Modulation of Brain Function during Executive Functioning in Autism with Tianeptine

Estia meeting 20/02/2017
Dr Rob Wichers
Clinical Research Worker / PhD Student
Content

• Background
• Serotonin
• Tianeptine
  – Response inhibition
  – Sustained attention
• Discussion
Autism Spectrum Disorder

- Repetitive behaviours -> linked to inhibition (Hill et al. 2011)
- Deficits in inhibition in autism (Hill et al. 2004)
- Inhibition related to serotonin: suppressing response (Crocket et al. 2010)

- ADHD and anxiety -> linked to sustained attention (Christakou et al. 2013; Forster et al. 2015)
- Deficits in sustained attention in autism (Sturm et al. 2004)
- Sustained attention related to serotonin: SSRI -> impair SAT (Riedel et al. 2005)
Serotonergic neurotransmission

\( \downarrow 5\text{-HT}_{2A} \) binding in anterior and posterior cingulate cortex, frontal and superior temporal cortex bilaterally, and in the left parietal cortex in Asperger’s syndrome (Murphy et al. 2006)

• Reduction in 5-TH Transporter (SERT) binding in the brain in ASD (Nakamura et al. 2010)
Serotonin in ASD

- 30% hyperserotonemia
- SLC6A4 (SERT gene) & ITGβ3 gene (associated with 5-HT)
- SSRIs increase brain serotonin
  - Controversial whether they are helpful
- Decreasing brain 5-HT with acute tryptophan depletion 'normalizes' atypical brain function during response inhibition in ASD (Daly et al. 2014)

---

2014)
Tianeptine

- Effective in the treatment of MDD and a spectrum of anxiety disorders.
- Minimal CNS, cardiovascular or body weight side effects
- No sexual dysfunction
- Superior to escitalopram in improving neurocognitive functions (Jeon et al 2014)
- Mode of action
  - u-opioid agonist
  - Restore normal neuroplasticity in limbic brain regions
  - Reverse stress-induced impairments in synaptic glutamate transmission
  - Previously thought of as a selective serotonin reuptake enhancer
Goal

Investigating the modulating role of tianeptine on inhibitory and sustained attention networks in ASD
Drug administration

1 hour

fMRI

How?

- Placebo or tianeptine (12.5 mg) conditions
- 8 days apart
- Administered via capsule

- Double-blind cross-over design
- Go No/Go task
- Sustained attention task
- Measuring Platelet Rich Plasma Serotonin (PRP-5HT) once prior to drug administration
How?

Response inhibition task

- Analysis: XBAM (non-parametric approach to minimize assumptions)

Sustained attention task
Sample

• 17 TD and ASD for GNG
• 19 TD and ASD for SAT
• No sign diff in age, IQ
• No sign diff in PRP 5HT
• Sign diff in obsessionality, anxiety and depression
Results

• Head movement
  – No significant difference between groups or drug status in both tasks

• Task performance
  – GNG: No significant effect of group, drug or group*drug interactions for the probability of inhibition or mean reaction time to Go or Oddball stimuli.
  – SAT: Mean reaction time was slower and intrasubject variability higher for ASD cases than for controls
    • No significant differences in performance after tianeptine!
Results Go/No-Go

Right Rostromedial Frontal Cortex

Cerebellum

(Wichers et al. under peer review, Brain)
Results Sustained Attention

(Wichers et al. under peer review, Neuropsychopharmacology)
Conclusion

- Modulation with tianeptine can ‘normalize’ brain function (and performance for SAT) during response inhibition and sustained attention in male adults with ASD
  - Suggests that tianeptine is a potential drug in targeting repetitive behaviours in ASD

- Tianeptine modulates brain activation in opposite directions in response inhibition and sustained attention mediated regions
  - Suggests that the neuropharmacological impact of tianeptine (and likely other antidepressants) is different in ASD
Future directions

• Open label study

• Or RCT?
Questions?