Basal forebrain volumes predict circuit specific functional sensitivity to muscarinic M_1 receptor antagonist biperiden on cognition.

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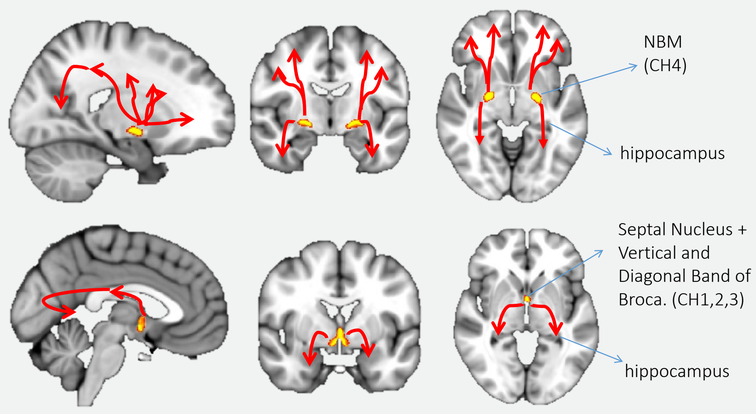
Background

- The basal forebrain (BF) cholinergic neurons provide the major source of cholinergic innervation to the cortex and hippocampus through two circuits A: Nucleus Basalis of Meynert (NBM) – cortical circuitry & B: Septal-Hippocampal circuitry. Cholinergic innervation of these circuits plays a key role in modulation of cognition through muscarinic M_1 receptors.
- BF cholinergic loss predicts faster cognitive deterioration in neurodegenerative disorders, including Alzheimer's Disease (AD).
- Relationship between BF nuclei volume and sensitivity to M_1 receptor antagonism is unknown and may underlie greater cognitive impairment in AD.
- BF volume may be an important biomarker to stratify patients that may be more sensitive to drugs targeting directly or indirectly the cholinergic system.

Brain Cholinergic Circuitry

A. Nucleus Basalis-Cortical circuitry (CH4-cortical)

B. Septal- Hippocampal Circuitry (CH1,2,3 –hippocampus)



A.1

Cognitive Domain	Behavioural Task
Executive Function	One Touch Stockings of Cambridge (OTS) Intra- Extra Dimensional Set Shifting (IED)
Working memory	Spatial Working Memory (SWM)
Attention and vigilance	Rapid Visual Processing (RVP)
Psychomotor speed	Reaction Time (RTI)

B.1

Cognitive Domain	Behavioural Task
Episodic memory (visual spatial)	Paired Associate Learning (PAL)
Episodic memory (verbal)	Verbal Recognition Memory (VRM)

Objective:

- To examine the cognitive deficit profile associated with M_1 antagonism by biperiden in healthy volunteers and a cognitive impaired group with psychotic disorders (appr. 1.5 SD lower).
- Determine whether BF volumes predict cognitive sensitivity to biperiden:
  - Determine relationship between CH4 volume and biperiden effect on cortically mediated cognitive domains (A/ A.1).
  - Determine whether CH1,2,3 volumes predict biperiden effects on septal –hippocampal mediated episodic memory (B/B.1).

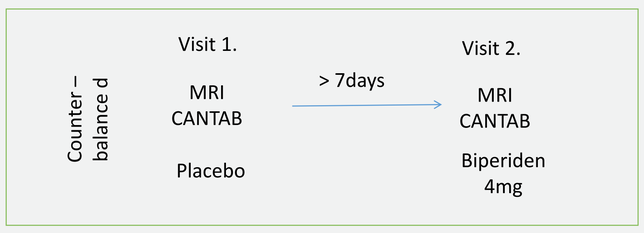
Methods

- Healthy volunteers and subjects diagnosed with a psychotic disorder were selected for the study.
- A randomised, placebo controlled, counterbalanced design was used in which all participants received placebo or 4 mg of M_1 antagonist biperiden with a minimal washout period of 7 days.
- BF volumes were quantified from T1-weighted structural MRI scans. All BF volumes measures were normalised for total brain segmentation volumes (test-retest reliability: ICC:0.97).
- Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to test cognitive sensitivity to biperiden.

Demographic Variables

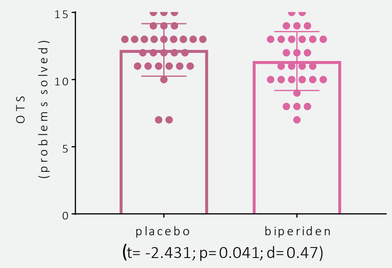
	Healthy volunteers	Cognitively impaired group (psychotic disorder)
N	30	29
Gender (M/F)	20/10	21/8
Age (yrs)	25.54(5.14)	21.56 (4.75)
IQ	108.07 (16.60)	101.10 (15.12)

Experimental Design



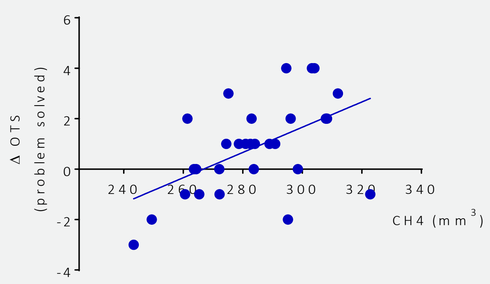
Results

Healthy volunteers



(t= -2.431; p=0.041; d=0.47)

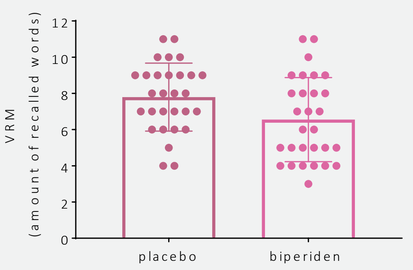
X: NBM (CH4) mm^3 → c′ → y: Δ OTS (executive function-planning)



Smaller CH4 BF volume predicted greater impairment in planning

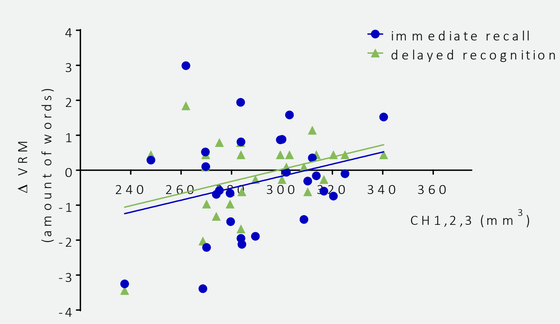
F=10.38, p=0.033, $R^{2=}$0.27

Cognitive impaired group (psychotic disorder)



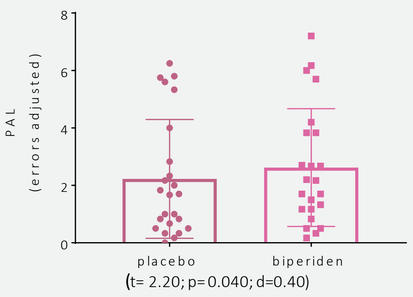
(t= 3.17; p=0.004; d=0.75)

X: Septal –Hippocampus (CH1,2,3) mm^3 → c′ → y: Δ VRM (episodic memory verbal)



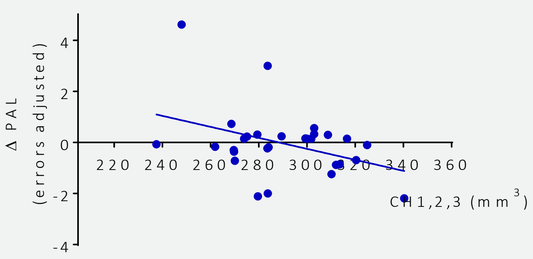
Smaller CH1,2,3 BF volume predicted greater impaired in immediate and delayed verbal episodic memory

F=5.91, p=0.023, $R^{2=}$0.18



(t= 2.20; p=0.040; d=0.40)

X: Septal –Hippocampus (CH1,2,3) Mm^3 → c′ → y: Δ PAL (episodic memory visual spatial)



Smaller CH1,2,3 BF volume predicted increased errors in cued recall.

F=4.68, p=0.040, $R^{2=}$0.14

Conclusions

- Planning and episodic memory (both verbal and visual) seemed more sensitive to M_1 modulation by biperiden than other cognitive domains.
- CH4 and CH1,2,3 nuclei volumes can predict circuitry specific cognitive responsivity to M_1 modulation.
- M_1 receptor modulation of executive functioning and episodic memory (both verbal and visual) may depend on the integrity of basal forebrain cholinergic neurons.
- BF nuclei volume may be a potential biomarker predictive of superior cognitive efficacy of drugs targeting the cholinergic system, including cholinesterase inhibitors, M_1 and M_4 receptor agonists and positive allosteric modulators.