

Psilocybin causes a functional dissociation between attention and working memory tasks

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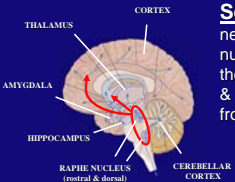
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Project Aims

- To explore the role of serotonin (5-HT) in attention & working memory in normal and “psychosis-like” human states.
- To tease out the relative contribution of the 5-HT_{1A/2A} receptor in any observed effects.

Introduction

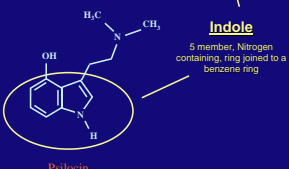
Serotonin (5-HT) - Serotonergic neurons originate in the Raphe nucleus in the brainstem. From here, the rostral neurons project into limbic & cortical areas (preferentially into frontal regions).



5-HT is an endogenous neurotransmitter involved in arousal (sleep/wake cycles), mood, appetite, temperature regulation, cognition & is also implicated in clinical psychosis.



Psilocybe mushrooms



Psilocybin is found in hallucinogenic *psilocybe* mushrooms. Psilocin, the active metabolite of psilocybin, is an agonist at 5-HT_{1A/2A} receptors & has a similar chemical structure to serotonin.

(↑ Cortical activity)
5-HT_{2A}

- Activation of 5-HT_{2A} receptor increases cortical activity. Activation of 5-HT_{1A} reduces the release of serotonin from the Raphe nuclei into the cortex.

(↓ 5-HT release)

Ketanserin - A selective antagonist at the 5-HT_{2A} receptor. Can be used to block psilocybin's 5-HT_{2A} mediated effects

Attention & Working memory

It is an advantage to be able to selectively direct & maintain **attention** while ignoring those events or objects deemed to be less relevant. **Multiple object tracking** is a task that measures sustained attention on a selected subset of targets amongst distractors (Pylyshyn & Storm, 1988).

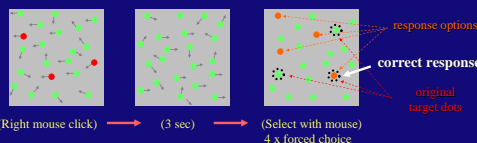
Working memory is a form of short-term memory enabling the storage & manipulation of information over short time periods (Baddeley, 1986). Attention & working memory are believed to be mutually dependent processes, subserved by similar regions of the frontal cortex (Courtney et al 1998; Culham et al 2001).

Psychosis - A number of clinical conditions (i.e. attention deficit disorder, autism, obsessive compulsive disorder & schizophrenia) are associated with abnormalities in attention and working memory. Future **drug development** depends on a comprehensive understanding of the pharmacology underlying these processes.

Methods

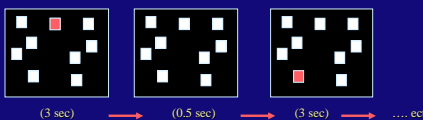
Multiple object tracking

- 20 randomly moving dots - subjects track subset of 2-8 target dots



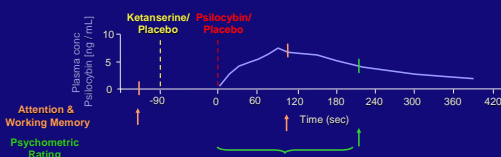
Spatial working memory

- Subjects have to reproduce a sequence of 2 - 9 spatial locations

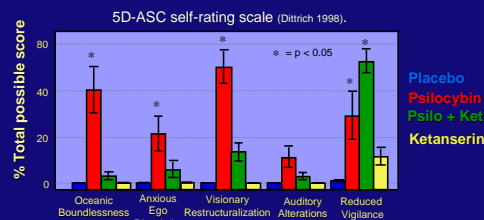


Experimental design

8 Healthy human subjects - 4 conditions: placebo; psilocybin (215 µg/kg); ketanserin (50mg/kg); psilocybin + ketanserin.

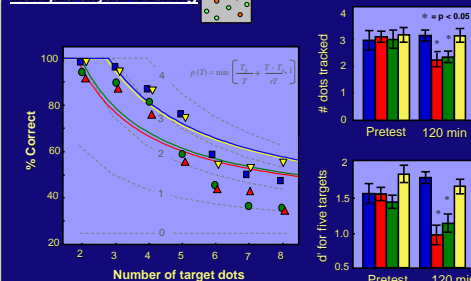


Subjective effects



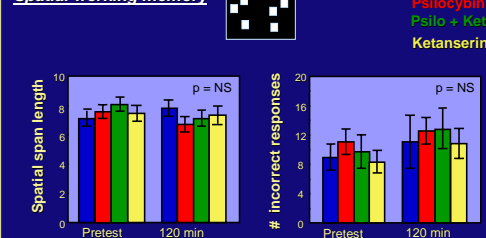
- Psilocybin produced subjective changes in conscious state.
- Ketanserin blocked most effects, except those relevant to attention & arousal.

Multiple object tracking

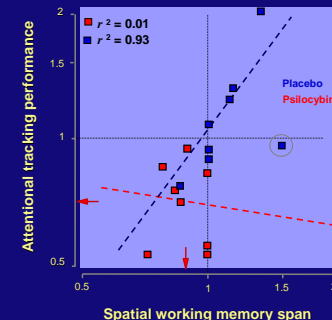


- Psilocybin reduced attentional tracking performance.
- Ketanserin pretreatment did not block this effect.

Spatial working memory



- Psilocybin alone (& in combination with ketanserin) had no effect on the total number of boxes remembered or the number incorrect boxes selected.



- Individual data provides further evidence of a functional dissociation with psilocybin having greater effect on attentional tracking performance.

Summary

- Hallucinogenic doses of the 5-HT_{1A/2A} agonist psilocybin impair multiple object tracking but not spatial working memory.
- Pre-treatment with the selective 5-HT_{2A} antagonist Ketanserin did not reduce this deficit.
- These findings suggest that it may be possible to tease apart the relationship between attention and working memory.
- Suggests involvement of the 5-HT_{1A} receptor in attention/arousal.

Future Directions

- Confirm the speculated involvement of the 5-HT_{1A} receptor with a selective 5-HT_{1A} agonist such as Buspirone.
- Investigate influence of impaired attention vs increased distractibility &/or impulsivity.

References

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 ** Note: More detailed account of this work will be published at: Carter, O., Burr, D., Pettigrew, J., Wallis, G., Hasler, F. & Vollenweider (in Press) Using psilocybin to investigate the relationship between attention, working memory and the Serotonin1A/2A receptors. *J Cog Neurosci*.