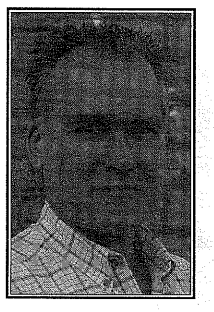
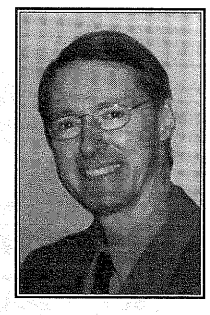
Antipsychotic Drugs and Memory in Schizophrenia





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Along with a senior graduate student in the Department of Psychology at Queen's, James Wasserman, we are engaged in an investigation of the effects of antipsychotic medications on learning and memory in schizophrenic patients. The drugs that are used to treat schizophrenia are valuable therapeutic tools that allow affected individuals to achieve better lives with relative freedom from symptoms. As is the case with many treatments, however, antipsychotic medications appear to have some undesirable effects; they may impair certain aspects of memory. However, our results suggest that various antipsychotic medications may differ in the types of memory they affect.

In the latter half of the 20th century, researchers began to realize that memory was not a monolithic concept. Dr. Brenda Milner, a brilliant neuropsychologist working at the Montreal Neurological Institute, observed that a patient suffering from amnesia was able to learn some things. Although he was unable to learn the names of new acquaintances or the floor plan of a new building, he showed improvement from day to day on a task involving tracing while viewing his hand reflected in a mirror. Other researchers found that patients suffering from Alzheimer's disease who were impaired in memory for names or places could similarly learn a task requiring eye-hand coordination.

These and related observations led Dr. Larry Squire of the Department of Psychiatry and Neuroscience, University of California at San Diego to formulate a taxonomy of long-term memory and associated brain structures. The type of memory loss seen in amnesic or Alzheimer's patients was termed "declarative" and seemed to rely on intact function of the medial temporal lobe and diencephalon. The types of memory that were preserved in these patients were termed collectively "non-declarative" but seemed to be of a number of subtypes. The learning of skills mentioned above seemed to rely on intact function of the striatum and other non-declarative memory types such as priming or learned fear responses depended on the neocortex or amygdala, respectively.

Work from Dr. Squire's laboratory showed that patients with Parkinson's disease also had memory impairments. These individuals could remember faces or floor plans, thus showing intact declarative memory, but they had difficulty with a form of non-declarative memory that depended on learning an association between stimulus cards and outcomes that were related probabilistically (the probabilistic classification task). As Parkinson's patients are known to suffer from a loss of dopamine neurons that project to the striatum, this form of non-declarative memory was associated with that structure.

Another group of researchers at the Department of Neurology, University of Iowa College of Medicine, including Drs. Antoine Bechara and Antonio Damasio, identified another non-declarative memory type that depended on intact function of a region of the pre-frontal cortex. They found that patients with damage to the ventromedial pre-frontal cortex were impaired in their ability to learn to choose advantageously from a set of four decks of cards where two of the decks provided better long-term prospects for gaining play money than the other decks. As control participants began to make choices from the good decks before they were aware of the differential contingencies associated with the different decks, the type of memory required for performing this gambling task was defined as non-declarative.

So what does all of this have to do with schizophrenic persons taking antipsychotic medications? Antipsychotics are classified as typical and atypical. Typicals are the older medications (e.g., chlorpromazine, haloperidol) that have a relatively high liability for causing motor symptoms like those seen in Parkinson's disease, termed extrapyramidal side effects. Atypicals are the newer medications (e.g., olanzapine, risperidone) that are defined as having relatively low liability for extrapyramidal symptoms. Researchers have shown that different classes of antipsychotics have different effects on the brain. Looking at their effects on intracellular molecular function, it was found that typical antipschotics induced immediate early gene expression in the striatum but not in the frontal cortex whereas atypicals produced this effect in the frontal cortex but not in the striatum.

This observation led us to investigate the possibility that schizophrenic patients treated with typical antipsychotic medications would be impaired in performance of the probabilistic classification task, because that task depends on the striatum and typicals affect the striatum. We hypothesized that these patients should not be impaired in performance of the gambling task, which depends on the frontal cortex. On the other hand, those patients treated with atypicals might be impaired on the gambling task because it depends on the frontal cortex and atypicals affect the frontal cortex, but not on the probabilistic classification task, which depends on the striatum. This is exactly what we found (Figure 1) and the results will appear in an upcoming issue of Schizophrenia Research. It is interesting to note that schizophrenic patients treated with either medication class did not differ in their performance on a declarative memory task. It appeared that the medications were affecting only non-declarative memory and only the subtype that relied on the region of the brain where the drugs were known to affect molecular processes.

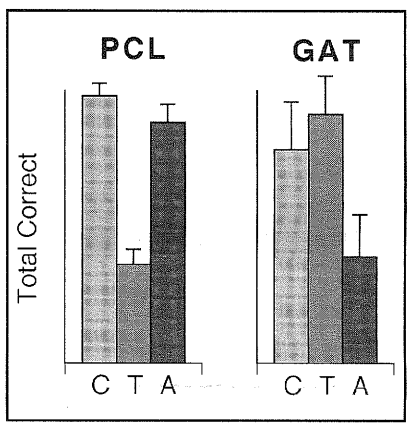

Fig. 1: Total correct on the probabilistic classification (PCL) and gambling (GAT) tasks for control (C) participants and schizophrenic groups treated with typical (T) or atypical (A) antipsychotic medications. Adapted from Beninger et al. (2003) Schizophrenia Research, in press.

The medication groups in this study included patients treated with a number of different atypical antipsychotic medications including olanzapine, risperidone, clozapine and quetiapine. Although we did not have sufficient numbers of participants taking any one of these atypicals to be able to carry out statistical analyses, a review of the scores on the probabilistic classification and gambling tasks of the small subgroups treated with specific medications suggested that not all of the atypicals were acting in the same way. This led to a study that is currently underway.

We are evaluating the effects of the atypicals olanzapine, risperidone and clozapine on performance of the probabilistic classification and gambling tasks by schizophrenic patients. For comparison we are including a group treated with typical antipsychotic medications. We also include a drug-free control group that is matched to the patient groups on age, gender and years of education.

The study is in progress and we have too few participants within each medication group to make any final conclusions. However, a picture is beginning to emerge. As expected, the control participants are learning both tasks. In a replication of the findings from the previous experiment, it appears that the schizophrenic patients treated with typical antipsychotics are performing normally on the gambling task but are impaired on the probabilistic classification task. In general, olanzapine appears to be having a greater effect on the gambling task than on the probabilistic classification task, also replicating our findings with an atypical group from the previous study. Risperidone, however, appears to be acting more like a typical than an atypical, impairing learning of the probabilistic classification task but not the gambling task! At present we have too few clozapine-treated participants to be able to draw even preliminary conclusions.

What does it all mean? These studies show clearly that different types of antipsychotic medications have different effects on the function of the brain. The implications of these different effects for day-to-day living are more difficult to identify. The entire area of non-declarative memory is still poorly understood. It is clear that there are learning processes influenced by the outcomes of our actions over repeated trials that shape our behavior in the absence of conscious awareness of this process. The consequences of these non-declarative memory processes include changes in the way we respond to stimuli in our environment, i.e., changes in the choices we make.

It will be the task of future studies to derive an understanding of how non-declarative memory processes mediated by the striatum or frontal cortex are important for different occupations or different activities of daily living. Armed with this type of information and with the results of studies like the ones described here, it will eventually be possible to make rational choices about medications that are informed by an understanding of the consequences of those choices for the specific activities engaged in by the patient.

Our research is aimed at a better understanding of the basic processes of memory and the sub-regions of the brain that mediate them with the goal of understanding how medications affect these processes. Only with continued investigations of these mechanisms will we achieve the best possible fit between the profile of the antipsychotic medication that is chosen and the characteristics of the patient receiving that medication.