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Abstract

Modern techniques have been applied to brain modeling, based on recent approaches in the artificial intelligence field that use brain-like "connectionistic" computational architectures. The model proposed by Cohen and Servan-Schreiber uses a gain parameter which they identify with dopamine function. They apply their model to neuroleptically treated schizophrenia patients who show improved task performance which they link to increased dopamine function and increased "gain" in the prefrontal cortex (PFC). However, evidence indicates that antipsychotic medications block dopamine (especially D2) receptors, decreasing mesolimbic and mesocortical dopamine function. If therapeutic dosages of neuroleptics diminish dopamine function, this would decrease gain in context modules needed for adequate task performance. Schizophrenia patients would perform more poorly by further reducing gain in their already compromised context modules. The current investigators suggest three possible ways to resolve this difficulty, to explain why normals perform more poorly when taking neuroleptics, although acute schizophrenia patients' performance may be enhanced in several areas. Evidence would suggest that multiple processes occur simultaneously in neuroleptically treated patients with some processes counterbalancing others.


In their recent article "A Theory of Dopamine Function and Its Role in Cognitive Deficits in Schizophrenia," Cohen and Servan-Schreiber (1993) apply modern techniques for brain modeling based on recent approaches in the artificial intelligence field that use brainlike "connectionistic" computational architectures. There are, however, problems with the thesis they present, because their data are interpreted in terms of patients treated with neuroleptics showing improved task performance, which is presumably linked to increased dopamine function and increased "gain" in the prefrontal cortex (PFC). One could question whether their proposed views are in accord with current evidence on the mechanisms of action of neuroleptic medications.

Overall, Cohen and Servan-Schreiber (1993) attempt to provide further computational evidence and new empirical evidence to support their earlier hypothesis that cognitive dysfunction in schizophrenia can be explained by reduced gain at nodes in a connectionist module that represents contextual informa-
tion required for the performance of specific cognitive tasks. In this model, reduced gain limits the influence of the contextual cues needed for the effective performance of cognitive tests. In their recent research, Cohen and Servan-Schreiber (1993) use the Continuous Performance Test (CPT; Rosvold et al. 1956) as the experimental task, and in previous research they have used the CPT, the Stroop test, and a lexical disambiguation task (Cohen and Servan-Schreiber 1992). In their attempt to explain schizophrenic deficit, they show that reduced gain (0.6) in computer simulated connectionist modules that represent contextual cues will prolong response latencies and increase error rates for these three tasks. A review of the psychostimulant literature that links increased dopaminergic neuromodulation with shorter latencies of response in these and similar cognitive tests is used to justify the identification of dopamine as involved in the neurobiologic control of gain for neurons in the PFC where the context modules are presumed to be located. The authors were able to simulate schizophrenic responses to these three tasks with computational models of the same tasks based upon the interplay between normally functioning stimulus and response modules and the context module that had diminished gain. This lends greater credence to this enterprise and strengthens the bridges between artificial intelligence, connectionist architectures, and the neurobiology of schizophrenia.

A closer look at this thesis, however, reveals a glaring omission in their presentation. They neglected to address a large body of literature on the action of antipsychotic medication in blocking dopamine receptors and decreasing mesolimbic and mesocortical dopamine function. Specifically, empirical evidence in the pharmacological literature indicates that the equivalence of therapeutic doses for humans of neuroleptics effectively shuts down in animals the mesocortical and mesolimbic dopamine input into prefrontal and premotor frontal cortical areas (Wise 1982). If therapeutic dosages of neuroleptics diminish dopamine function, would not this diminished dopamine function further decrease gain in context modules needed for adequate task performance by schizophrenia patients? This alternate view of Cohen and Servan-Schreiber’s model implies that neuroleptics will make individuals with schizophrenia perform more poorly by further reducing gain in their already compromised context modules. This prediction, based on the literature on neuroleptic effects, contradicts Cohen and Servan-Schreiber’s prediction that medicated schizophrenia patients should perform better than unmedicated schizophrenia patients on the CPT.

More specifically, the authors compared a group of normals to unmedicated and medicated schizophrenia patients on the CPT by using the stimulus pattern AX as a target. Their findings in unmedicated schizophrenia patients were consistent with classical results on schizophrenia patients (i.e., greater false alarm responses to BX stimuli under conditions of prolonged interstimulus intervals). Their model predicted these results in terms of decreased gain leading to more rapid degradation of context mediated internal stimuli. However, the medicated schizophrenia patients showed fewer false alarms under these conditions. This is consistent with a “therapeutic” effect, but it is in contrast to the further decreased gain one might expect when neuroleptics block dopamine receptors in the PFC.

Evidence that neuroleptics do indeed diminish behavior which is linked to cortical function is borne out in neuroleptically treated patients. Thus, patients who take neuroleptics, which reduce dopamine and presumably reduce gain, behave less energetically (both physically and cognitively) and report feeling more sluggish and less mentally alert (Harrow et al. 1994). The behavior and reports of normal volunteers who have tried neuroleptics fit those reported for patients, with normals showing deficit-like behavior in terms of a reduction in the richness and complexity of their thinking, as well as anhedonic effects, after neuroleptic administration.

This fundamental contradiction to their model does not automatically invalidate the thrust of the authors’ assertion that the gain parameter is involved in schizophrenic cognitive impairments. It does, however, raise questions concerning their identification of dopamine neuromodulation as the control factor of the neuronal gain parameter and the interpretation of their research data.

A proposed alternate model is one in which the addition of neuroleptics reduces the effects of dopamine in both limbic and frontal areas; but by differentially reducing aspects of limbic input on the cognitive process, to a greater extent one increases the effectiveness of PFC functions for acutely psychotic patients. We sug-
gest that this possibility and two others be considered.

1. Because of the differential distribution of dopamine receptors and/or the sensitivity of receptors, neuroleptics can be expected to partially reduce gain in both mesolimbic and mesocortical areas but to have a differentially greater effect in mesolimbic versus mesocortical networks for acutely psychotic patients. Neuroleptics, which block D2 receptors and result in reduced gain in frontal areas, lead to reduced thinking and poorer cognition for all people, including those with schizophrenia. However, for those acutely disturbed people with excessive limbic interference (possibly people with excessive or poorly controlled internal ideation disrupting their reality-oriented cognition), the beneficial effects of neuroleptics, which lead to reduced dopamine neuromodulation, reduced gain, and a reduction of limbic system interference, outweigh the reduced gain in the frontal lobe. Thus, for acutely psychotic patients, the reduced limbic system interferences outweigh the reduced richness of thinking (or more impoverished thinking) brought on by this type of neuroleptic therapy.

This view could fit in with the hypothesis of Weinberger (1987) and could be applied to the model of Cohen and Servan-Schreiber (1993). Weinberger (1987) proposed a neurodevelopmental model of schizophrenia in which dopaminergic input through the mesocortical pathway to the dorsolateral PFC enhances the PFC's ability to exert a feedback inhibitory effect upon the limbic system. According to this outlook, the developmental "lesion" of schizophrenia involves diminished mesocortical dopaminergic activity and a corresponding increase in mesolimbic dopaminergic activity, with diminished frontal lobe activation and disinhibition of limbic activity (Weinberger 1986, 1993). The view would then be that neuroleptic drugs may serve to differentially inhibit the mesolimbic system, provided the limbic area does possess an increased activity level.

The model of Cohen and Servan-Schreiber could be integrated with this view if the context modules were located in the dorsolateral PFC modulated by the mesocortical pathway (neurodevelopmentally diminished in schizophrenia).

2. As a second possibility, there could be a mix of states of heightened gain (producing positive symptoms) on the one hand, and reduced gain (producing negative symptoms) on the other hand distributed within or between various cognitive modules in schizophrenia patients. By blocking dopamine receptors in noncontext modules, neuroleptics may serve to paradoxically improve function provided by previously impaired context modules. This type of mechanism could fit in with a model such as that of Hoffman (1993) who focuses on the importance of "paracytic foci" in leading to reality distortions. Within this framework one could hypothesize that neuroleptics may diminish gain in noncontext modules that have "paracytic foci" (Hoffman 1993) which interfere with weakened context modules.

3. As a third possibility, it is conceivable that some therapeutic effects of neuroleptics may be a result of other mechanisms associated with neuroleptic use that does not involve dopamine, although the action of neuroleptic medications in blocking dopamine receptors is emphasized by many. Thus, neuroleptics may have a therapeutic effect on schizophrenia patients independent of dopamine blockage, and possibly one that compensates indirectly for some reduction in gain, even that induced by the drugs themselves.

The above considerations relating to increased PFC functioning after neuroleptic administration might better fit the results for the medicated group (1993) in Cohen and Servan-Schreiber's study and also explain why normals perform more poorly when taking neuroleptics, whereas the performance of acute schizophrenia patients may be enhanced in some areas. Cohen and Servan-Schreiber also note that the approach they have taken offers the potential for generating new ideas in the area. We agree with the authors in their contention that the models they use provide the potential for the discovery of new ideas in brain-behavior relationships in schizophrenia, and in this respect, go beyond just the testing of current ideas. However, they stand to diminish the potential positive impact of their models and resulting insights by their failure to discuss or acknowledge data (e.g., on neuroleptic effects) that have the potential to challenge their hypothesis.

Overall, it seems extremely probable that multiple processes are going on at the same time in neuroleptically treated groups, perhaps with some processes counter-balancing others. For instance, dopamine may be excitatory in some parts of the limbic system (e.g., hippocampal-accumbens neurons), which might increase short-term memory capacity, whereas in other parts it might ex-
ert an inhibitory effect (e.g., subiculo-accumbens neurons) (Henriksen and Giacchino 1993), which would lead to less effective integration of long-term memory, creating difficulty in monitoring functions. The likelihood that multiple processes are involved, and the current imperfect understanding of how these processes interact, would indicate that the above models and, of even more importance, alternate models should be presented and advanced by others on the complex effects of neuroleptics in the PFC. Various alternate models on neuroleptic effects in the PFC and limbic areas should be subject to further discussion. Such discussion could help to advance the field's thinking on an issue of theoretical importance that has not been dealt with sufficiently in the past.

Finally, we note that the CPT task used by Cohen and Servan-Schreiber, in conjunction with the experimental model they discuss, presents a potentially valuable paradigm for initiating the study of schizophrenic deficit in detail. However, a future need is application of the model to cognitive phenomena that are unique to schizophrenic and psychotic disorders, such as delusional and hallucinatory behavior. Thus, it would seem important that cognitive models in this area address the following issues: (1) Why do individuals with schizophrenia believe things that are not true, and hold on to these false beliefs or delusions despite strong evidence to the contrary? (2) What mechanisms are involved? (3) How would one fit such an understanding into modern brain-behavior models and into a connectionist view?

References


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