activity as an intermediate variable rests on a very tenuous assumption. In most cases the acute schizophrenic patients were not only taking dopamine-blocking medications when tested, but their dosages tended to be higher than those of the chronic schizophrenic patients. Thus, unless Gray et al. posit a substantial delay in dopamine-blocking activity after drug administration, these acute schizophrenic patients may not have been hyperdopaminergic at the time of testing, as they assume. In schizophrenic subjects, the connection between current symptoms and disrupted latent inhibition appears to be much clearer at present than the connection between dopaminergic overactivity and disrupted latent inhibition. As Baruch et al. (1988) correctly note, direct measures of dopamine activity in schizophrenic patients are needed to establish the latter link.

One other issue regarding temporal aspects of the model deserves comment. The authors' presentation of cognitive dysfunction in schizophrenia might lead the reader to assume that cognitive abnormalities are limited to acute symptomatic periods. On the contrary, a substantial body of evidence now indicates that some information-processing dysfunctions are present during periods of clinical remission in schizophrenic patients, as well as among first-degree relatives of schizophrenic patients (Asarnow et al., in press; Holzman 1987; Nuechterlein, in press; Nuechterlein & Dawson 1984b). These cognitive dysfunctions are hypothesized to be linked to vulnerability to schizophrenia, rather than to periods of active schizophrenic symptoms. Such relatively enduring cognitive dysfunctions are temporally well-matched to a static underlying neuropathology.

Given these temporal considerations, a comprehensive model of schizophrenia would need to explain a combination of enduring cognitive dysfunctions and episode-linked cognitive dysfunctions. Gray et al. suggest that their model is consistent with the view of Frith (1979) that schizophrenia arises from a disruption in automatic processing. A possibility noted by Nuechterlein and Dawson (1984b) is that such a disruption in automatic processing occurs only during acute positive symptom periods, whereas other limitations affect controlled information processing at high processing loads during periods of remission. Such multiple-process formulations may be necessary to account for the diverse temporal patterns of cognitive dysfunctions in schizophrenia.

Gray et al. are to be commended for their creative and ambitious efforts to provide a cross-sectional model of positive symptoms that integrates cognitive, neurochemical, and neuroanatomical aspects. We would encourage them to incorporate more fully into their model the longitudinal perspectives regarding schizophrenia.

Bases for irrelevant information processing in schizophrenia: Room for manoeuvre

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The trend is to move away from the strong version of the dopamine (DA) hypothesis of schizophrenia. What better way than with Gray et al.'s suggestion that the subicular-accumbens pathway is where the impairment can be observed in positive schizophrenia (PS)? They incorporate current evidence of temporal lobe dysfunction (the frontal lobe is largely put to one side), yet still allow for the partial therapeutic effect of D2 antagonism in those with PS. Is this reasonable?

A weakness of Hemsley's, Frith's, and Gray's formulation of the psychological processes underlying PS is the overuse of dichotomies (Occam's Razor) to solve a heterogeneous problem. The PS problem is identified in terms of errors of willed-intention versus stimulus processing (Frith), response versus stimulus set (Hemsley), controlled versus automatic processing (Gray and others). A look at the range of event-related potentials recorded in discrimination tasks with attentional demands and the variables affecting them suggests that such dichotomies may be oversimplifications of the processes under discussion (Hackley et al. 1978; Hillyard et al. 1978).

Yet the postulate that more processing capacity is allocated to irrelevant stimuli is "congruent" with the common view that PS subjects are more distractible and thus have fewer resources for processing relevant stimuli. Direct support comes from a recent ERP study of P3a versus P3b in schizophrenics on a 3-tone oddball task (Grillon et al. 1990). [See also Naatanen: "The Role of Attention in Auditory Information Processing as Revealed by Event-related Potentials and Other Brain Measures of Cognitive Function" *BBS* 13(2)1990.] The N2 and related mismatch negativity component (MMN) as indicators of stimulus evaluation and stimulus mismatch have been less frequently studied in PS. N2 latencies are longer in schizophrenics (Brecher et al. 1987; Grillon et al. 1990). In our current work with a 3-tone oddball task, the MMN (derived as rare – standard ERP) develops over 240–280 msec in controls. A comparable frontal negativity develops in PS subjects 110 msec later (if at all), when posteriorly an (abnormal) P3 is already showing. This is supportive of Hemsley's "weakening of the influence of stored representations on perception" and is logically compatible with a monitoring problem (Frith).

Gray et al. rightly attach importance to the schizophrenic who "can see the details but has difficulty to extract the meaning." Schizophrenics have difficulty in seeing the wood for the trees, the figure for the tachistoscopically presented dashes of Schwartz-Gilmore & Place (1980; Wells & Levanthal 1984). Reviewing this work, Straube & Oades (1991) note that this problem is not restricted to PS subjects. Furthermore, gestalt perception is not a controlled process (Robertson 1986) – the type of processing Gray and others suggest is impaired in PS. One could argue that many schizophrenics show impaired information processing 10–80 msec after its receipt, where many authors would have difficulty saying that processing was controlled (e.g., critical stimulus duration and transient channels in masking studies, Balogh & Merritt 1989; Saccuzzo & Braff 1981, and prepulse inhibition, Baker et al. 1990). Gray et al. could rightly object, however, that although these findings relate to subjects with schizophrenia-like symptoms, their target group (PS) has not been appropriately studied. As selective attention seems capable of altering processing at this early stage, however (e.g., Hackley et al. 1987), we propose that the schizophrenic deficit in information processing is better termed concept-driven. The difference here is that controlled processing of a set of events leads to changes that affect the processing of *future* events.

Schizophrenic processing is usually impaired when there is no clear stimulus-response contingency. In interpreting a proverb, schizophrenics often "select" individual words/stimuli and make associations with these independent of the context. When the subject must take account of the context of "A," the response is concept-driven. An example of such a task is an "if-then" situation (if stimulus "A" on "B" then do "X," but if "A" on "C" then do "Y"). Animals can rapidly learn such contingencies *unless the hippocampus is damaged* (Sutherland et al. 1989). Such tasks require an ability to store stimulus configurations and to match new ones to them. This ability is fundamental in generating appropriate responses during conversation (Hemsley), monitoring the goal of a speech plan (Frith), and it recalls Gray et al.'s suggestion that "the integration of stored information . . . for perceptual control is the site of the impairment."

Gray et al. focus very narrowly on the subiculum and its input to the accumbens. It is not clear whether input over the *entorhinalis* is important to their scheme. Here anatomical anomalies have recently been reported (Beckmann 1991; Falkai et al. 1988b). Do they include the *presubiculum*? From here

efferents pass to the entorhinalis and prefrontal cortex, where hypofrontal activity by various measures may not just reflect chronic or negative symptoms (Weinberger 1987) but even symptom state (Hawton et al. 1990). Do Gray et al. wish to subsume the function of these areas in their hypothesis? Can they explain why precommissural fibers from the subiculum to the accumbens *and* septum but not postcommissural fibers to the hypothalamus should be so susceptible to hippocampal or cholecystokinin (CCK) dysfunction (the role of the hypothalamus in PS has not been widely discussed)?

The *septum* is conspicuously absent from the argument. It receives a marked VTA-DA input (and input using most known transmitters besides) and, like the entorhinalis, is crucially placed to gate input to the hippocampus. This is particularly important in view of a putative DA role in switching referred to by Gray and myself (sect. 7, para. 2). But "congruent" with their hypothesis is the coincidence of the frequent age of first showing schizophrenic symptoms (16–20) and normal myelination processes in the subiculum (Benes 1989).

Gray et al. have been searching for a way to link DA activity to temporal lobe pathology in a theory of PS. By analogy with nigral-DA and its protective role in epilepsy, I suggest a VTA-DA role in the septal and entorhinal hippocampal-gates protecting against PS/information processing dysfunction. [My analogy takes into account the anticonvulsant effects of DA agonism (Loescher & Czuczwar 1986), decreased ascending DA activity associated with decreases of seizure thresholds (Turski et al. 1990), higher temporal lobe DA activity (Louw et al. 1989), changed subcortical D2 binding (Csernansky et al. 1985) associated with seizure foci, and protective effects of pars reticulata stimulation (Sabatino et al. 1988)].

Gray et al. note, if we overlook details (sect. 3, last para.), that DA utilization or D2 binding increases 28d after hippocampal surgery in the rat. They ask whether damage to subicular input can produce a functional impairment that is reversed by neuroleptics. They may recall that the report of Oades & Isaacson (1978) supports this prediction. Rats learned over 11 10-trial sessions to find 4 food pellets placed in the same 4 holes of a 16-hole board without visiting nonfood holes. They visited holes in an individually specific sequence on 8/10 trials. A preferred sequence did not develop in animals with hippocampal damage (H) or those treated with haloperidol. However, haloperidol treatment, from session 4, reduced errors by 28% in H animals (7–8% in saline/drug lesion/sham controls). On withdrawal of haloperidol (2-day pause before retest), the H group made 30 errors, whereas controls made 3–5 more errors on average. A similar *partial* normalization of performance or symptoms is often reported for PS subjects who respond to neuroleptics.

The bias of Gray et al.'s review of neurobiological studies with latent inhibition (LI) or conditioned blocking (CB) is a bit misleading. Let me briefly take some reports at face value, although I have no room here to discuss their strengths and weaknesses.

The report that amphetamine in the accumbens of the rat disrupts LI (Solomon & Staton 1982) certainly supports Gray et al. D2 supersensitivity disrupts LI (Crider et al. 1986), apparently reconciling the effects of increased DA utilization and D2 binding. But this supersensitivity was generated by chronic haloperidol treatment that renders other projection regions supersensitive. Indeed, this group (Kamer et al. 1981) dissected the septum out along with the accumbens. The septum, septal DA, and septal opiate receptors are not without various effects in this paradigm (Burton & Toga 1982; Gallagher et al. 1987; Oades et al. 1985). In addition, damage to the mamillary bodies and ventral hippocampus, but not to the dorsomedial thalamus or dorsal hippocampus, can attenuate CB (Rickert et al. 1981). This study, and also Garrud et al. (1984), show that hippocampal damage does not interfere with LI or CB in everyone's hands, despite contrary reports (Nicolle et al. 1989). Although Gray et al. do report on serotonin studies, they are too dismissive of the complexities of the effects of noradrenergic manipulations on LI and CB (e.g., Caza 1984; Mohammed et al. 1986; Rickert & Lorden 1989).

Oades et al. (1987) reported on the effect of 6-OHDA lesions in the PRF and septum on CB. Depletion of septal DA and DOPAC (decreased DA use or changed DA/NA ratios) was associated with the eventual facilitation of CB (latency of response to redundant information); impaired CB after PRF treatment seemed to depend on coincidental decrease of DA in the septum (increased use). Both manipulations were without effect on NA, DA, and DOPAC in the accumbens and striatum. This argues against too narrow a focus on the n. accumbens in the hypothesis of Gray et al.

Gray et al.'s account of disrupted LI in PS subjects remains equivocal when these showed more symptoms and severe ones than the chronic patients; the groups were also not matched for medication. Currently in Essen we are comparing the CB performance of schizophrenics, neurotics, and healthy controls with their urinary monoamine excretion. A large range of values for DA excretion in schizophrenics (usually $\leq$ to controls) reflects symptom and treatment differences and varies as a hyperbolic function with the expression of blocking. A similar relationship in controls is restricted to a far narrower range of values for both DA and blocking. At a general level the implication supports the argument of Gray et al. that the type of information processing measured by this paradigm is influenced by DA activity. Its locus and specificity to PS has not yet been demonstrated, however.

In conclusion, yes, Gray et al.'s hypothesis is reasonable, but some manoeuvres are needed to accommodate the results of others.

Is another loop needed to explain schizophrenia?

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It would seem that there is now no lack of theoretical models of schizophrenia – lately, one has appeared every year or so. Each presentation adds some unexpected new twist to our gropings for insight into the complex psychopathology of schizophrenia. The Gray, Feldon, Rawlins, Hemsley & Smith target article is of this nature. It provides some intriguing new ideas and poses several important questions.

One of the first commendations one can make of Gray et al.'s article concerns its practicality. The authors state clearly that their model deals primarily with acute schizophrenia (Type I) and the so-called positive symptoms rather than the chronic state (Type II). The Gray et al. model has not been weakened by attempting to "stretch" its conclusions to incorporate both acute and chronic states.

Another major asset of the model is that it places emphasis on the role of inadequate interactions between stored experience and current perception as a primary causal factor in thought disorder and other positive symptoms of schizophrenia. This is a satisfying biological construct because it is congruent with views of clinicians who see schizophrenic patients' failure to profit from or use stored experience. It may be, however, that the schizophrenic disturbance is coupled with information-processing deficits (e.g., Braff & Saccuzzo 1985; Freedman et al. 1987; Geyer & Braff 1987). Such deficits would be identified with brain circuitry other than that involved in the Gray et al. model.

Gray et al. have presented a model in which units of motor programs (termed motor steps) become temporally interwoven into a sequential pattern of behavior directed toward a specific goal. Judgments as to the selection of appropriate motor steps are shouldered by circuitries outside of the motor programs

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Target article abstract

The neuropsychology of schizophrenia

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Abstract: A model is proposed for integrating the neural and cognitive aspects of the positive symptoms of acute schizophrenia, using evidence from postmortem neuropathology and neurochemistry, clinical and preclinical studies of dopaminergic neurotransmission, anatomical connections between the limbic system and basal ganglia, attentional and other cognitive abnormalities underlying the positive symptoms of schizophrenia, specific animal models of some of these abnormalities, and previous attempts to model the cognitive functions of the septohippocampal system and the motor functions of the basal ganglia. Anatomically, the model emphasises the projections from the septohippocampal system, via the subiculum, and the amygdala to nucleus accumbens, and their interaction with the ascending dopaminergic projection to the accumbens. Psychologically, the model emphasises a failure in acute schizophrenia to integrate stored memories of past regularities of perceptual input with ongoing motor programs in the control of current perception. A number of recent experiments that offer support for the model are briefly described, including anatomical studies of limbic-striatal connections, studies in the rat of the effects of damage to these connections, and of the effects of amphetamine and neuroleptics, on the partial reinforcement extinction effect, latent inhibition and the Kamin blocking effect; and studies of the latter two phenomena in acute and chronic schizophrenics.

Keywords: attentional deficit; basal ganglia; dopamine; limbic system; memory; neuroleptics; perception; schizophrenia; septohippocampal system

The neuropsychology of schizophrenia

In recent years there has been a notable increase in attempts to construct models of the neural dysfunction that underlies schizophrenia, considered either as a single diagnostic entity or after separation into subtypes or particular symptom clusters within this entity (e.g., Schmajuk 1987; Swerdlow & Koob 1987; Weinberger 1987). At the same time, other workers have tried to provide a fresh interpretation of schizophrenic symptomatology in terms of an underlying defect in specific aspects of cognitive functioning (e.g., Frith 1987; Hemsley 1987). There have even been a few fledgling attempts to grapple with the much more daunting task of constructing a model of schizophrenic dysfunction to encompass, and above all to integrate, both its neural and its cognitive aspects (Frith & Done 1988; Joseph et al. 1979; McKenna 1987; Swerdlow & Koob 1987a). It is our intention to offer here a tentative model of the latter kind.

The model aims to bring together: (1) the postmortem evidence of neuronal loss and cytopathology in limbic regions of the temporal lobe in schizophrenic brains (Beckmann et al. 1987; Bogerts et al. 1985; Brown et al. 1986; Jeste & Lohr 1989; but see Christison et al. 1989); (2) the evidence of specific neurotransmitter loss in these same regions (Roberts et al. 1983); (3) neuropharmacological evidence from both clinical and animal studies suggesting dopaminergic hyperactivity in at least the acute phase of a schizophrenic illness (Swerdlow & Koob 1987a); (4) recent advances in neuroanatomical knowledge of the connections between the limbic system and the basal ganglia (Kelley & Domesick 1982; Nauta & Domesick 1984; Totterdell & Smith 1986; 1989); (5) previous suggestions of specific attentional and other cognitive deficits in schizophrenia (Frith 1987; Hemsley 1987a); (6) specific animal models of some of these deficits (Solomon et al. 1981; Weiner et al. 1981; 1984; 1988; Weiner, Izraeli-Telerant & Feldon 1987f); (7) previous attempts to model some of the cognitive functions of the limbic system and basal ganglia in relation to the neuropsychology of anxiety (Gray 1982a; 1982b) and motor function (Groves 1983; Swerdlow & Koob 1987a); and, finally, (8) some of the specific symptoms of schizophrenia, especially the "positive" symptoms most characteristic of the acute stage of the illness.

Given the current state of knowledge in many of the relevant areas, much of the model is highly speculative. It is readily open to experimental testing at a number of points, however, not only with clinical material but also in experiments with animals. Until recently, animal models of schizophrenia seemed implausible, because clinical descriptions emphasised abnormalities in the sphere of

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