation in a concurrent task-dependent cortical activation23. In the present study we have again observed abnormal fronto-temporal interactions that are modulated post-drug (data not shown). We suggest that in schizophrenia there is a dysregulation in the dopaminergic modulation of circulatory neuronal activity with a consequent impairment in the functional integration of more remote, but anatomically connected, cortical regions. The findings provide a methodology for reconciling neurochemical theories with those that suggest an abnormality in cortico-cortical interactions in schizophrenia.