Basal forebrain volumes predict circuit specific functional sensitivity to muscarinic M1 receptor antagonist biperiden on cognition.

Geer Bakker PhD1,2,3, Pradeep J. Nathan PhD 1,4,5, Alex Godwood MSC1, Claudia Vingerhoets PhD2,3, Jan Booj PhD MD2, Oswald Bloemen PhD MD4,6, Matthan W. Caan PhD2, and Therese van Amelsvoort PhD MD1,2,3.

1Heptares Therapeutics, Cambridge, United Kingdom, 2Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location AMC, Netherlands, 3Department of Psychiatry and Neuropsychology, Maastricht University, Netherlands, 4Brain Mapping Unit, Department of Psychiatry, University of Cambridge, United Kingdom, 5School of Psychological Sciences, Monash University, Melbourne, Australia, 6GZC Central Center for Mental Health Care Innova, Netherlands.

WhileNotYetValid

**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 M1 receptors.
- BF cholinergic loss predicts faster cognitive deterioration in neurodegenerative disorders, including Alzheimer’s Disease (AD).
- BF volume may be an important biomarker to stratify patients that may be more sensitive to drugs targeting the cholinergic system.

**Methods**

- **Objective**
  - To examine the cognitive deficit profile associated with M1 antagonism by biperiden in healthy volunteers and a cognitive impaired group with psychiatric 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/4.3).
    - Determine whether CH1,2,3 volumes predict biperiden effects on septal–hippocampal mediated episodic memory (B/B.1).

- **Experimental Design**
  - Randomised, placebo controlled, counterbalanced design was used in which all participants received placebo or 4 mg of M1 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).

- **Background**
  - 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 M1 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.

- **Healthy volunteers**
  - 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)

- **Cognitive impaired group**
  - Gender (M/F) 10/20 8/21
  - Age (yrs) 25.54(5.14) 21.56 (4.75)
  - IQ 108.07 (16.60) 101.10 (15.12)

- **Results**
  - Planning and episodic memory (both verbal and visual) seemed more sensitive to M1 modulation by biperiden than other cognitive domains.
  - CH1,2,3 nuclei volumes may predict circuit specific cognitive response to M1 modulation.
  - CH4 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, M1 and M2 receptor agonists and positive allosteric modulators.

- **Conclusions**

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