Role of 5HT and catecholamines in the modulation of reward, punishment and behavioural inhibition using precursor depletion and fMRI in healthy volunteers.

Role of 5HT and catecholamines in the modulation of reward, punishment and behavioural inhibition using precursor depletion and fMRI in healthy volunteers.

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Introduction

Dietary amino acid depletion

- Dietary depletion of tyrosine/phenylalanine (Tyr/Phe) and tryptophan (Trp) induces reductions in brain dopamine (DA) and serotonin (5HT) metabolites, respectively.

Citalopram

- Citalopram is a highly selective and potent 5HT reuptake inhibitor with minimal effects on noradrenaline (NE) and DA.

Behavioural Inhibition

5HT is implicated in behavioural inhibition. Disorders with a dysfunctional 5HTergic system often present with deficits in impulsivity.

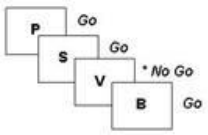
Reward and Punishment

- Electrochemical, physiological, pharmacological and imaging studies have identified DA and 5HT as important in the neurochemistry of reinforcement (reward and punishment).
- Neuroimaging studies have outlined a number of key regions involved in reinforcement including the dopaminergic midbrain, ventral striatum, amygdala, basal forebrain, orbitofrontal cortex (OFC).

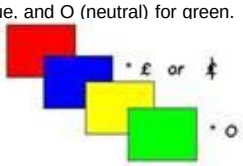
Methods

Cognitive Tasks

1. Go/No-Go – subjects respond to all letters in Go blocks. Participants inhibit the response when they see the letter V in No-Go blocks, which are 50% of letter presentations.



2. Reward/No Reward – subjects press when they see a blue or green square. They are rewarded with £ on 50% occasions if they respond quickly enough on blue, and O (neutral) for green.



3. Loss/No Loss – subjects again must respond as quickly as possible to coloured boxes but this time are punished with £ on 50% of occasions if they do not respond quick enough.

Citalopram Methods

- 12 subjects were tested twice in a single blind crossover design.
- Age range 19 – 36, mean age 24.7 years.
- The infusion process was 7.5mg over 7.5 minutes.
- The infusion took place 20 minutes before the tasks were undertaken.

Imaging Details

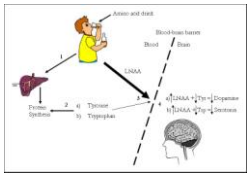
- Data acquired on a 1.5T Philips Gyroscan
- Whole brain coverage achieved with 40 slice volumes, 3.5mm apart. In plane resolution 3x3mm. TR 5 seconds.
- Analysed using SPM2, random effects model.

Tyrosine/phenylalanine and tryptophan depletion

- 36 subjects will be recruited to give 3 groups of 12, each of which will receive one of three drinks: one missing tyrosine and phenylalanine (TP-), one missing tryptophan (TRP-) and a balanced drink containing both of these (Bal).
- Participants will be physically healthy without previous psychological problems
- Age range 18-65

Amino acid depletion

1. Amino acid drink missing tyrosine/tryptophan stimulates protein synthesis by liver.
2. Endogenous tyrosine/tryptophan taken up by liver for protein synthesis.
3. Large amounts of neutral amino acids compete with depleted tyrosine/tryptophan for entry across the blood-brain barrier.
4. Little entry of tyrosine/tryptophan into the brain, therefore brain dopamine/serotonin levels reduced.



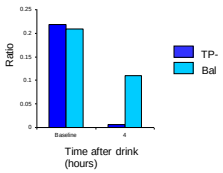
- The same cognitive tasks from the citalopram study will be administered.
- Dietary tryptophan depletion is being used in conjunction with citalopram data in order to provide complimentary data to issues involving the 5HT system.

Results

Scanner problems have led to the depletion study being stalled and imaging data were therefore not available for analysis.

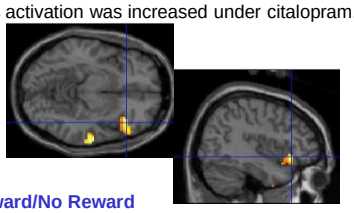
Dietary tyrosine depletion

- Previous research, including work from this group, demonstrated a significant time x drink interaction in plasma ratio of tyr/phe to the other large neutral amino acids, following administration of a balanced amino acid drink (Bal) or a drink missing tyr and phe (TP-) [$F_{(1,6)}$=74.7, p<0.0001].



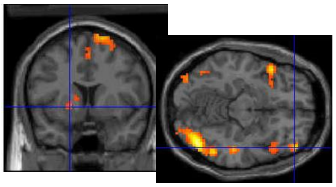
Go/No-Go

A main effect of task was observed in the right lateral orbitofrontal cortex when subjects were inhibiting responses (no-go blocks).
This activation was increased under citalopram.



Reward/No Reward

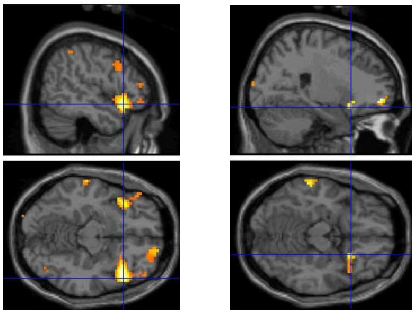
- A main effect of task was observed in the right OFC, left putamen and caudate nucleus.



Loss/No Loss

- A main effect of task was observed in bilateral orbitofrontal cortex.
- The activation in this region was attenuated by citalopram.

Main effect | Citalopram



Hypotheses

- Reward will activate regions of the ventral striatum, medial orbitofrontal cortex, anterior cingulate and dopaminergic midbrain.
- Loss will activate areas including the lateral orbitofrontal cortex and amygdala.
- Response inhibition will activate regions of prefrontal cortex, particularly the lateral orbitofrontal cortex.
- Dietary tyrosine/phenylalanine and tryptophan depletion will modulate activity in the regions described above.
- The effects of citalopram and tryptophan depletion on 5HT levels leads to the hypothesis that there will be differential neuronal activity in the 5HT systems involved in reward, loss and response inhibition.

Discussion

- 5HT manipulation has been shown to affect tasks investigating reward, loss and response inhibition.
- Dietary depletion of tyrosine and tryptophan depletes DA and 5HT metabolites respectively, and consequently neurotransmitter levels.
- Using a combination of tyrosine and tryptophan depletion along with fMRI should show the effects of depleted DA and 5HT neurotransmission.
- Contrasting tryptophan depletion results with data from the citalopram study will contribute to our understanding of the putative functions of 5HT in the brain.

Acknowledgements

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