<u>Behavior and LFP analyses in an Alzheimer's disease rat model (human ApoE4 KI) - Nick</u>

Rat 381's code folder has all the required functions and codes to create the data struct and do analyses.

Behavior data analyses:

1. Head scans on the circle track
2. Object-place-association task

Electrophysiology analyses:

Rat 381 – ApoE4 Alzheimer's

Rat 326Z (and potentially more WT rats will be added soon) – Wild-Type

Based on Kemere et al. 2013

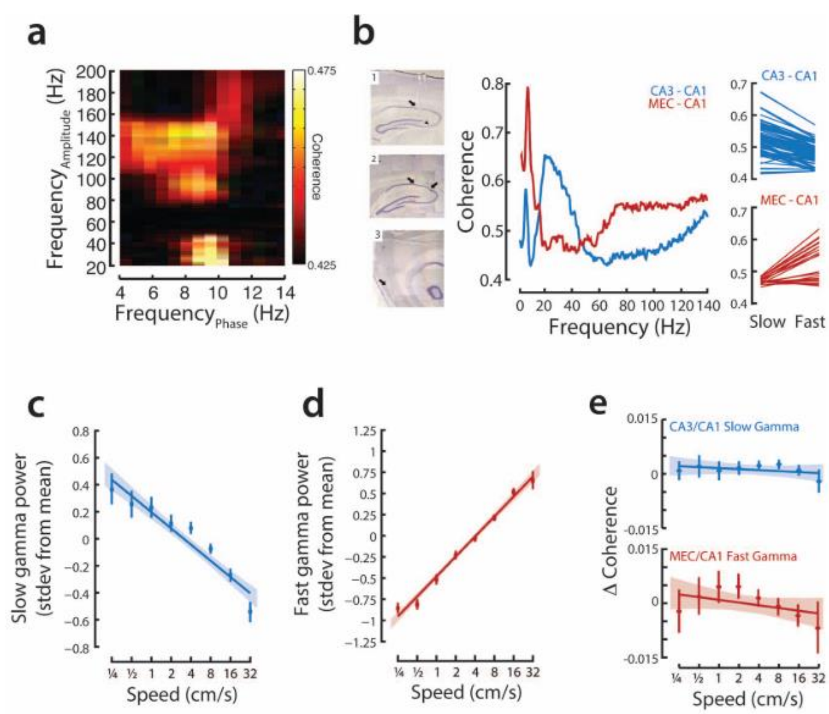

Figure 3. Slow and fast gamma oscillations in CA1 are modulated by speed. a, There are two distinct gamma bands in CA1. Shown is an example cross-frequency coherence plot from a novel run session showing that gamma power (y-axis) is modulated by the theta phase (x-axis). **b,** CA1 is more coherent with CA3 in slow gamma range and more coherent with layer 3 of the medial entorhinal cortex in fast gamma range. Coronal and sagittal sections show electrolytic lesions in recording sites from CA3-CA1 recordings (1) and CA1-MEC recordings (2 and 3). Coherence plots for a representative pair of CA3-CA1 (blue) and MEC-CA1 (red) recordings. There is a pronounced peak in the slow gamma range (25–55 Hz) of CA3-CA1 coherence, and a noticeable increase in the fast gamma range (~70–130 Hz) of MEC-CA1 coherence. Slow gamma coherence was greater than fast gamma coherence for 80 out of 85 pairs of CA3-CA1 recordings (z-test for proportions, $p<10^{-5}$; $n=5$ animals), while fast gamma coherence was greater than slow gamma coherence for 19 out of 22 pairs of MEC-CA1 recordings (z-test for proportions, $p<10^{-5}$; $n=3$ animals). **c,** Population data showing normalized power of slow gamma vs. speed. Points represent binned means with standard error using logarithmically spaced bin centers; line represents linear regression of underlying data with 95% confidence intervals. **d,** Population data showing normalized power of fast gamma oscillations vs. speed. Points and line as in (**c**). **e,** There are very small changes in coherence as a function of behavioral state. **(top)** Average change in coherence between CA3 and CA1 in the slow gamma frequency band ($n=4$ animals) as a function of speed (average slow gamma coherence between CA3 and CA1 = 0.51). Coherence was measured for all tetrode pairs. For each pair, the deviation from the mean value in each 500 ms time window was calculated. Each time window was associated with the appropriate speed. Shown are the regression of speed and change in coherence with 95% C.I. and binned histograms as in (**c**). Change in coherence vs. speed is not significantly different from zero (bootstrap test). **(bottom)** Average change in coherence between MEC and CA1 in the fast gamma frequency band ($n=3$ animals, average mean fast gamma coherence between MEC and CA1 = 0.49). Change in coherence vs. speed is not significantly different from zero (bootstrap test).
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Some important excerpts relevant to the analyses:

In particular, we noted that there were changes in power in three physiologically relevant frequency ranges (Figure 2), two associated with CA3 drive: slow gamma (20–55 Hz) and ripple (150–250 Hz) oscillations, and one which has been associated with EC drive: fast gamma oscillations (,65–140 Hz).

Found that the normalized power of slow gamma was largest when the animal was still and decreased smoothly with the log of movement speed.

Find that the correlation between speed and gamma power is largest when the speed and gamma power are measured at the same time (lag = 0) and decreases rapidly with increasing lags.

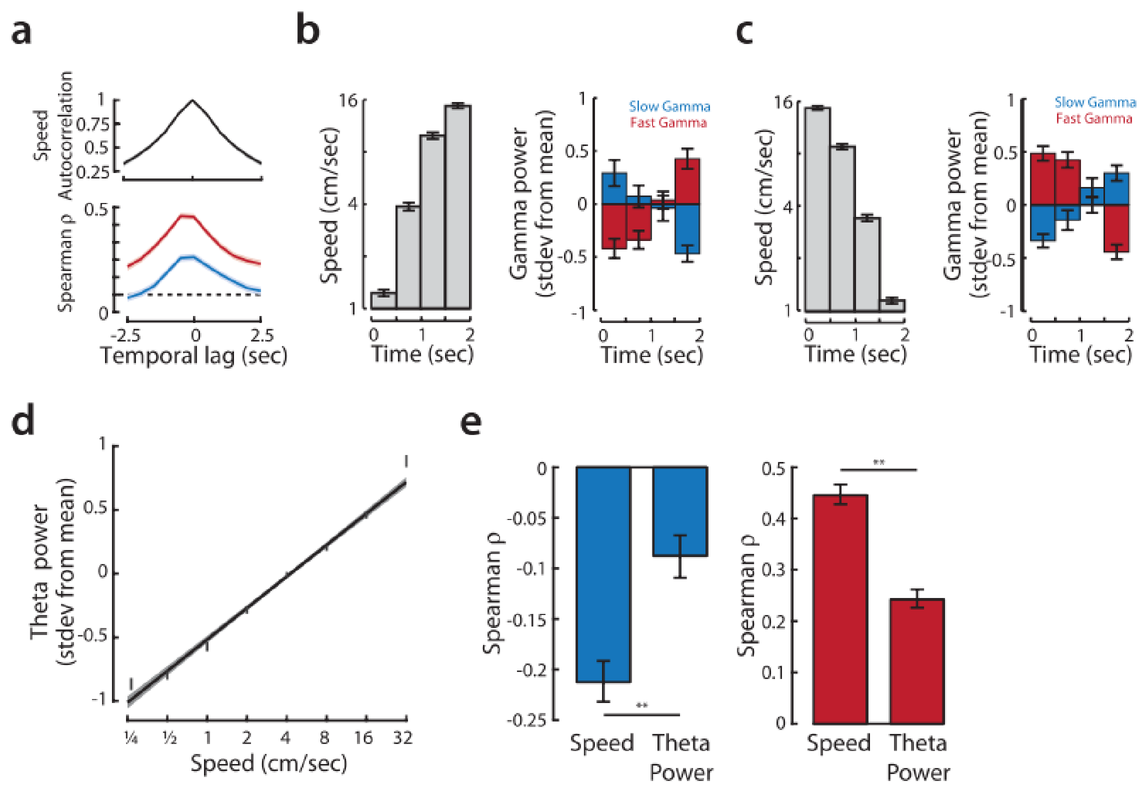
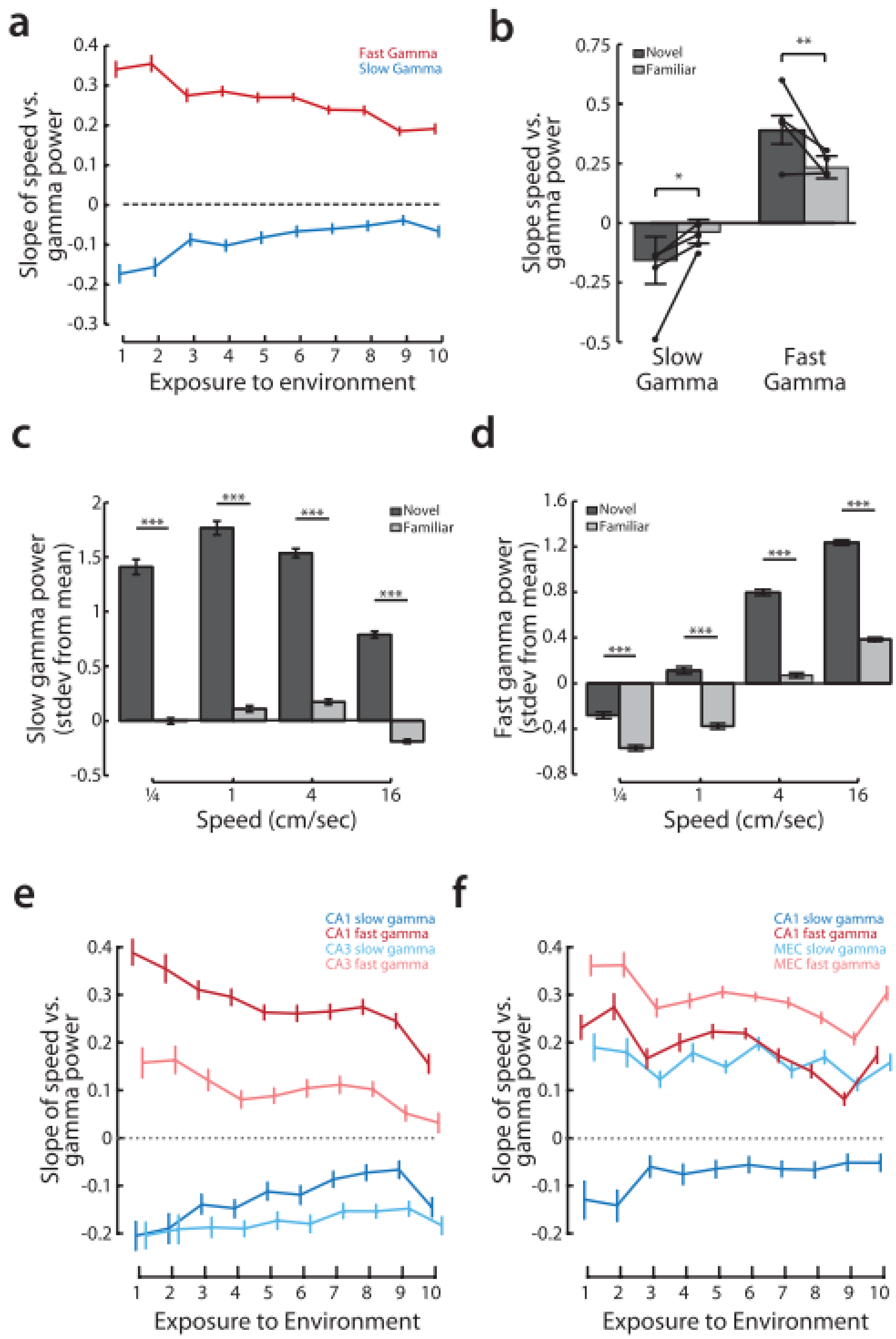


Figure 4. Modulation of gamma oscillations by speed in CA1 is rapid. a, (top) The autocorrelation of speed (shown with bootstrap 95% confidence interval) during the first exposure shows a rapid fall-off of on the timescale of ~1 second. **(bottom)** Both fast and slow gamma power is most modulated by the animal's speed measured within a second of the gamma power estimate, implying a rapid timescale of modulation. Shown are the Spearman correlation and bootstrap 95% confidence interval of fast (red) and slow (blue) gamma power with log(speed) for offsets in speed measurement ranging from −2.5 to 2.5 s relative to the 0.5 s window used to estimate gamma power. **b,** Rapid and opposing changes in the power of slow and fast gamma are apparent in 2 second windows over which rats' speed increase from less than 2 cm/s to more than 10 cm/s. **(left)** Increasing mean speed (with standard errors) in 0.5 s windows corresponding to the isolated increasing speed incidents. **(right)** Mean slow gamma power (blue bars with standard errors) decreases significantly, while fast gamma simultaneously increases significantly (red bars) over the course of the two-second increasing speed events. **c,** Same analysis as (**b**) but for 2 s windows when speed decreased from more than 10 cm/s to less than 2 cm/s. Periods of decreasing speed are marked by an increase in slow gamma power (blue bars) and a concomitant decrease in fast gamma power (red bars). **d,** Correlation between theta power and log(speed). The graph shows population data of normalized power of theta oscillation (7–9 Hz) vs. speed, both measured over 0.5 s windows. Points represent binned means with standard error; line shows linear regression of underlying data with 95% confidence intervals. **e,** Speed is a better predictor of fast and slow gamma power than theta power. Comparison of Spearman correlation log(speed) or theta power with fast gamma power (red) and slow gamma power (blue). Depicted are correlations with bootstrap 95% confidence intervals. **$p<0.01$.
doi:10.1371/journal.pone.0073114.g004



a
Fast Gamma
Slow Gamma
Slope of speed vs. gamma power
Exposure to environment
b
Novel
Familiar
Slope speed vs. gamma power
Slow Gamma
Fast Gamma
c
Novel
Familiar
Slow gamma power (stdev from mean)
Speed (cm/sec)
d
Novel
Familiar
Fast gamma power (stdev from mean)
Speed (cm/sec)
e
CA1 slow gamma
CA1 fast gamma
CA3 slow gamma
CA3 fast gamma
Slope of speed vs. gamma power
Exposure to Environment
f
CA1 slow gamma
CA1 fast gamma
MEC slow gamma
MEC fast gamma
Slope of speed vs. gamma power
Exposure to Environment

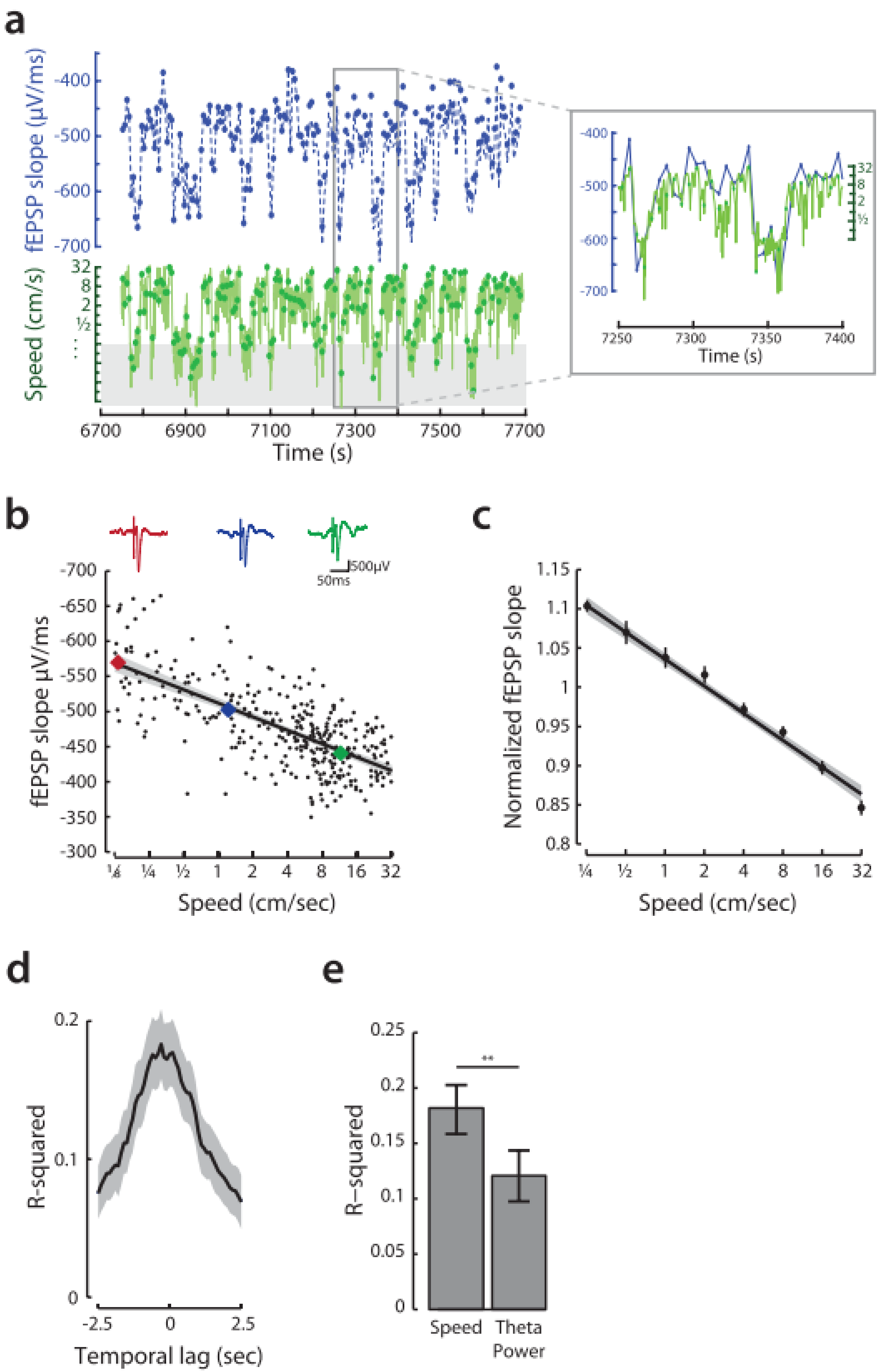
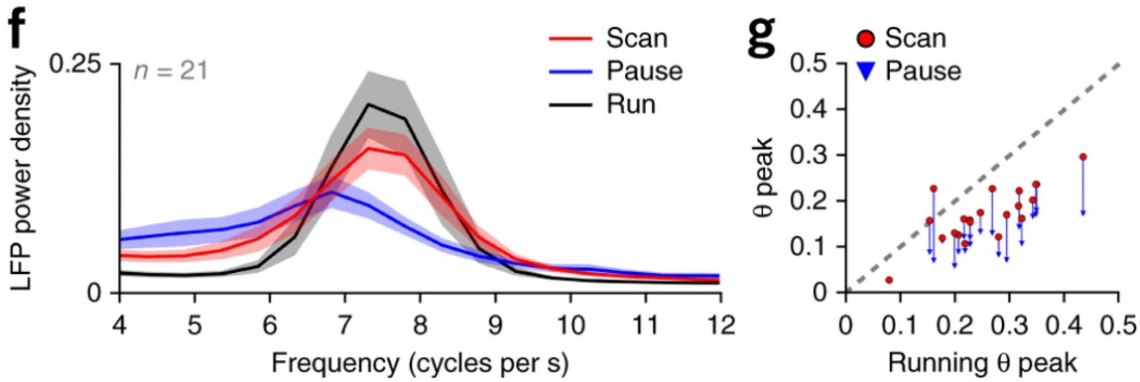


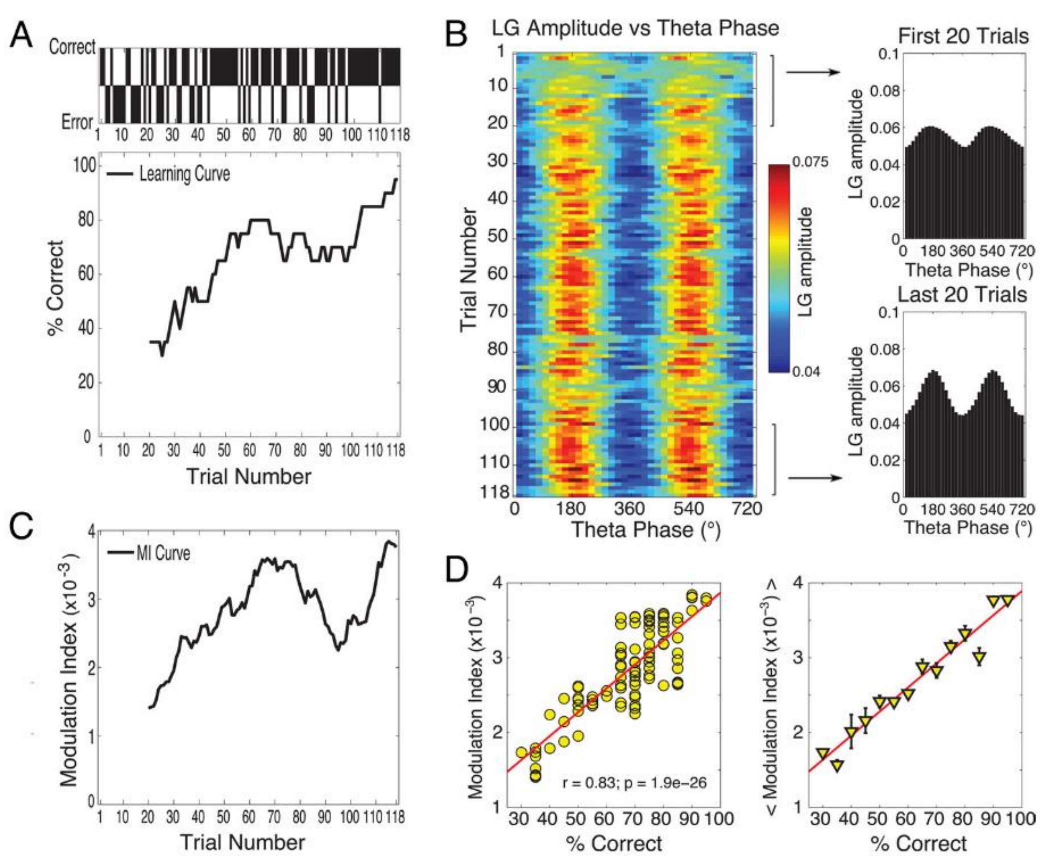
Figure 7. Rapid modulation of the Schaffer collateral pathway as a function of movement speed.

Additionally, we have to explore these (some example plots from other studies for reference):

From Monaco et al. 2014



From Tort et al. 2009



Here is the outline for figures: (3 panels)

Panel 1 - Behavior analyses results from ApoE4 and ApoE3 rats.

Panel 2 – Pure LFP Power Spectrum plots for specific bands and their differences when compared between Rat 381 and WT rat/s.

Panel 3 – Phase-Phase and Phase-Amplitude coupling measures and their plots compared between Rat 381 and WT rat/s.

For Nick:

The actual details/plot designs will have to be come up based on these ideas and the reference papers that are shared.