

Charles H. Large, PhD.

Kaar SJ, Nottage J, Sanchez VA, Sajjala A, Sharman AM, van den Berg F, Alvaro G, Hutchison JB, Hirner M, Anderer P, Lagler M, Friedrich S, Howes OD, Umbricht D.

SIRS Pharma Pipeline

April 2022

Disclosures

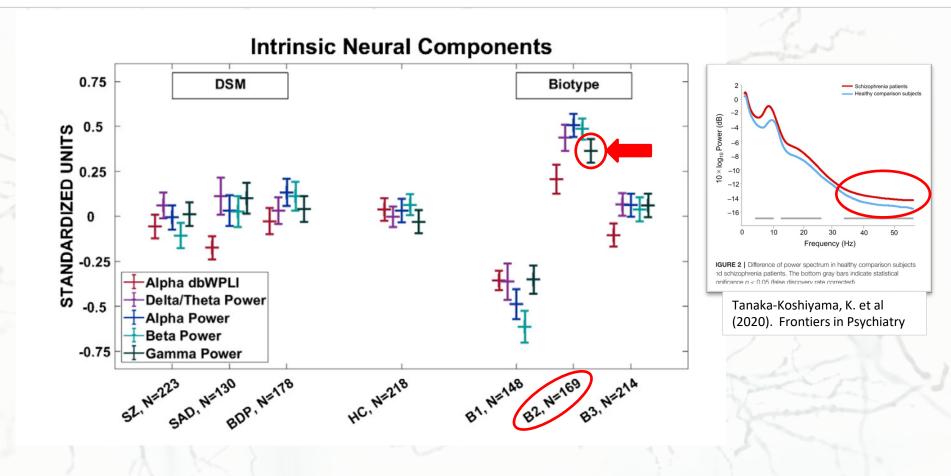


Abnormalities in Gamma Oscillations in schizophrenia point to dysfunction of Parvalbumin-Positive Interneurons (PVINs)

- Increased resting state gamma power
- Decreased power and phase locking to 40 Hz auditory stimuli (ASSR)
- Decreased evoked power and phase locking to auditory stimuli 50 to 100 ms post-stimulus (*Early Auditory Gamma Band Response*)

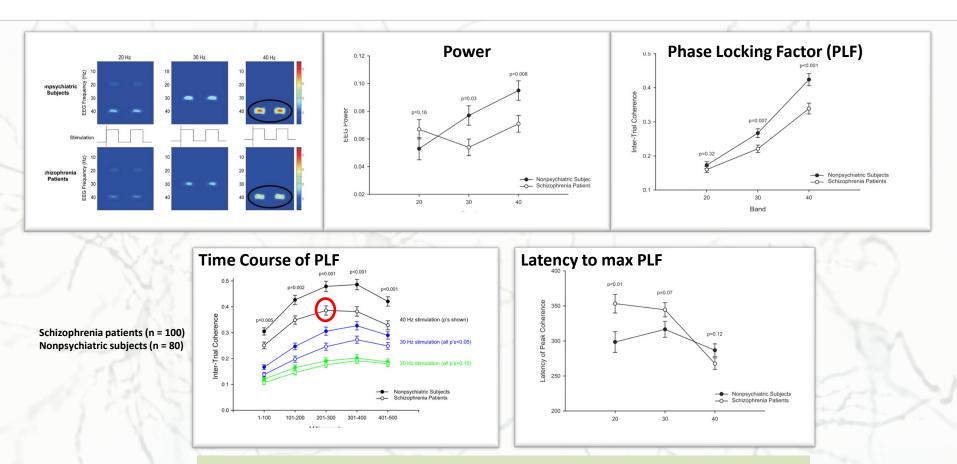
Increased resting state gamma power

B-SNIP Consortium



Thomas, O., Parker, D., Trotti, R., McDowell, J., Gershon, E., Sweeney, J., Keshavan, M. S., Keedy, S. K., Ivleva, E., Tamminga, C. A., Pearlson, G. D., & Clementz, B. A. (2019). Biomarkers in Neuropsychiatry, 1, 100002.

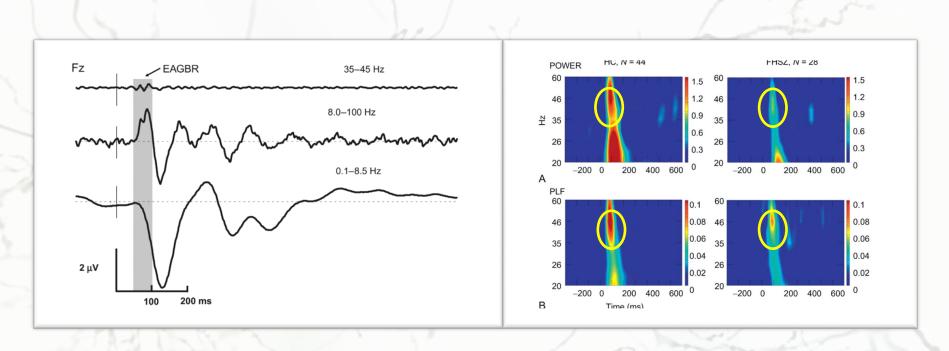
Abnormal power and Phase Locking Factor (PLF) in the Auditory Steady State Response (ASSR)



Represents the resonance of cortical circuits at the frequency of the driving stimulus

Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma Band Oscillations Reveal Neural Network Cortical Coherence Dysfunction in Schizophrenia Patients.

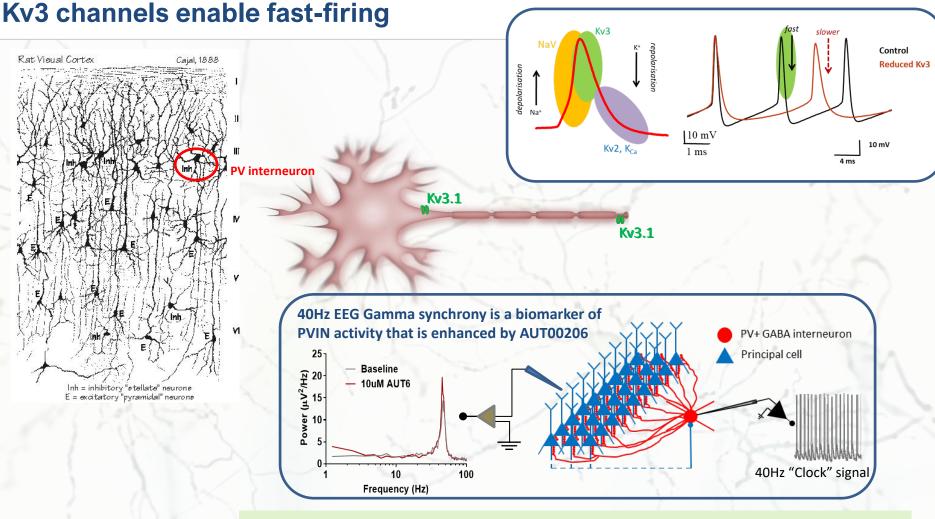
Early Auditory Gamma Band Response (EAGBR) abnormalities in schizophrenia



Represents the stimulus-evoked primary sensory response to an auditory stimulus

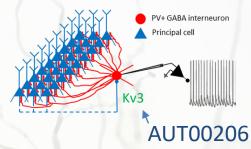
Taylor, G. W., McCarley, R. W., & Salisbury, D. F. (2013). Early auditory gamma band response abnormalities in first hospitalized schizophrenia. *Supplements to Clinical Neurophysiology*, *62*, 131–145.

Parvalbumin interneurons (PVINs) are critical components of cortical circuits underpinning cognition and sensory integration

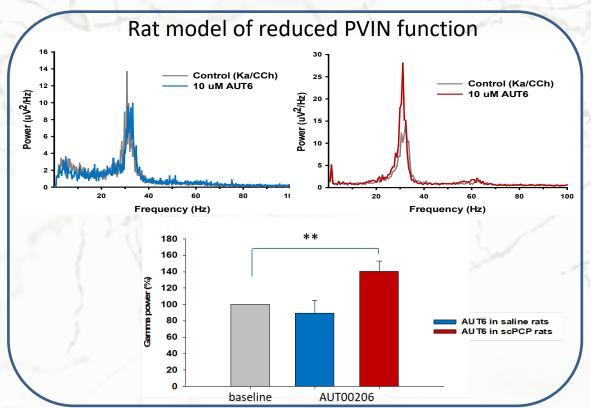


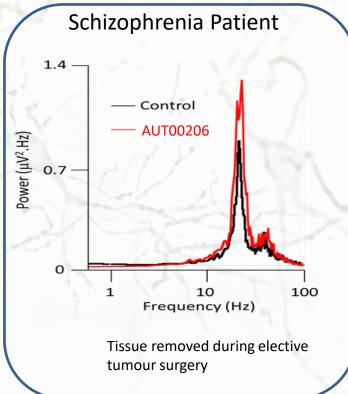
Reduced firing of PVIN leads to loss of synchronisation of cortical networks leading to a broad range of cognitive and sensory symptoms observed in schizophrenia

AUT00206 increases gamma power *in vitro* in brain slices obtained from rats and a patient with schizophrenia



Gamma oscillations were induced by the application of kainic acid and carbachol





AUT00206 improves real-world auditory processing in patients with schizophrenia, also relevant to FXS

AUT00206 improved Word-in-Noise performance in subjects with Schizophrenia

Word-in-Noise (WIN):

+ We observed a significant improvement in WIN performance in AUT00206-treated patients vs placebo when words were presented at 40dB HL (a difficult listening situation):

| SNR 50 post-hoc analysis | BL | Day 1 | Day 5 | Day 21 | CfB D21 |
|--------------------------|------|-------|-------|--------|---------|
| AUT00206 | 9.76 | 8.16 | 7.76 | 7.20 | -2.56dB |
| Placebo | 9.60 | 9.60 | 10.8 | 10.4 | +0.8dB |

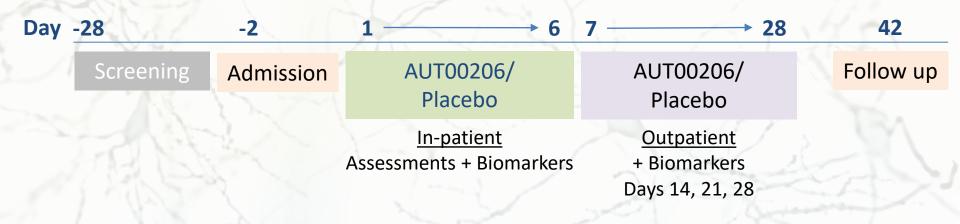
- + There was a trend for improvement in the AUT00206 group on D5 (p=0.085) and a significant improvement by Day 21 (p = 0.016)
- + 70% of the AUT00206 subjects showed an improvement in WIN performance by D21, with only 25% showing an improvement on placebo
- + A 2.5dB improvement in signal-to-noise is considered highly clinically relevant



Based on these clinical and preclinical data, we hypothesised that treatment with AUT00206 would improve measures of the Early Auditory Gamma Response in patients with schizophrenia

A randomised, double-blind, placebo-controlled study of the safety, pharmacokinetics and exploratory pharmacodynamics of AUT00206 in patients with recently diagnosed schizophrenia

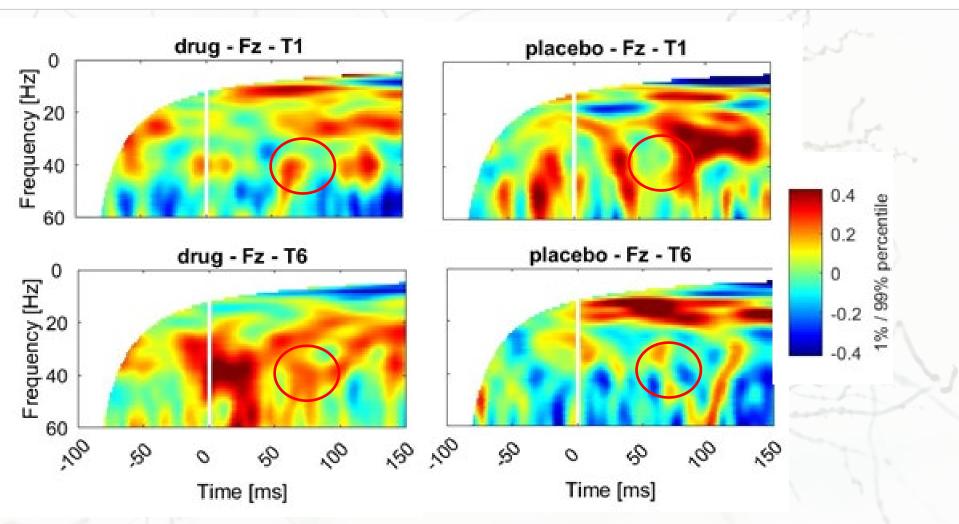
- 24 male subjects, aged 18 50 years
- Schizophrenia first diagnosis within last 5 years
- Taking 1 or 2 antipsychotics (excluding clozapine)
- Baseline PANSS: ~78
- 2:1 randomisation (AUT00206 800mg bid vs placebo)



Clinical and exploratory biomarker assessments were completed by all subjects. Resting state and induced and evoked gamma oscillations were investigated in resting state EEG (eyes closed), 40 Hz auditory steady state response (ASSR), and in response to standard stimuli in an auditory oddball paradigm at baseline. Tests were conducted at baseline, day 1, and three further days over a 28-day period. Absolute power and phase locking factor (PLF) at midline electrodes and latencies to reach their peaks were the key dependent variables

Early Auditory Gamma Response:

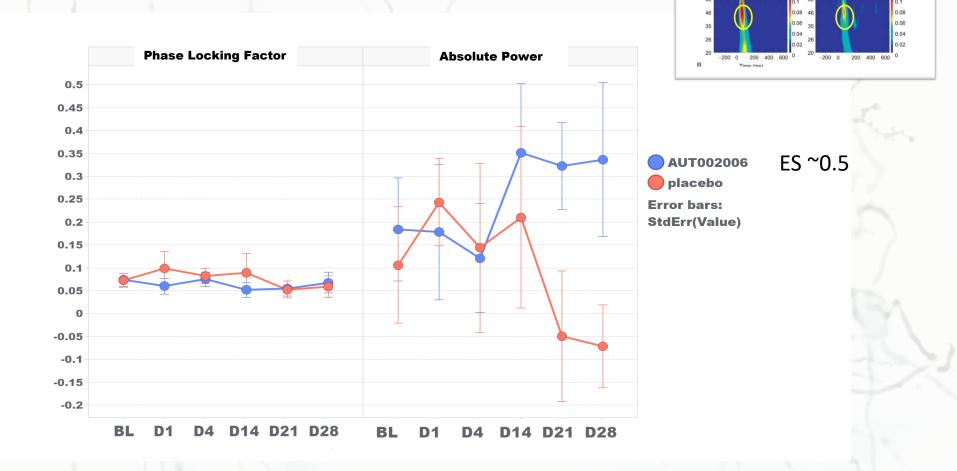
Effect on Power but not on PLF



Frequency-time plots show the gamma response ~50ms (EAGR) following auditory stimuli as part of a P300 paradigm. The EAGR is increased in the AUT00206 group at Day 28 (n=16), but not in the placebo group (n=8)

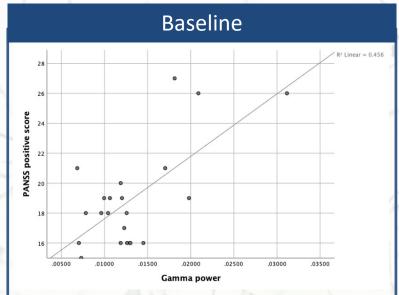
Early Auditory Gamma Band Response:

Effect on Power but not on PLF



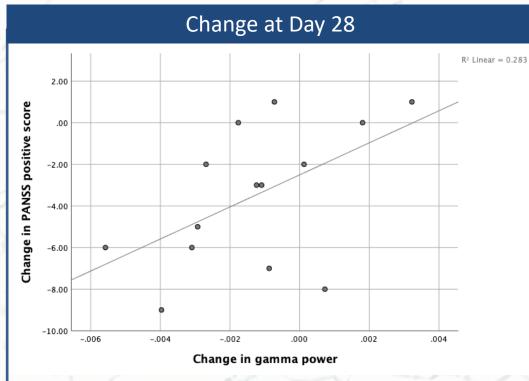
Fz Electrode. Power changes compared to pre-stimulus baseline shown in dB (10*log10(Data/pre-stimulus baseline). Pre-stimulus baseline -75 to 0 ms pre-stimulus.

Correlation between resting state Gamma power and PANSS positive score



Positive correlation between frontal resting gamma power (μ V/Hz) with baseline PANSS positive symptom severity score (n=22, r = 0.675 p < 0.001)





Change in PANSS positive score from baseline to day 28 in the AUT00206 group was correlated with change in frontal resting gamma power (μ V/Hz) (n = 14, r = 0.532, p = 0.05)

A change correlation was not observed in the placebo group, but this may be in part due to the low number of subject (n=8)

Summary and Conclusions

| Paradigm | Pov | ver | PLF | | Latency to Max Power | | Latency to Max PLF | |
|-------------------------------------|----------|----------|----------|-----|----------------------|----------|--------------------|----------|
| | Schiz | AUT | Schiz | AUT | Schiz | AUT | Schiz | AUT |
| Resting State | ↑ | \ | | | | | | |
| 40-Hz ASSR | \ | = | \ | = | ? | \ | =↓ | \ |
| P300 oddball | = | = | = | = | | | | |
| Early Auditory Gamma Response | \ | ↑ | \ | = | | | | |

= No difference between HC and patients or No effect of AUT00206

- Treatment with AUT00206 improved measures of gamma oscillations in schizophrenia
- Consistent with positive modulation of Kv3 channels enhancing the function of PVINs
- ❖ A larger study will be required to confirm these findings and explore efficacy versus clinical symptoms.
- These data suggest the utility of AUT00206 in the treatment of disorders of PVIN dysfunction, including schizophrenia and Fragile X Syndrome

Acknowledgements



Howes O
Kaar S
Angelescu I
Nour M
Reis Marques T
Nottage J



Sanchez V

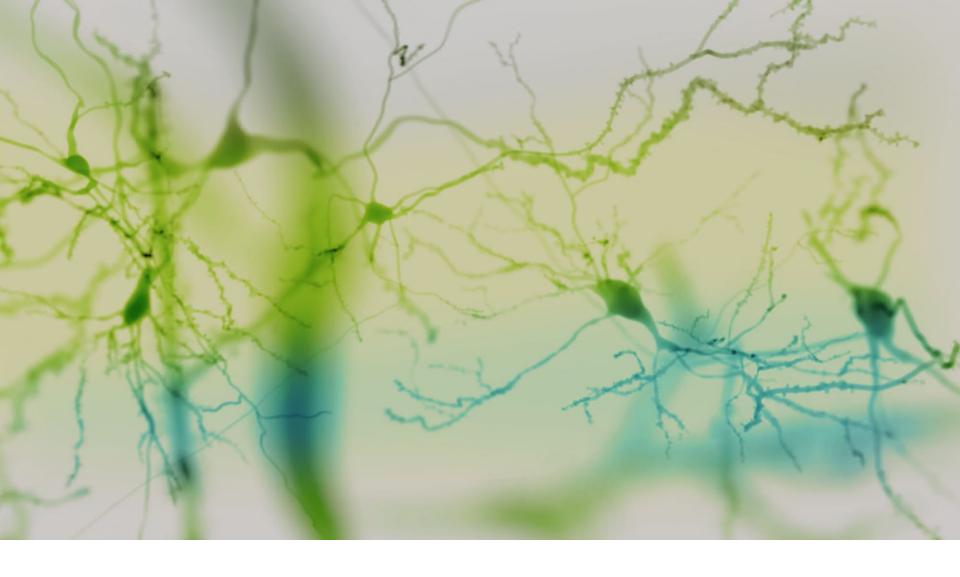


Hirner M Anderer P Lagler M Friedrich S



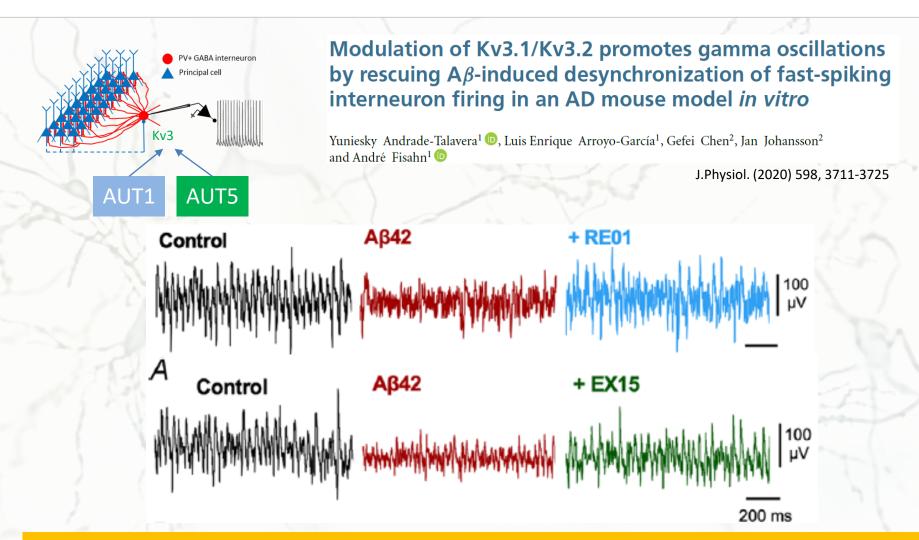
Umbricht D Sajjala A Sharman AM Alvaro G Hutchison JB

Thank You for your attention!



Additional Information

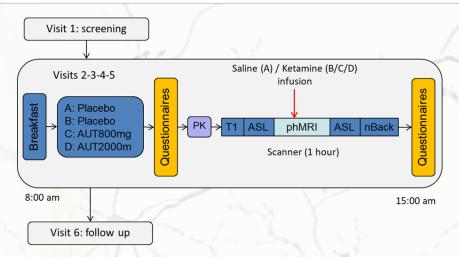
Kv3 Positive Modulators increase gamma power *in vitro* in brain slices under conditions of PVIN deficit

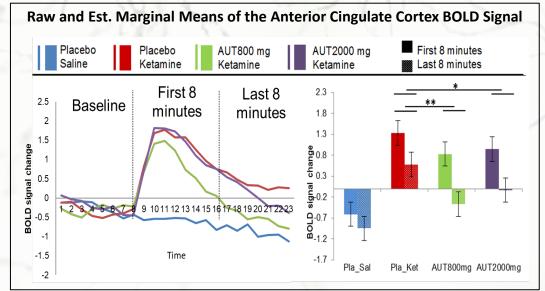


"...results on the cellular mechanisms underlying the actions of EX15 (AUT5) and RE01 (AUT1) on neuronal network dynamics, namely AP firing synchronisation, firing frequency, and preferred phase-angle firing in relation to ongoing gamma oscillations, suggest that these compounds may have pro-cognitive potential."

AUT00206 demonstrates CNS target engagement in healthy volunteers

Ketamine Challenge in healthy volunteers



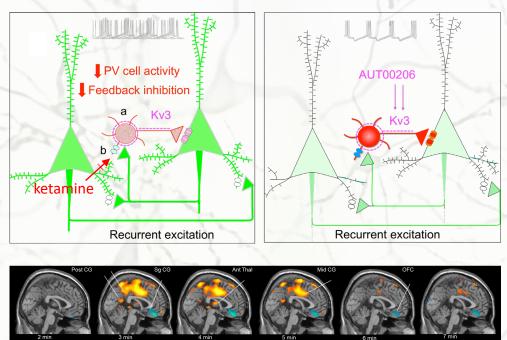


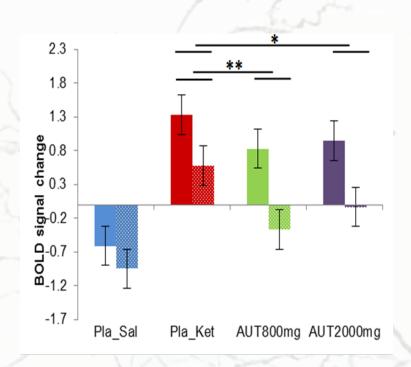
Headline Results

- Primary outcome measure: AUT00206 significantly reduced the ketamine-induced BOLD response in the primary ROI, the anterior cingulate:
 - Main effect of treatment p<0.001
 - 800mg: p=0.003, 2000mg: p=0.04
- N-back task: AUT00206 significantly prevented the deactivation of the thalamus induced by ketamine during the N-back task (p<0.05) and the ketamineinduced increase in response bias (p<0.05)
- Resting state connectivity: AUT00206 significantly prevented ketamine-induced disruption of defaultmode network and salience network connectivity.

AUT00206 reduced the BOLD response induced by ketamine in humans (and rodents)

Ketamine-induced BOLD response in anterior cingulate cortex in healthy volunteers





Deakin et al. 2019, SIRS

AUT00206 improves auditory processing in patients with schizophrenia, also relevant to FXS

AUT00206 increased the amplitude of auditory Mismatch Negativity in subjects with Schizophrenia

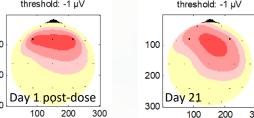
Mismatch Negativity (MNN):

- + MMN responses were evoked using auditory oddball stimuli (pitch and duration deviants)
- + Patients with schizophrenia typically show a reduced MMN amplitude:

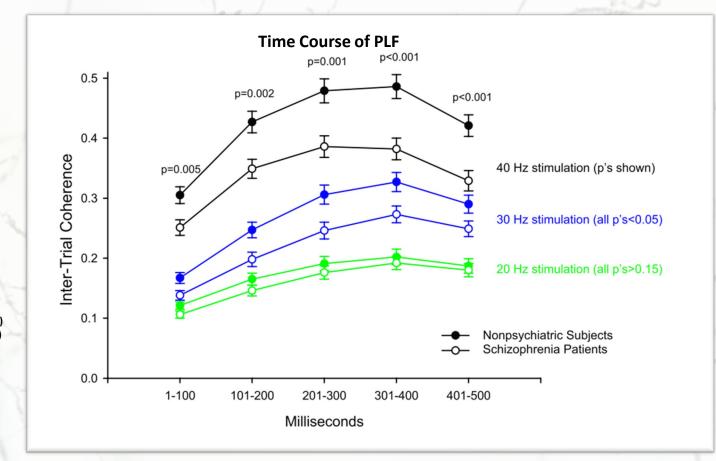
| Fz electrode | AUT00206 change from baseline (μV) | Placebo change from baseline (μV) |
|--------------|---------------------------------------|--------------------------------------|
| Day 1 | -0.57 | +0.80 |
| Day 4-6 | -0.66 | -0.59 |
| Day 14 | -0.20 | +0.04 |
| Day 21 | -0.49 | +1.28 |
| Day 28 | -0.62 | +0.15 |

- + AUT00206 produced a numerical improvement in MMN amplitude from Day1 to day 28
- + Placebo produced a variable effect, with no consistent improvement in MMN
- + Post-hoc analysis showed that statistical separation from placebo in responders (subjects showing a >1μV increase in MMN amplitude over frontal electrodes: threshold: -1 μV threshold: -1 μV

Relevance to sensory processing impairment in FXS



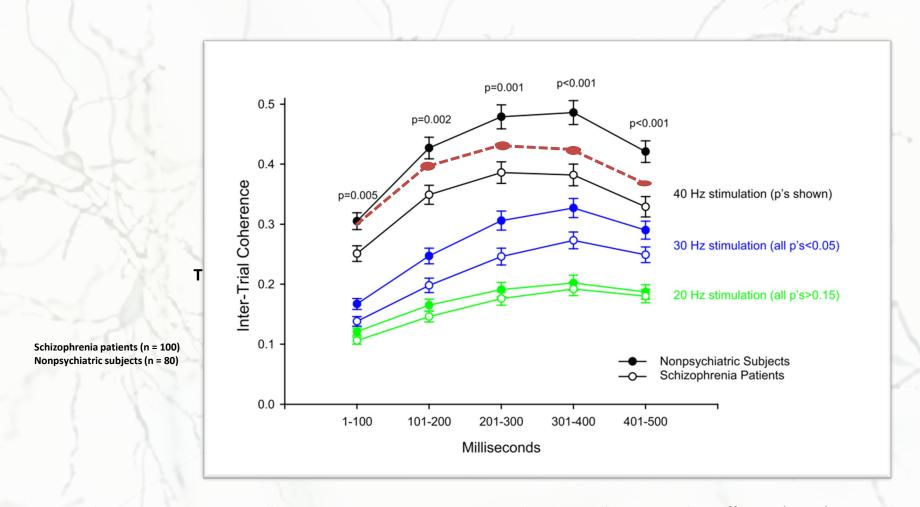
Abnormal power and Phase Locking Factor (PLF) in the Auditory Steady State Response (ASSR)



Schizophrenia patients (n = 100) Nonpsychiatric subjects (n = 80)

Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma Band Oscillations Reveal Neural Network Cortical Coherence Dysfunction in Schizophrenia Patients.

Abnormal power and Phase Locking Factor (PLF) in the Auditory Steady State Response (ASSR)



Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma Band Oscillations Reveal Neural Network Cortical Coherence Dysfunction in Schizophrenia Patients.

Increased resting state gamma power

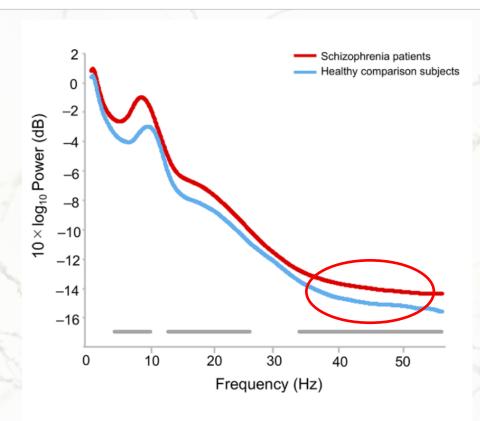
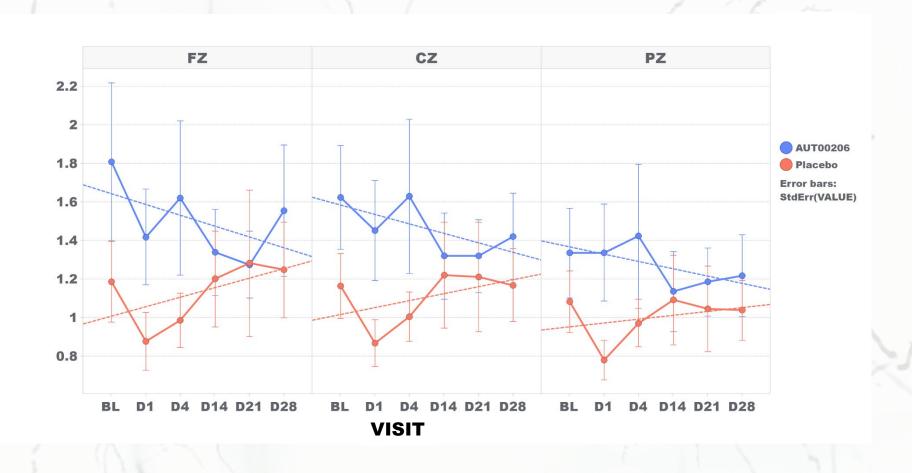


FIGURE 2 | Difference of power spectrum in healthy comparison subjects and schizophrenia patients. The bottom gray bars indicate statistical significance p < 0.05 (false discovery rate corrected).

Tanaka-Koshiyama, K., Koshiyama, D., Miyakoshi, M., Joshi, Y. B., Molina, J. L., Sprock, J., Braff, D. L., & Light, G. A. (2020). Abnormal Spontaneous Gamma Power Is Associated With Verbal Learning and Memory Dysfunction in Schizophrenia. Frontiers in Psychiatry, 11.

Trend for reduction of resting state gamma power



40 Hz ASSR: No effect on power but on latencies to Maximum of Evoked and Induced Power and Phase Locking Factor

