Investigation into Predictive Error Signal Abnormality in Major Depression and Schizophrenia

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I - SUMMARY OF THE STUDY

Background

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.

Several lines of evidence suggest a critical role for the **dopamine (DA)** system in the pathogenesis and treatment of both illnesses since:

- **Anhedonia** (inhability 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. → Low DA function in MDD ??
- Most **antidepressants** increase **serotonin** (5-HT) and/or noradrenalin 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 inhibit 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 schizophrenic symptoms act by blocking DA receptors. → High DA function in Schizophrenia ??

However, there are **no** consistent studies demonstrating → low DA levels in MDD / high DA levels in schizophrenia

One possible explanation is that previous studies have investigated "***tonic***" (or long timescale) levels of DA and not "***phasic***" (brief duration) DA levels.

DA neurons code a phasic **reward prediction error signal** that animals use as "teaching signal" to learn:
- stimulus-reward associations (**pavlovian conditioning**)
- stimulus-response-reward associations (**instrumental conditioning**)

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

Temporal difference (TD) models are reinforcement learning algorithms that provide a mathematical description for the DA prediction error signal (or **TD signal**).

The TD signal is believed to contribute to the attribution of "**incentive salience**", the process by which a stimulus grasps attention and motivates goal- directed behaviour by associations with reinforcing events.
- Abnormally reduced TD signals in MDD would imply reduced salience of, and attention to, rewarding events, such as occurs in Anhedonia.
- Abnormal TD signals in schizophrenia could imply an aberrant assignment of salience to external objects and internal representations leading to delusions and hallucinations

Aim of the study

To investigate hypothesised abnormal phasic dopamine signals in MDD and schizophrenia using TD modelling and fMRI.

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 schizophrenic data and on comparing the results obtained with both groups of patients.

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

Hypotheses

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

• **Healthy controls given a selective serotonergic reuptake inhibitor (SSRI) *acutely*, have reduced TD reward-learning signals**

Materials and Methods

Participants

- 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

Instrumental learning paradigm

- On every trial participants had to choose one of two fractal pictures
- One of the pictures was associated with a high probability of obtaining drops of water ("**reward**") and the other with a low probability of obtaining drops of water. These probabilities varied during the task.

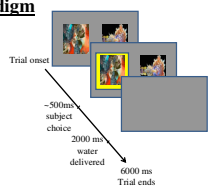

Fig.1 Instrumental task

Temporal difference 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 time step the model estimates a prediction of future reward $V(t)$
The TD prediction error signal is computed by comparing the value at time $t+1$ to that at time t :

$\delta(t)=r(t)+\gamma V(t+1)-V(t)$

$r(t)$=reward at time t ('1' for water delivery, '0' for no-water delivery)
$V(t)$= predicted value at time t
γ = discount factor (determines how more important are earlier rewards than later rewards) We used $\gamma = 1$

• 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.
• Behavioural fit
The model parameters such as the learning rate (alpha) and the exploration/exploitation coefficient (beta) were adjusted to maximize the probability (or likelihood) of the actual subjects choices under the model. We used alpha = 0.1 and beta = 0.6.

Image analysis

- We used SPM2 for the image analysis.
- Each subject specific TD signal was sampled at the time of the pictures presentation and at the time of water delivery and used as a regressor for 1st level analysis.
- A priori regions of interest were: **rostral and dorsal anterior cingulate, ventral and dorsal striatum, amygdala, hippocampus, insula, ventral tegmental area and retroesplenial cortex**.

These regions have been associated with emotions, have shown abnormal functioning in MDD and/or exhibit a TD signal.

Results

Unmedicated controls

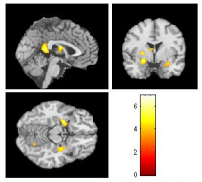

Fig. 2 TD signal activation in unmedicated controls. Regions significant at p<0.05 FDR whole brain corrected : **Retrosplenial cortex, Thalamus, Amygdala, Ventral and Dorsal striatum.** Image display at p<0.001 uncorrected, minimum of 20 voxels per cluster.

Medicated controls

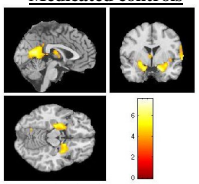

Fig. 3 TD signal activation in medicated controls. Regions significant at p<0.05 FDR whole brain corrected : **Retrosplenial cortex, Thalamus, Amygdala, Ventral striatum and Somatic motor cortex.** Image display at p<0.001 uncorrected, minimum of 20 voxels per cluster.

Depressive patients

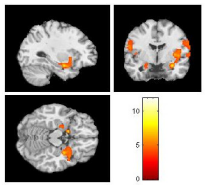

Fig. 4 TD signal activation in depressive patients. Regions significant at p<0.05 FDR whole brain corrected : **Amygdala Right insula and Motor cortex (Brodmann area 4).** Image display at p<0.001 uncorrected, minimum of 20 voxels per cluster.

Unmedicated controls > patients

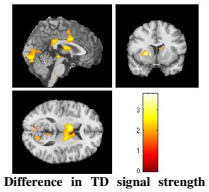

Fig. 5 Difference in TD signal strength in patients compared to controls. Patients had **reduced** activation in: **Retrosplenial cortex, Thalamus, Dorsal anterior cingulate** (p<0.01 uncorrected) **and Dorsal striatum** (p<0.05 FDR small volume corrected) Image display at p<0.05 uncorrected, minimum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

Patients > Unmedicated controls

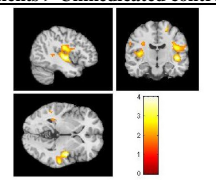

Fig. 6 Difference in TD signal strength in patients compared to controls. Patients had **increased** activation in the right **Insula** (p<0.05 FDR small volume corrected). Image display at p<0.05 uncorrected, minimum of 20 voxels per cluster.

Med. controls > Unmed. controls

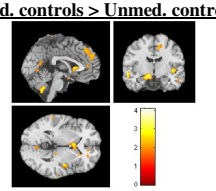

Fig. 7 Difference in TD signal strength in medicated controls compared to unmedicated controls. Med. controls had **increased** activation in the **Amygdala-Hippocampus complex** (p<0.05 FDR small volume corrected). Image display at p < 0.05 uncorrected, minimum of 20 voxels per cluster.

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 striatum, retroesplenial cortex, thalamus and dorsal 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 analysis is required to clarify these increases in activation in patients.**

• **Medicated controls showed an increased activation in the amygdala-hippocampus complex. This indicates that 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.**

References

• Kapur, S., 2003. "*Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia.*" Am J Psychiatry 160,13-23
•Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele J.D. 2008a "Abnormal temporal difference reward-learning signals in major depression" Brain (*IF 8.5*) (in press)
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