Magnetoencephalography (MEG) in a First-in-Human Trial to Demonstrate the Functional Consequences of Target Engagement by DT-101, a Novel AMPA Receptor Positive Allosteric Modulator

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- **DT-101, a novel AMPA receptor positive allosteric modulator (PAM), produced dose-related modulation of human brain activity in a First-in-Human (FiH) MEG study**
- **Across complementary paradigms probing the cortical excitation–inhibition balance, DT-101 demonstrated effects on oscillatory activity consistent with AMPA receptor potentiation**
- **MEG can be used as a non-invasive technique for measuring functional pharmacodynamic brain effects with high sensitivity, and for informing dosing regimen for Phase 2 development**
- **First use of MEG in a FiH clinical trial, and to our knowledge, the first report of electrophysiological responses in humans to an AMPAR PAM**

BACKGROUND

What is MEG?

Magnetoencephalography (MEG) is a non-invasive technique that measures magnetic fields generated by neuronal electrical activity.

Signals arise primarily from postsynaptic currents in cortical pyramidal neurons and provide a direct measure of brain activity with millisecond temporal resolution. Measurable MEG signals represent synchronous activity from tens of thousands of aligned neurons.

MEG is well suited to detect pharmacological modulation of cortical oscillations, particularly for mechanisms affecting high frequency oscillations

MEG vs electroencephalography (EEG)

MEG and EEG both measure neuronal activity with millisecond temporal resolution but differ in key properties relevant to pharmacodynamic studies

- **Source localisation:** Magnetic fields, as measured with MEG, are not distorted as they pass through tissues, unlike electrical currents measured with EEG. This enables accurate localisation of neuronal sources with MEG
- **High-frequency sensitivity:** MEG has superior signal-to-noise ratio and artefacts can be removed more accurately with MEG than EEG. This is particularly relevant for beta/gamma oscillations (>20 Hz) where muscle artefacts may overwhelm the true EEG signal
- **Availability:** MEG systems are not portable and require specialised magnetically shielded rooms – this makes MEG use in multi-site later stage clinical trials very challenging. MEG is the most sensitive measure to define pharmacodynamic responses – but EEG may then be sufficient to confirm responses in larger populations

MEG in FiH Study

- Integrating MEG into a FiH study enables assessment of drug effects on human brain function at the earliest clinical stage
- A key challenge in drug development for psychiatric disorders is the lack of functional pharmacodynamic biomarkers
- In this FiH clinical trial, MEG was incorporated into repeat-dose and single-dose crossover components to assess the effects of DT-101 on brain activity
- The crossover design described here enabled within-participant comparisons across dose levels, increasing sensitivity to detect pharmacodynamic effects.
- DT-101 is an AMPA receptor PAM and is expected to modulate cortical excitation–inhibition balance. The frequency and amplitude characteristics of cortical oscillations provide markers of this balance – with the Visual Gamma and Auditory Steady State Response being well established paradigms for generating gamma oscillations in sensory cortex

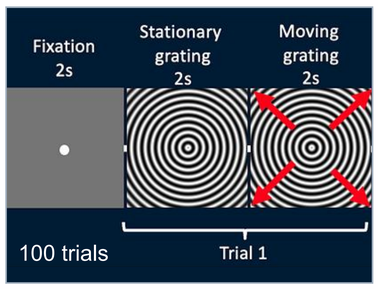
STUDY DESIGN

MEG incorporated into DT-101 FiH Study Design

- Aim: To assess effects of DT-101 on cortical oscillatory activity
- Double-blinded, 3-way crossover added into FiH, along with single and multiple ascending dose parts
- Single doses of placebo, 9 mg and 18 mg DT-101 in randomised order
- Treatment visits separated by washout period
- N = 19 healthy volunteers
- MEG recorded at Tmax (~60 min scan)
- Scans at similar time of day to mitigate against time-of-day effects
- Structural MRIs collected to enable source localisation

A. Visual Gamma

- High-contrast visual gratings elicit sustained increases in gamma frequency (>30 Hz) oscillations in early visual cortex
- Visual gamma oscillation characteristics are stable within individuals over several weeks – suitable for pharmacodynamic studies [1]
- Gamma oscillations reflect local cortical excitation–inhibition balance [2]
- Sensitive to AMPAR modulation – demonstrated with MEG and AMPA antagonist perampanel [3]



Visual Gamma: baseline fixation period with 50% luminance grey background, followed by stationary then moving annular gratings (100% contrast, 2.3 cpd).

B. Auditory Steady State Response (ASSR) at 40 Hz

- 40 Hz blocks of auditory tones/clicks entrain cortical activity
- Well established from EEG research – biomarker of sensory processing that is disrupted in several psychiatric disorders, particularly studied in schizophrenia
- ASSRs reflect local cortical excitation–inhibition balance [4]

C. Resting State

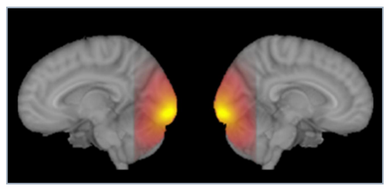
- Eyes-open recording of spontaneous brain activity (10 min)
- Reflects global network dynamics of the brain at rest
- Sensitive to AMPAR modulation – demonstrated with MEG and AMPA antagonist perampanel [5]

RESULTS

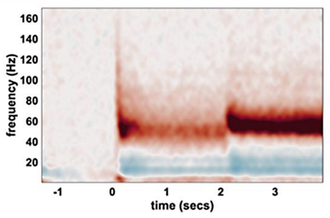
DT-101 Modulates Cortical Oscillatory Activity in Healthy Adults

A. Visual Gamma: Dose-dependent increases in oscillatory activity

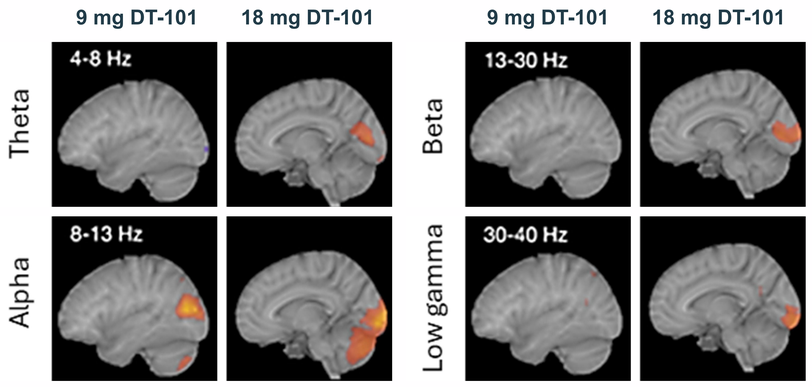
- DT-101 dose-related increases in oscillatory activity across several frequency bands
- Consistent with shift in cortical excitation–inhibition balance [2,3]



MEG data co-registered to each individual's MRI. Beamformer reconstruction identified peak voxel for each individual, which was always in early visual cortex.



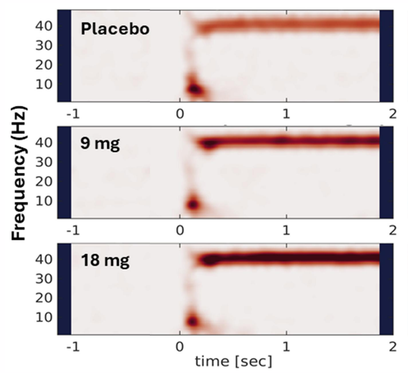
Virtual sensor time–frequency plots at peak voxels showed expected neural responses - with gamma oscillations sustained for the duration of grating presentation. The frequency and amplitude of gamma oscillations is increased to moving gratings (2-4 s).



Orange colours show areas of increased activity to DT-101 vs placebo (Bayes factor >3) DT-101 dose-dependently increased activity in several frequency bands, particularly alpha to gamma.

B. ASSR (40 Hz): Increased evoked power with DT-101

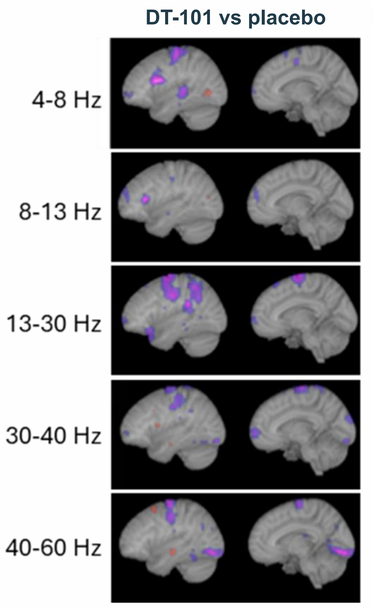
- DT-101, 18 mg increased evoked power vs placebo (right hemisphere)
- Trend towards increased phase coherence



MEG data co-registered to each individual's MRI and ASSR localised using eLORETA.

In the right hemisphere, DT-101 18 mg gave stronger evoked power than placebo ($p = 0.04$, FDR corrected). A trend for enhanced inter trial phase coherence ($p = 0.03$ uncorrected) with 18 mg DT-101 was also observed.

No significant differences were found with DT-101 9 mg, or in the left hemisphere. Hemispheric differences in ASSR are widely reported, with ASSR often stronger in right hemisphere.



C. Resting State: DT-101 modulates resting activity

- DT-101 associated changes were mainly reduced activity across several frequency bands
- High consistency in the areas of 9 mg and 18 mg DT-101 associated changes in resting activity
- Direction (decreased activity) broadly opposite to the AMPAR antagonist perampanel [5]

Purple colours show areas of decreased activity to DT-101 vs placebo (Bayes factor >3). DT-101 primarily decreased activity across frequency bands

CONCLUSION

- **Convergent effects of DT-101 across paradigms demonstrate target engagement at the level of cortical circuits**
- **Results support AMPAR potentiation as a mechanism to modulate excitation–inhibition balance in humans**
- **Modulation of excitation-inhibition balance in patients with major depressive disorder expected to drive synaptic plasticity**
- **Data helped inform dose selection for Phase 2 trials in patients with major depressive disorder**

Disclosures

JBS, SEW, JRA are full-time employees of Draig Therapeutics; RH, NJ, NAH, KDS have no financial disclosures; this study was funded by the Wellcome Trust.

Contact us at info@draigtherapeutics.com

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