Investigation into Predictive Error Signal Abnormality in Major Depression and Schizophrenia

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I - SUMMARY OF THE STUDY

Major depressive disorder (MDD) and schizophrenia are two common psychiatric illnesses whose causes are yet unknown and for which fully effective treatments remain to be developed.

Anhedonia (inability to experience pleasure) is a core symptom of depression and DA neurons are known to be critical in a wide variety of pleasurable experiences and reward.

Most antidepressants increase serotonin (5-HT) and/or norepinephrine levels. Since monoamines levels change in the course of hours while the therapeutic effects occur in the course of weeks, it is thought that other mechanisms must be involved in recovery from depression. It has been proposed that antidepressants might have a secondary effect on the DA system. Furthermore, since acute 5-HT increases inhibitory reward-related approach behaviours, a common interaction between DA and 5-HT with different effects of acute (DA system inhibition) versus chronic (DA system enhancement) antidepressant administration has been suggested.

Psychotic symptoms (delusions, hallucinations) are typical in schizophrenia.

“Recreational” drugs that stimulate the DA system can cause psychosis in healthy subjects.

Drugs that successfully treat schizophrenia symptoms act by blocking DA receptors.

However, there are no consistent studies demonstrating high DA levels in MDD patients while no “phasic” (brief duration) DA levels.

DA neurons code a phasic reward prediction error signal that animals use as “teaching signal” to learn.

Learning occurs when there is a difference between the predicted and the actual outcome, leading to a dopamine prediction error signal.

II - PRELIMINARY ANALYSIS OF THE INSTRUMENTAL TASK FOR THE DEPRESSION DATA

Methods

On a first stage of the study, patients with MDD, and controls both unmedicated and medicated with the antidepressant citalopram, were scanned using fMRI during the following 3 tasks:

- Pavlovian learning task
- Instrumental learning task
- Social motor response learning task

On a second stage of the study (not finished yet) schizophrenic patients are scanned while performing the same 3 tasks.

The pavlovian and the social motor response tasks have been already analyzed for the depression data and the results have been reported (Kumar et al 2008a, Kumar et al 2008b). Future work will focus on the analyses of the instrumental task for the depression data, as well as on the analyses of the three tasks for the schizophrenia data and on comparing the results obtained with both groups of patients.

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Hypotheses

- Antidepressant-unresponsive MDD is associated with reduced TD reward-learning signals

Patients

- 20 controls and 15 MDD patients (Beck or Hamilton depression score > 21) matched for age, sex and IQ
- Controls were re-scanned after receiving the SSRI citalopram at a dose of 20 mg/day for 3 days
- Controls had acute SSRI administration did alter TD signals in controls although not in the expected direction. Again, further work is needed to confirm and explain this finding.

Materials and Methods

Temperature learning model

- We used a standard “actor-critic” TD model
- Each subject’s sequence of choices and outcomes were used as inputs to the model
- On every step the model estimates a prediction of future reward R(t+1)
- The TD prediction error signal is computed by comparing the value at time t+1 to that at time t:
  \[
  \delta(t) = r(t) + \gamma V(t+1) - V(t)
  \]

- Learning occurs by updating the predicted values using the corresponding TD error signal
- The TD error signal is also used to update action values that the model uses to compute the probabilities of taking every action.

Discussion

The pattern of activation found in healthy subjects was consistent with previous findings, particularly, with the results obtained with the pavlovian task (Kumar et al 2008a).

In agreement with our first hypothesis, depressed patients had reduced TD signals in the retrolateral prefrontal cortex, thalamus and dorsolateral cingulate. However, abnormally increased TD signals were also found in the insula of patients. Intriguingly, in the pavlovian task patients showed an increased activation in the ventral tegmental area. Further analyses are required to clarify these increases in activation in patients.

Unmedicated controls > patients

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Patients > Unmedicated controls

Fig. 3 TD signal activation in medicated controls. Regions significant at p<0.05 FDR whole brain corrected. Retrolateral cortex, Thalamus, Amygdala, Ventral and Dorsal striatum. Image display at p<0.05 uncorrected, minimum of 20 voxels per cluster.

Fig. 4 TD signal activation in depressed patients. Regions significant at p<0.05 FDR whole brain corrected. Amygdala Right insula and Motor cortex (Broca's area 4). Image display at p<0.01 uncorrected, minimum of 20 voxels per cluster.

Fig. 5 Difference in TD signal strength in patients compared to controls. Patients had reduced activation in Retrolateral cortex, Thalamus, Dorsal anterior cingulate (p<0.01 uncorrected) and Dorsal striatum (p<0.05 FDR small volume corrected). Image display at p<0.05 uncorrected, minimum of 20 voxels per cluster.

Fig. 6 Difference in TD signal strength in patients compared to controls. Patients had increased activation in the right insula (p<0.05 FDR small volume corrected). Image display at p<0.05 uncorrected, minimum of 20 voxels per cluster.

Fig. 7 Difference in TD signal strength in medicated controls compared to unmedicated controls. Med controls had increased activation in the Amygdala-Hippocampus complex (p<0.05 FDR small volume corrected). Image display at p<0.05 uncorrected, minimum of 20 voxels per cluster.

Fig. 1 Instrumental task

Fig. 2 TD signal activation in unmedicated controls. Image display at p<0.001 uncorrected, minimum of 20 voxels per cluster.

References


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