

REPORT DOCUMENTATION PAGE

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14. ABSTRACT Genetic inhibition of two genes, an orphan GPCR and a kinase, have been shown to produce changes in the behavior of mice that suggest the ability to promote sleep and to promote extended wakefulness. One of these is a well-known clock gene, but its effects on normal sleep-wake states had not been characterized. Pharmaceutical investigation of either of these genes appears to be very limited, but could be fruitful in developing compounds to modulate human wakefulness and sleep. The phenotype of a third gene, that had been seen to consistently affect circadian rhythm of activity in early breeding generations, was lost following additional breeding. Further evaluation of this gene may require examination of particular genetic					
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					19b. TELEPHONE NUMBER 281-863-3120



Final Report

Investigation of Murine Models for Sleep, Wakefulness and Target Discovery

October 2007



Study Outline

- Task 1
 - Sleep/wake architecture of Lexicon C57BL6/sv129 (F2) mice
 - Evaluate behavior of F2 mice as related to amount of sleep
- Task 2
 - Evaluate sleep/wake patterns & behavior of Lexicon KO mice for genes known to affect sleep and circadian rhythm
 - Casein kinase I, epsilon (CSNK1E)
 - GABA-A α 1 (GABRA1)
- Task 3
 - Evaluate sleep/wake patterns & behavior of Lexicon KO mice with altered circadian rhythm of locomotor activity
 - GPR710N1
 - PRT282T1

Task 1

- Characterized basic sleep/wake EEG pattern of Lexicon mice

- Lexicon C57BL6/sv129 (F2) mice
 - Record & analyze every 10 sec of EEG/EMG for 5 days
 - Recordings begin 10-14 days following transmitter implantation (DSI F20EET)
 - Recordings begin 2.5 days following being placed into recording homecage
-
- Lexicon C57BI6/sv129 (F2) mice showed comparable sleep/wake pattern to that of JAX (Jackson Labs) C57BL/6J mice
 - Male and female F2 mice exhibited comparable sleep/wake pattern and sleep quality

Reminder:

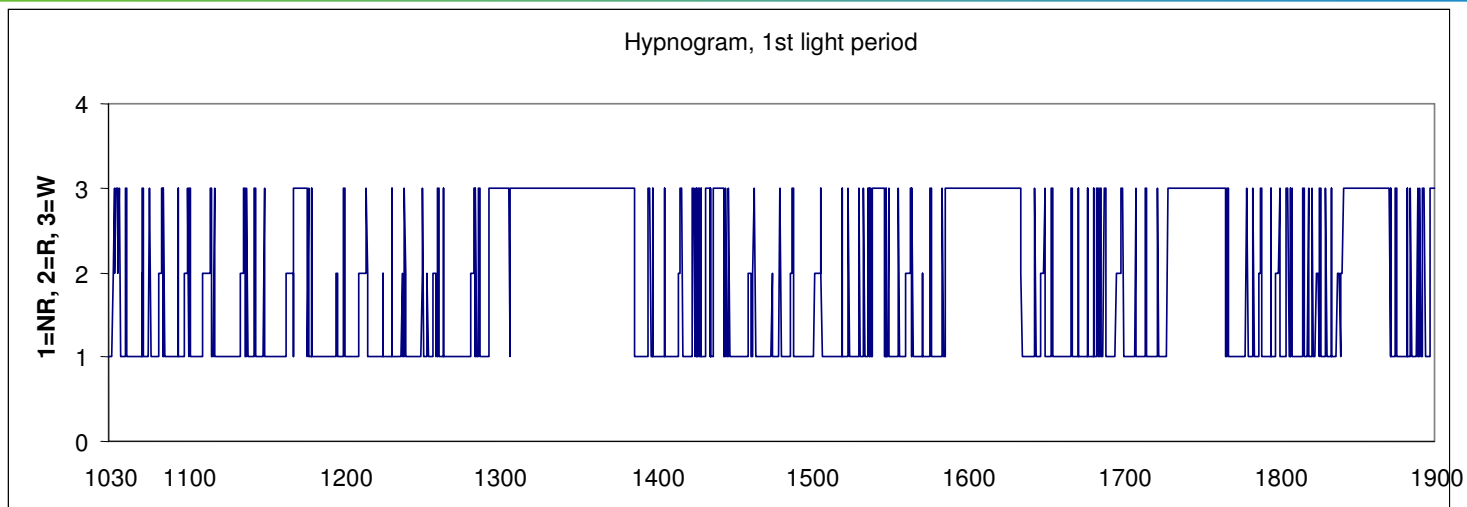
Subjective day = dark period for rodents (opposite humans)

Subjective night = light period

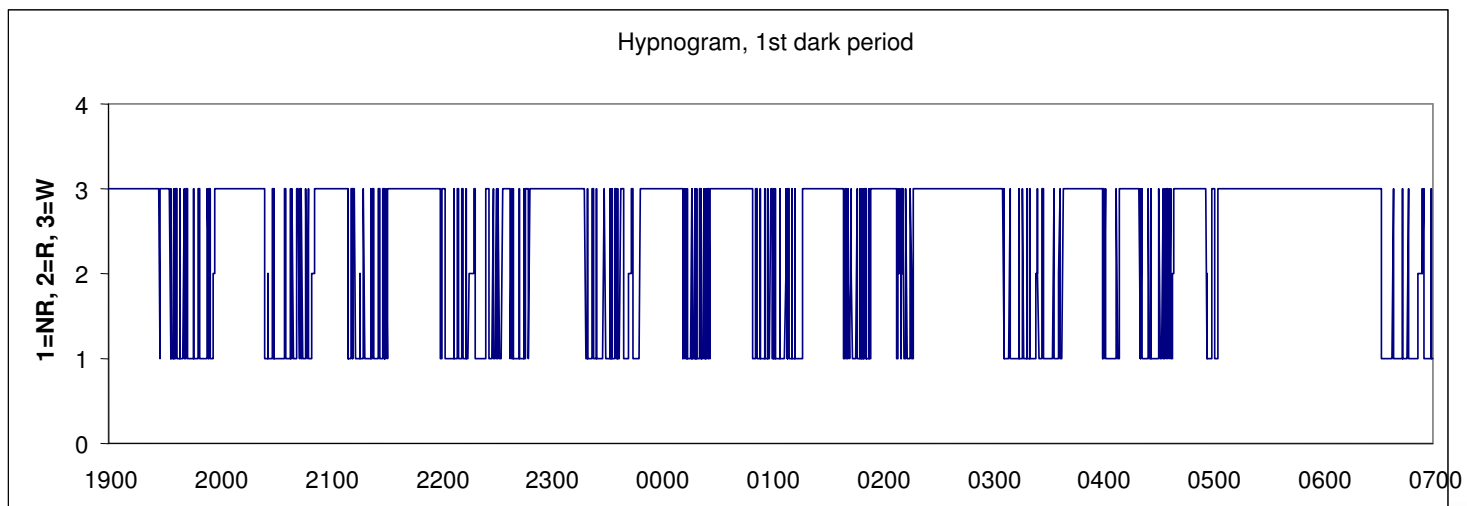
hint:

- think day & dark both start with 'd', and
- night rhymes with light

Sleep Pattern of a Representative Mouse–1st 24 hrs

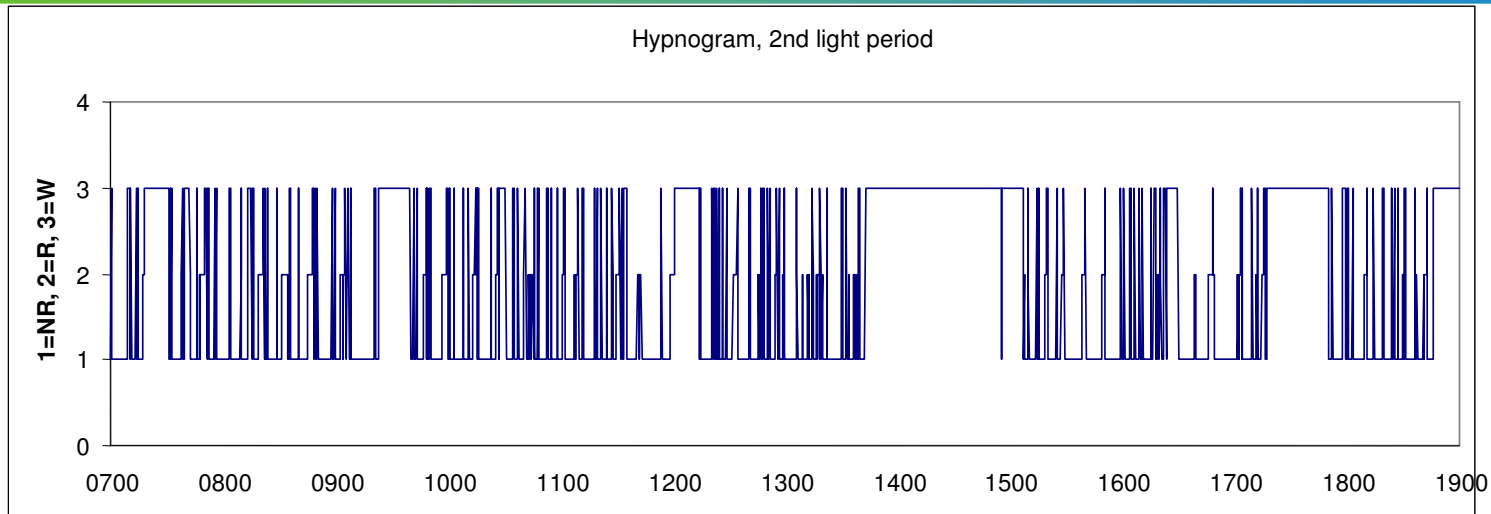


Subjective
Night

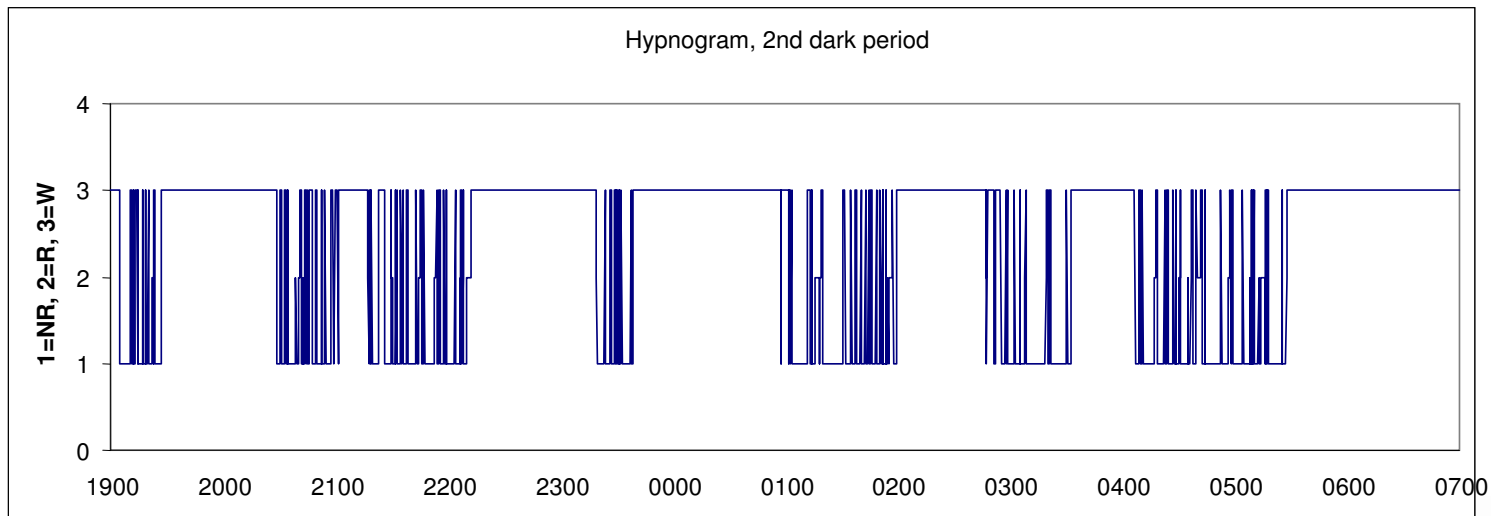


Subjective
Day

Sleep Pattern of a Representative Mouse–2nd 24 hrs

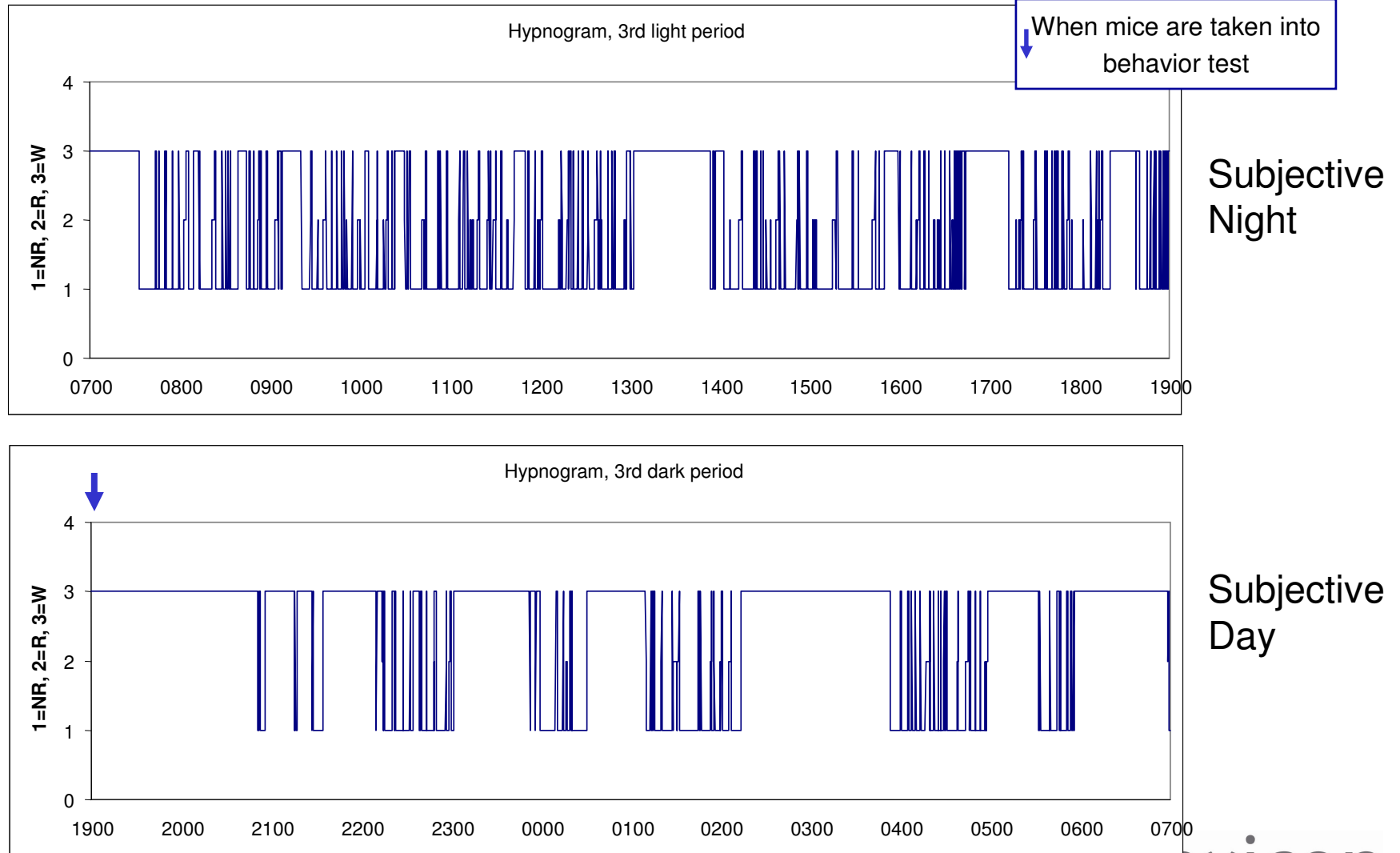


Subjective
Night



Subjective
Day

Sleep Pattern of a Representative Mouse–3rd 24 hrs



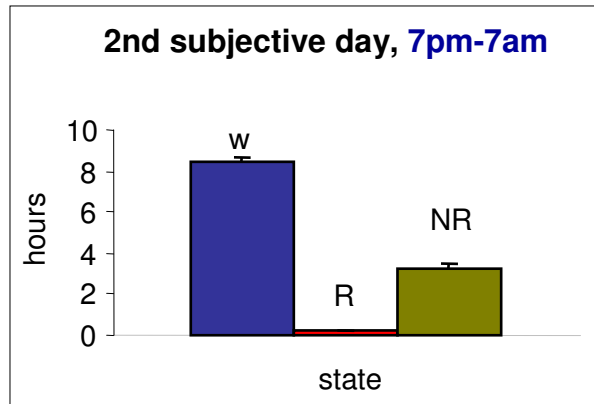
Vigilance State Distribution:

Female & male F2 mice show normal pattern of wakefulness and sleep

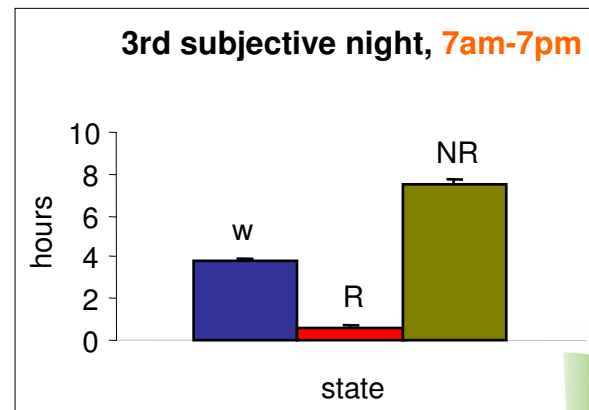
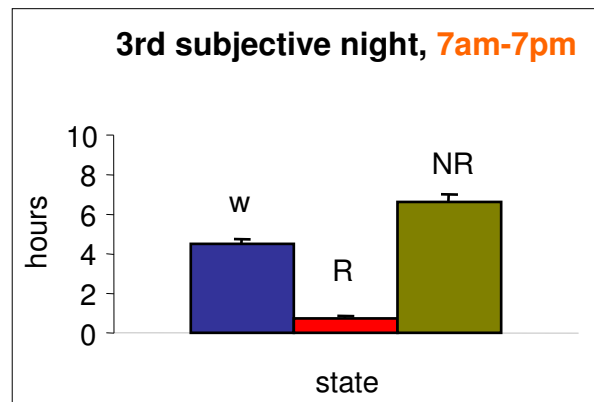
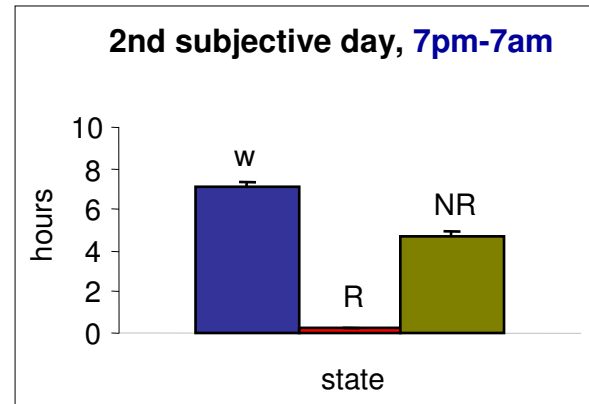
In 3rd 24 hr period:

- both females & males stay awake longer in subjective day, and
- sleep longer in subjective night; (basically repeating pattern from earlier 24hrs)

F2 Females



F2 Males

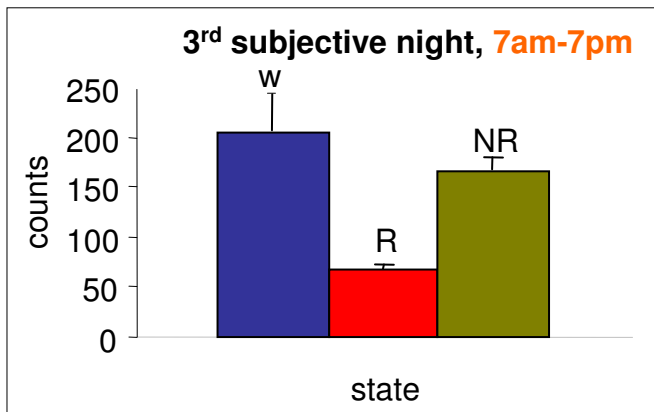
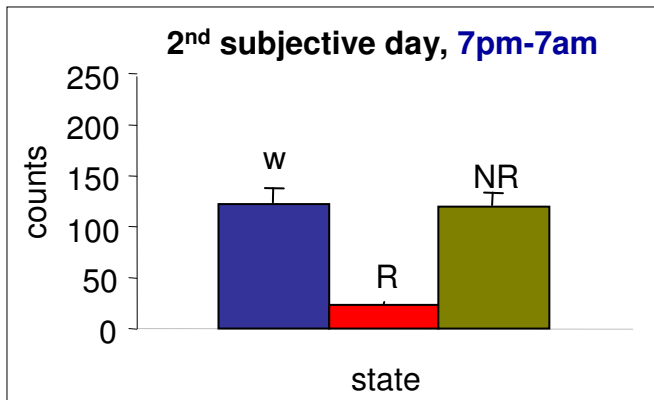


Vigilance State Bout Counts: Normal Pattern Seen

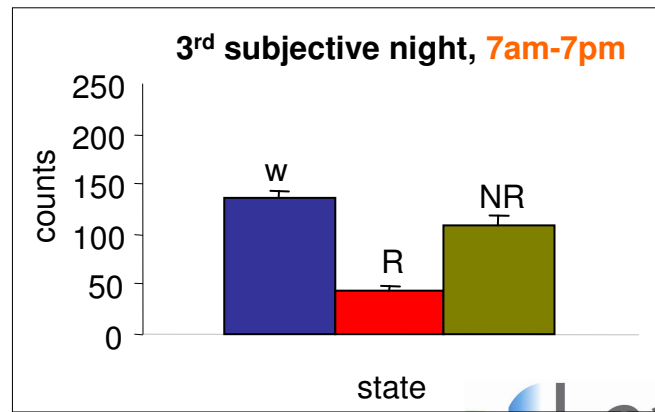
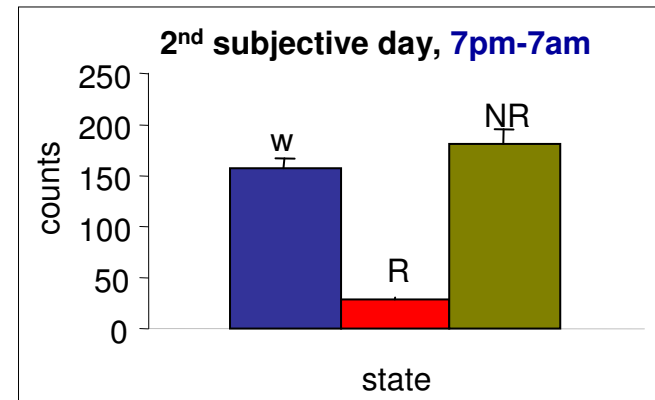
(Bout counts show transition frequency between sleep and waking)

Different from humans, mice exhibit polyphasic sleep with many transitions between states.

F2 Females



F2 Males



Comparable Sleep Pattern: Lexicon F2s & JAX C57BL/6J

– remember “dark” = subjective day; “light” = subjective night

JAX	in min		bouts count		average min of each bout		in min		bouts count		average min of each bout	
	Light_Sleep	Light_Wake	Light_S Bouts	Light_W Bouts	Light-SB	Light-WB	Dark_Sleep	Dark_Wake	Dark_S Bouts	Dark_W Bouts	Dark-SB	Dark-WB
Males												
Mean	466.8	253.2	158.6	158.9	3	1.6	267.3	452.7	127.7	127.9	2.1	3.7
SD	30.7	30.7	22.3	22.3	0.5	0.3	46.2	46.2	22.6	22.6	0.4	1
Females												
Mean	432.0	288.0	187.0	187.5	2.3	1.6	250.9	469.1	133.3	133.5	1.9	3.7
SD	29.0	29.0	17.5	17.5	0.3	0.2	54.8	54.8	23.2	23.2	0.2	1.0

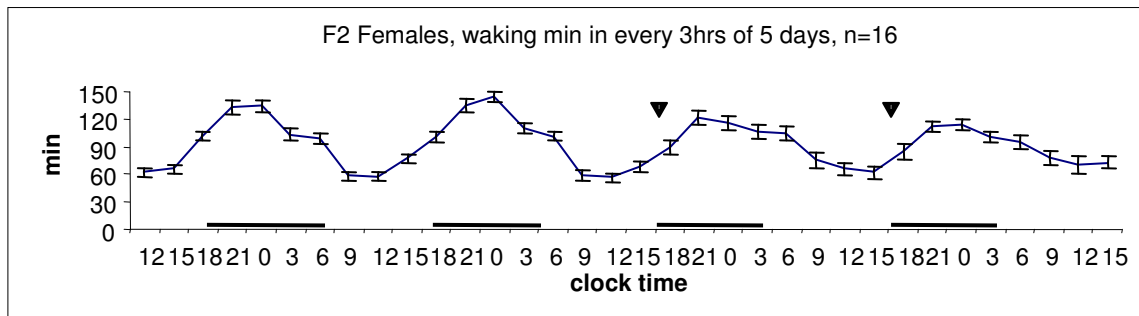
(in Jackson Lab data, n=100 in each gender)

(Lexicon, 2nd night & 3rd day (females, n=16, males, n=14, REM min added into total sleep min))

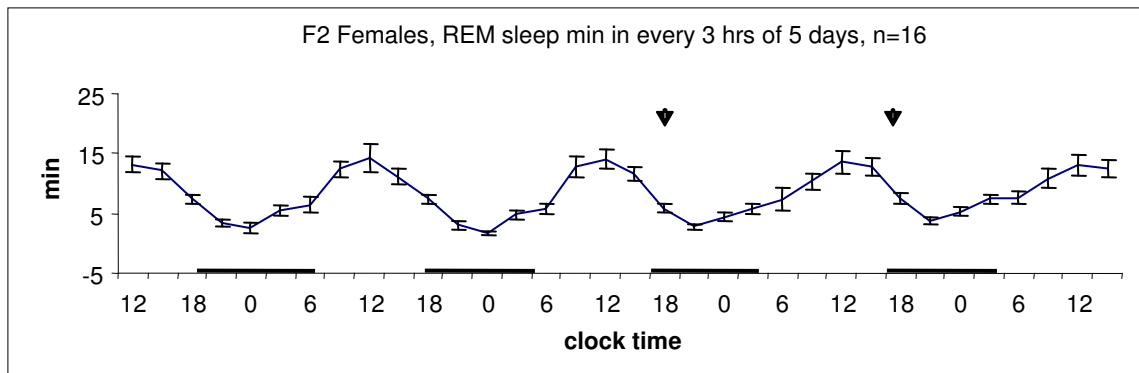
	in min		bouts count		average min of each bout		in min		bouts count		average min of each bout	
	L_Sleep	L_Wake	L_SBouts	L_WBouts	AvgLSB	AvgLWB	D_Sleep	D_Wake	D_SBouts	D_WBouts	AvgDSB	AvgDWB
Males												
Mean	487.4	229.4	191.0	137.6	2.5	1.8	295.8	423.5	183.0	158.0	1.6	2.8
SD	43.4	35.7	44.2	35.0	0.6	0.6	59.6	60.7	57.0	37.0	0.5	0.9
Females												
Mean	464.7	252.2	179.4	148.8	2.5	1.8	220.2	497.8	123.3	127.8	2.0	5.4
SD	45.9	37.9	29.7	28.3	0.6	0.6	49.0	51.1	54.5	59.6	0.8	4.0

F2 Female Mice – Normal distribution of Wake, REM, & NREM EEG across all Light/Dark Cycles (in 3hrs bins)

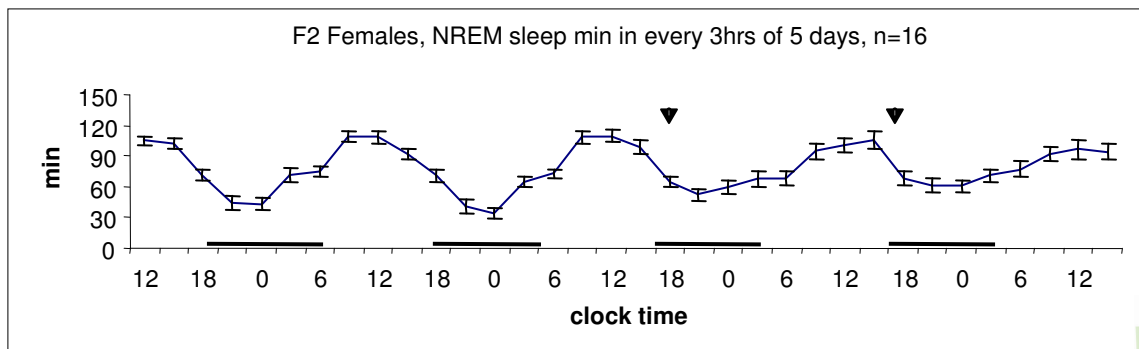
Females



WAKE



REM

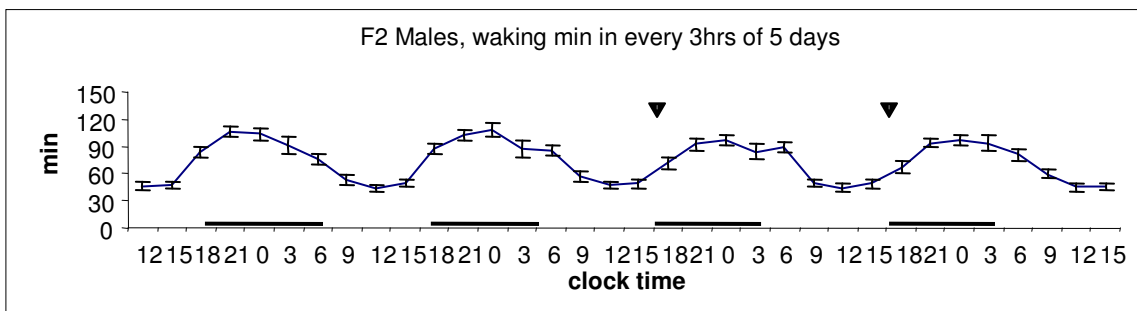


NREM

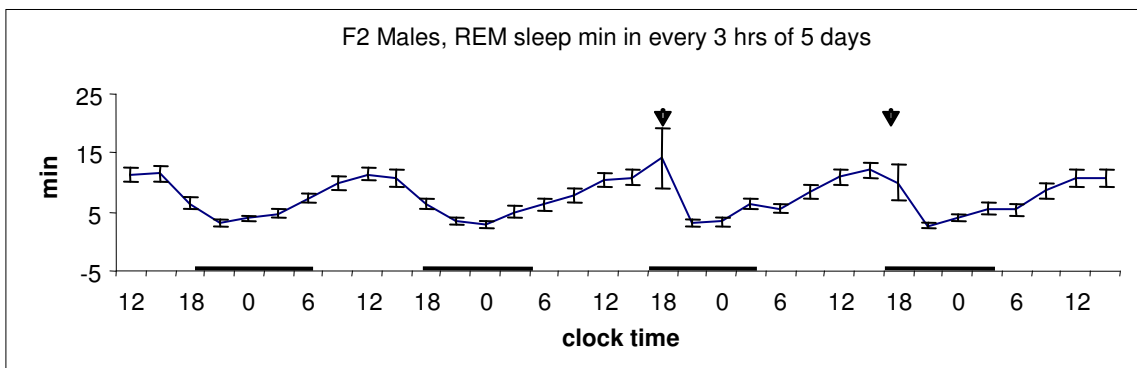


F2 Male Mice – Normal distribution of Wake, REM, & NREM EEG across all Light/Dark Cycles (in 3hrs bins)

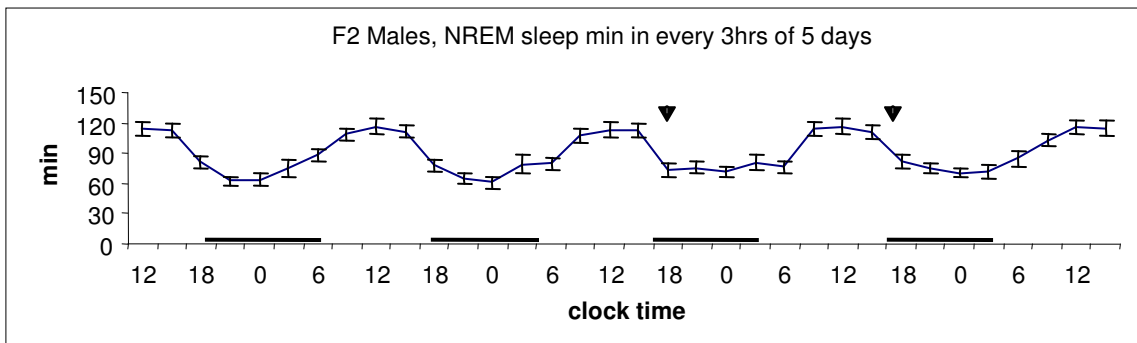
Males



WAKE



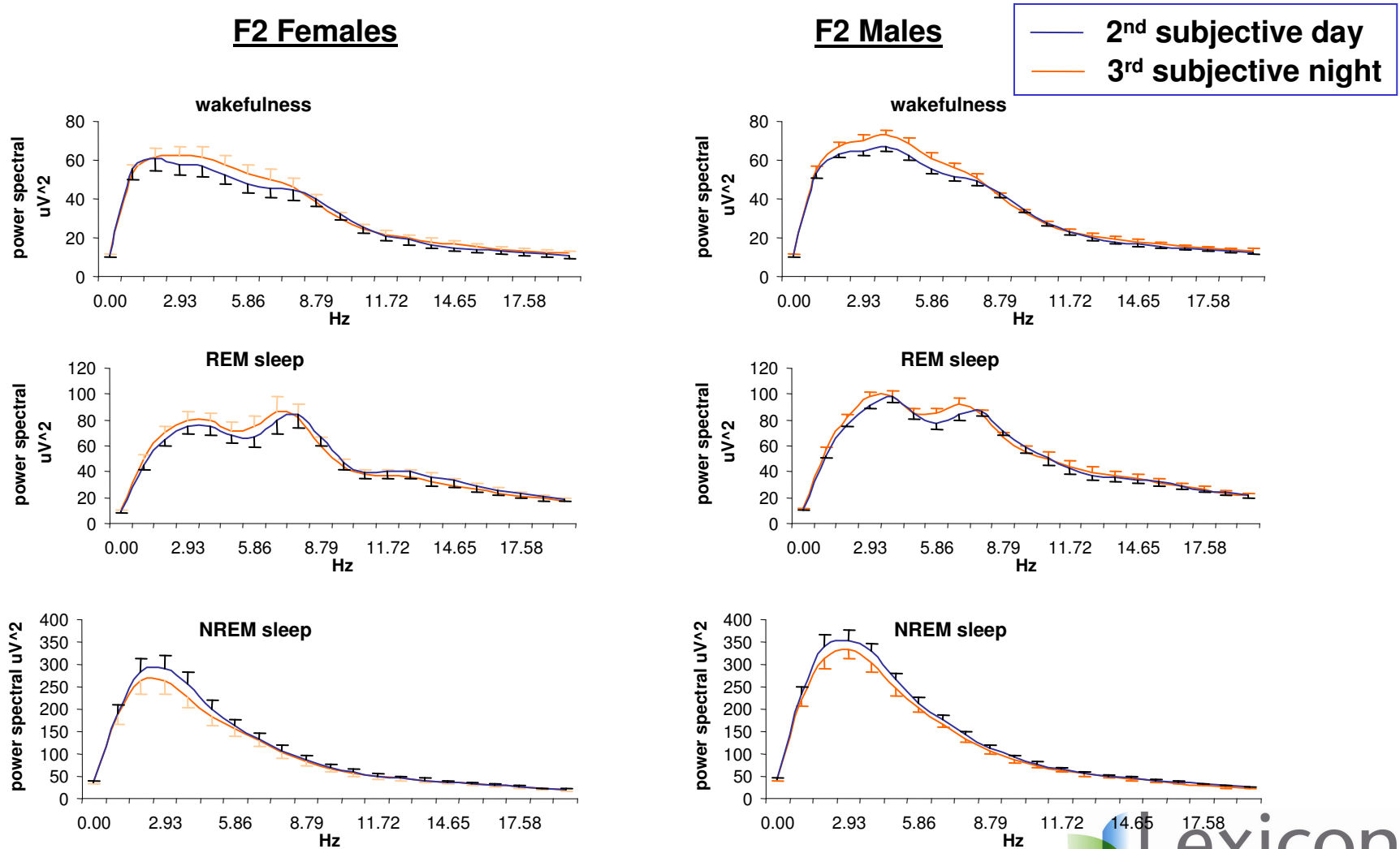
REM



NREM



F2 Mice – Normal EEG Power Spectra of Wake, REM, & NREM States in Subjective Night & Subjective Day



Summary of Sleep/Wake Architecture of Lexicon C57BL6/sv129 (F2) Mice

- Lexicon F2 mice exhibit a standard circadian rhythm of locomotor activity and EEG states, with no evidence of abnormal electrographic activity public reports.

Task 1

- Evaluate behavioral assays

Evaluate and implement behavioral assays for detection of behavioral differences related to length or quality of sleep

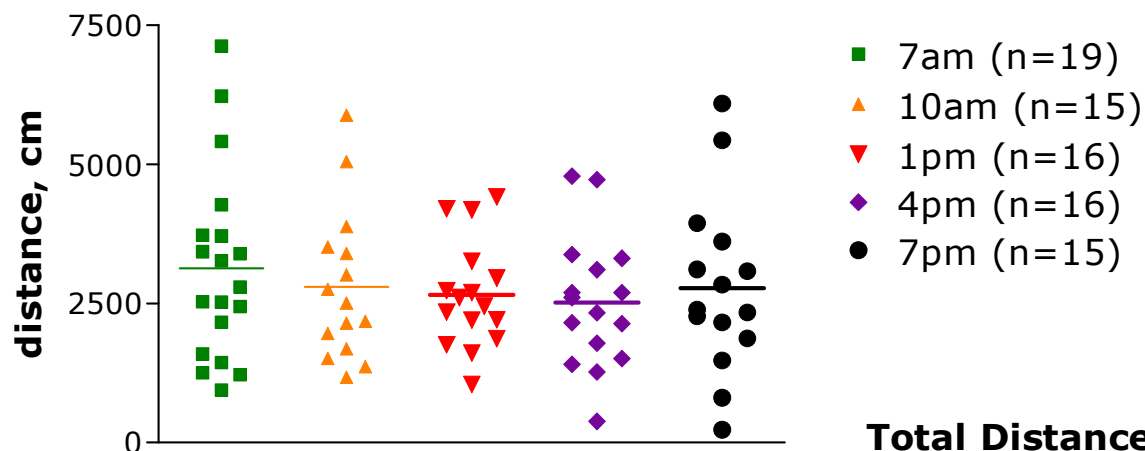
- Assays -
 - Novel open-field - general control for activity, but also assesses exploration & habituation & provides anxiety-related clues
 - Conditioning - learning & memory
 - initially used trace conditioning protocol with 5 training trials
 - No differences observed; concerned that 5 trials was too arousing
 - switched to delay conditioning, 2 training trials

Effect of Duration of Sleep/Time of Day on Behavior: Novel Open-Field

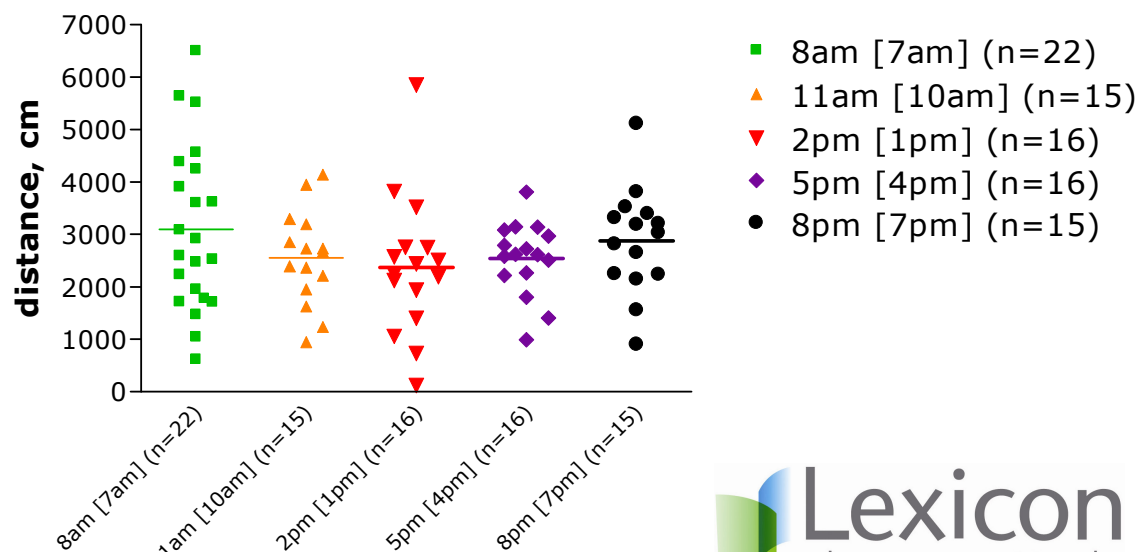
- Open Field Assay: 30 minutes (six 5-minute intervals)
 - F2 male and female WT's
 - 5 independent groups
 - Tested @
 - 7am (“no sleep” or “before going to bed”),
 - 10am (3 hrs sleep),
 - 1pm (6 hrs sleep),
 - 4pm (9 hrs sleep) ,and
 - 7pm (full night's sleep)
-
- No significant differences in locomotor activity or exploration

Locomotor Activity - No Differences

Total Distance-Males

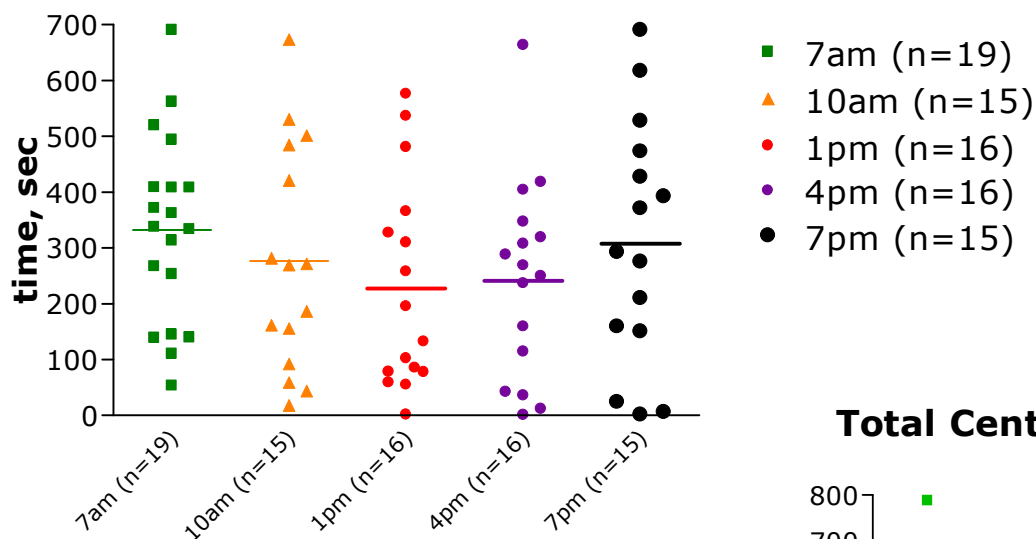


Total Distance-Females

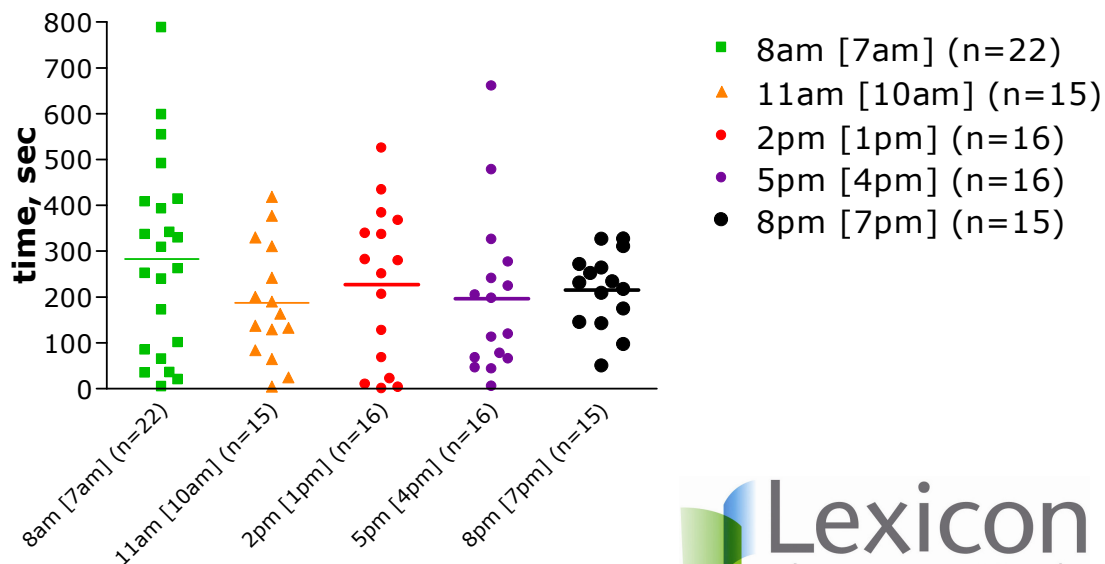


Anxiety Measure (Time-in-center) – No Differences

Total Center time-Males



Total Center time-Females



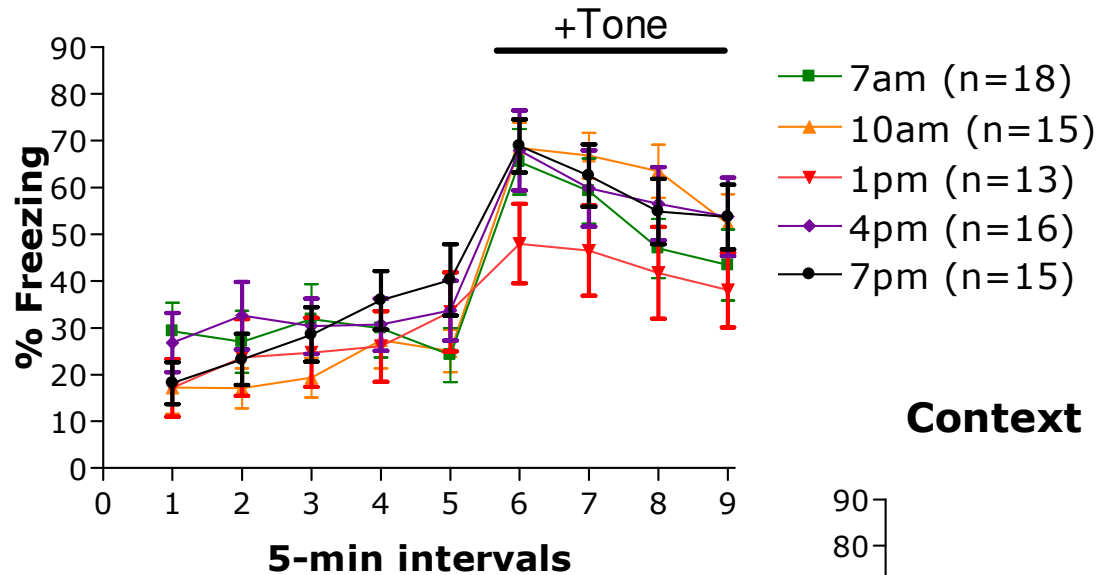
Effect of Duration of Sleep/Time of Day on Behavior: Delay Fear Conditioning

- F2 males and females
 - Trained and tested @
 - 7am (“no sleep” or “before going to bed”),
 - 10am (3 hrs sleep),
 - 1pm (6 hrs sleep),
 - 4pm (9 hrs sleep) ,and
 - 7pm (full night’s sleep)
-

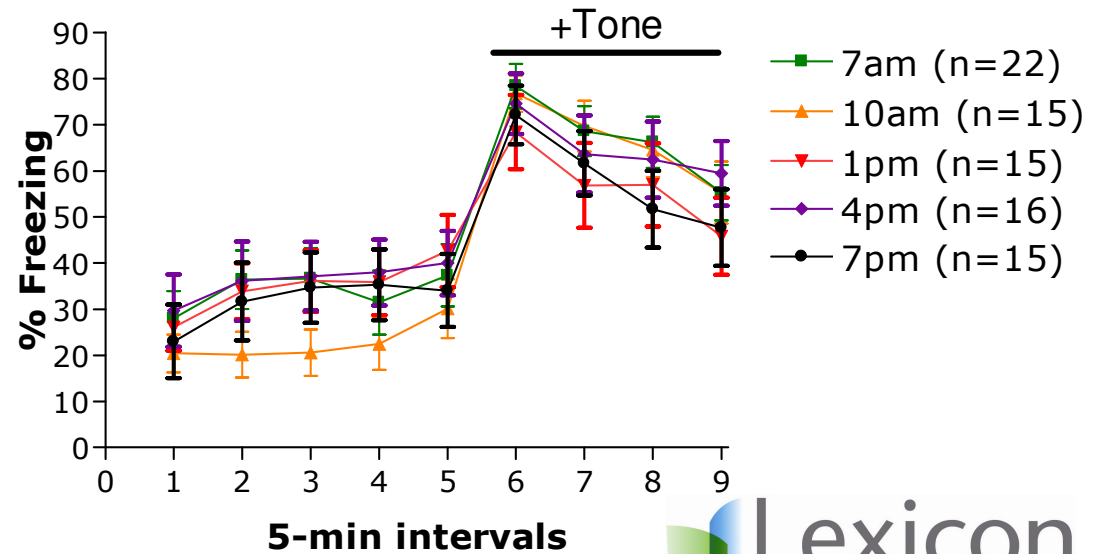
- No differences as a result on length of subjective night/sleep

Delay Fear Conditioning: No effect of length of subjective night on performance

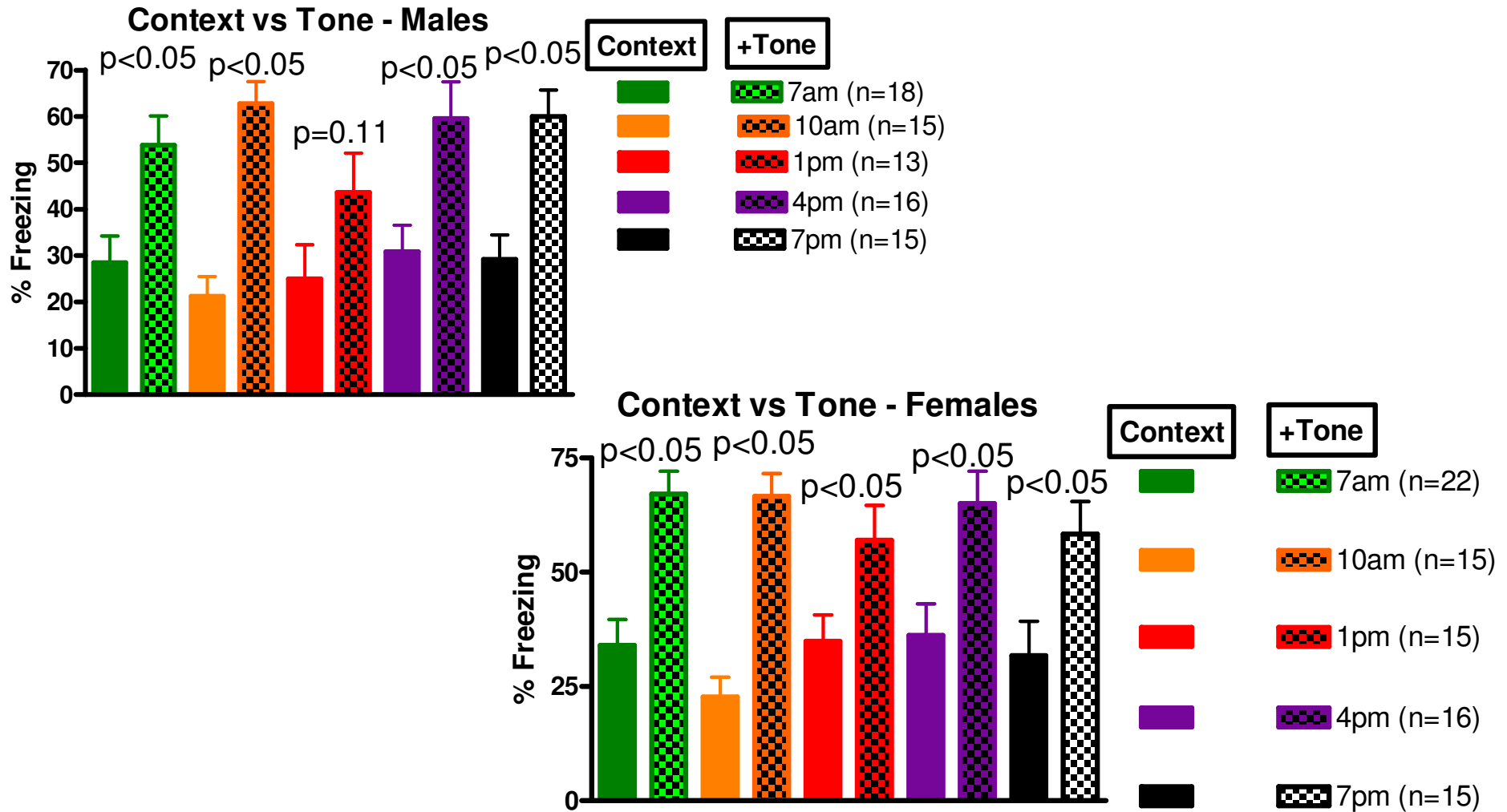
Context + Tone- Males



Context + Tone - Females



Delay Fear Conditioning: No effect of length of subjective night on performance of context vs tone



Summary of evaluation of behavioral assays to detect differences in behavioral performance related to length or quality of sleep

- In the final analysis, no significant differences in the behavior of WT mice were detected by either the:
 - novel open field assay (measuring total locomotor activity & exploratory patterns that can be affected by anxiety levels) or
 - fear conditioning assay (using either a delay or trace conditioning paradigm) following awakening them at various times in their subjective night
- Some early trends, e.g., in the 1 p.m. (6 hrs of subjective night) group, became non-significant with additional mice tested
- The polyphasic sleep pattern of rodents is likely to be a major factor for this lack of effect. However, the behavioral variability of the F2 mice may also contribute

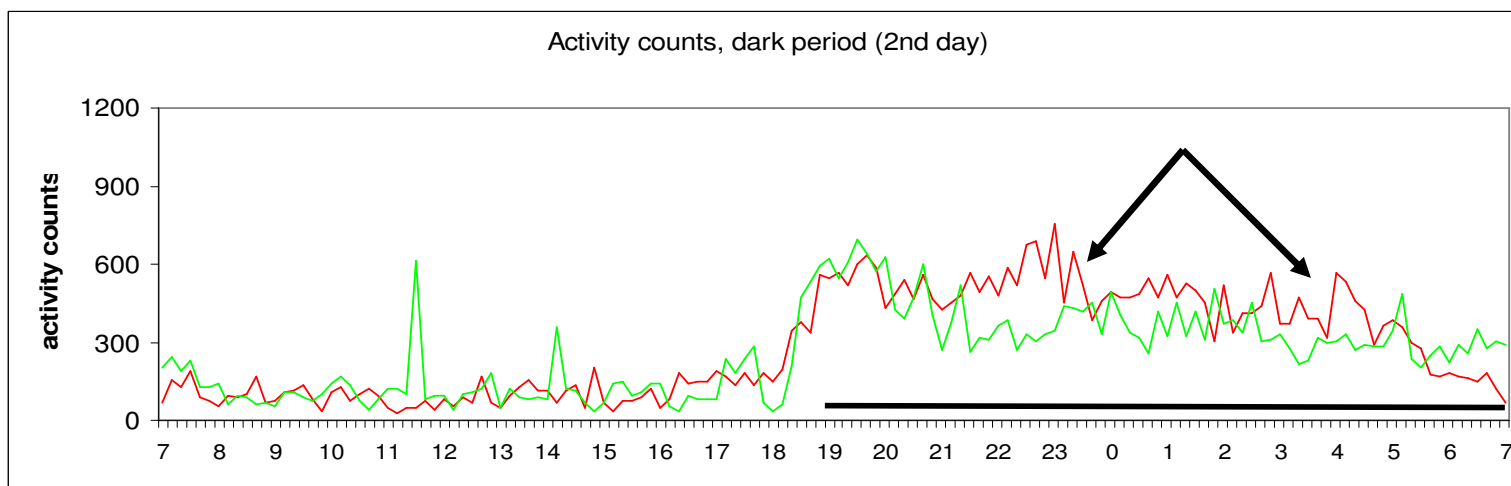
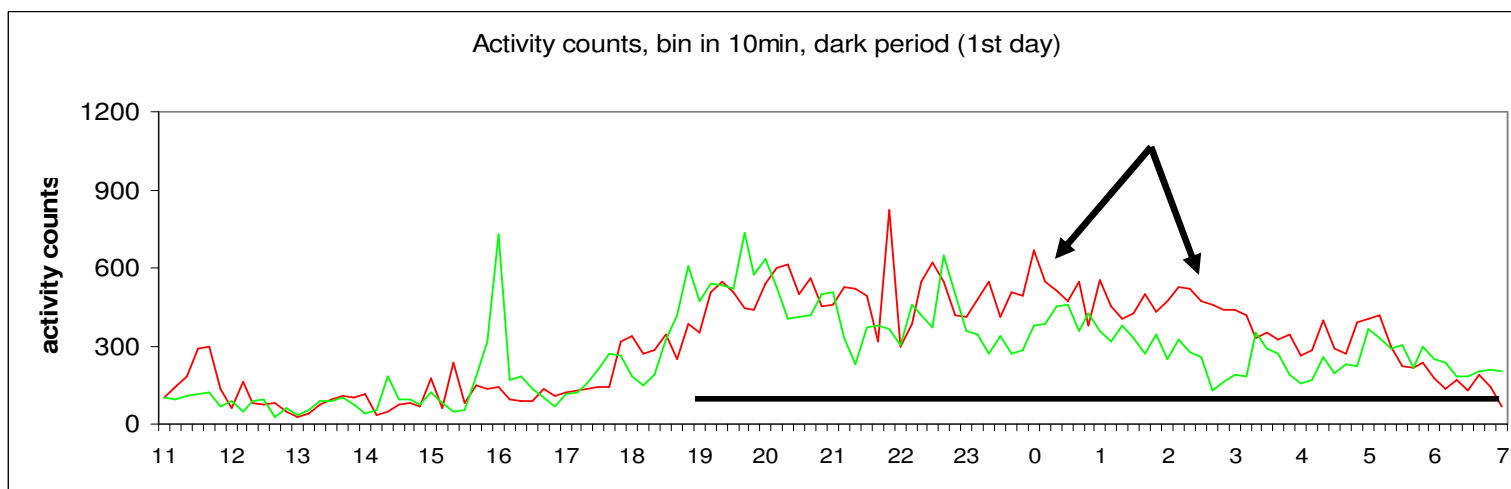
Task 2: Evaluate sleep/wake patterns & behavior of Lexicon KO mice for genes known to affect sleep and/or circadian rhythm

- CSNK1E
- GABRA1

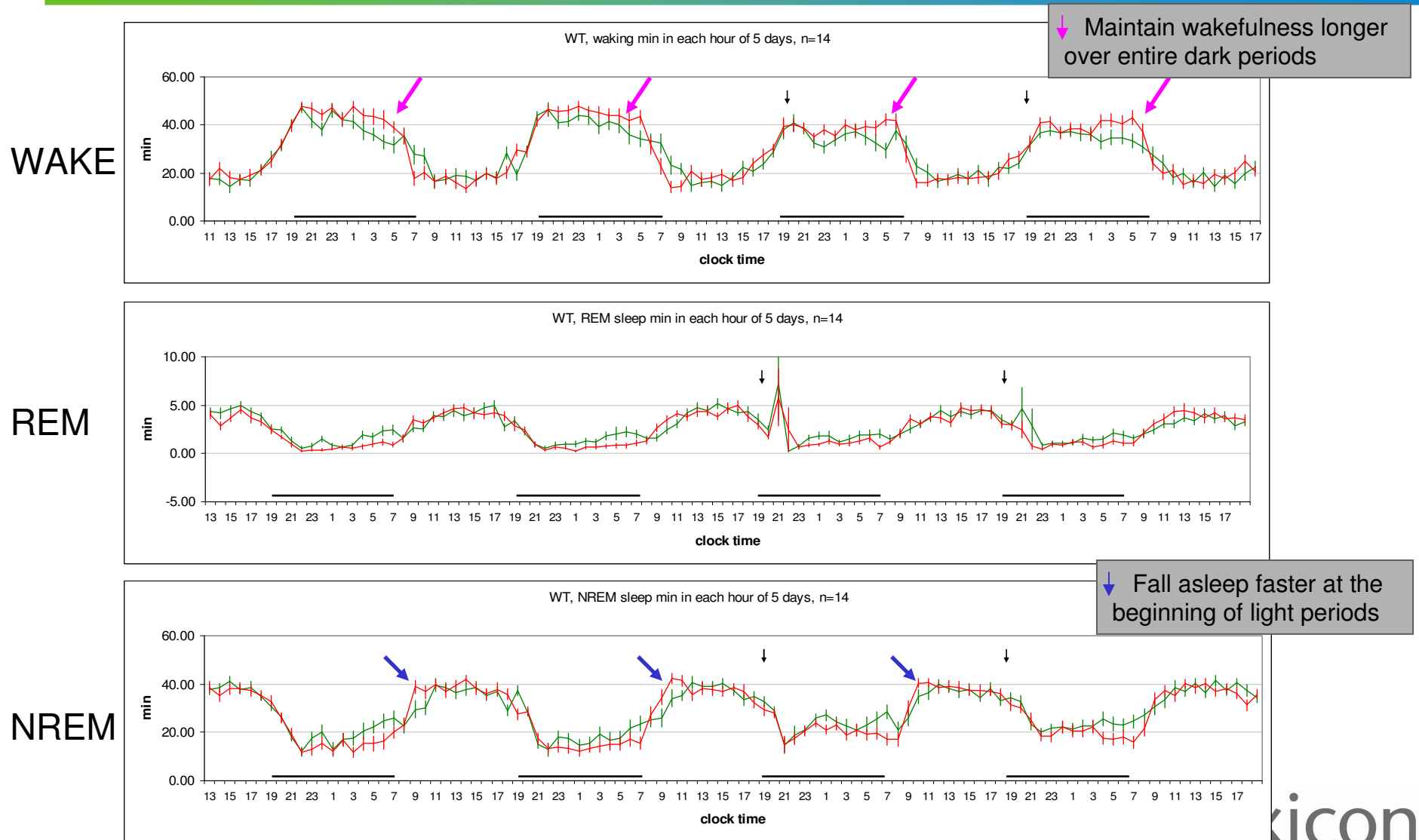
Task 2: CSNK1E

- The gene is casein kinase 1, epsilon subunit
 - Proposed substrates for CSNK1E are PER proteins, components of the circadian clock in mammals
 - It is closely related to the double-time gene of *Drosophila* (Kloss et al., 1998).
 - Tau is a semidominant autosomal allele of CSNK1E that greatly shortens period length of circadian rhythm in Syrian hamsters (Lowery et al., 2000).
-
- In normal light cue environment, CSNK1E mice exhibited the same 24hrs circadian rhythm as WT mice
 - CSNK1E mice exhibited more waking time throughout subjective day and fell asleep faster in subjective night
 - EEG power density at beta frequency in waking and REM states were slightly higher in CSNK1E mice
 - CSNK1E mice behave normally in OFA and TAC tests

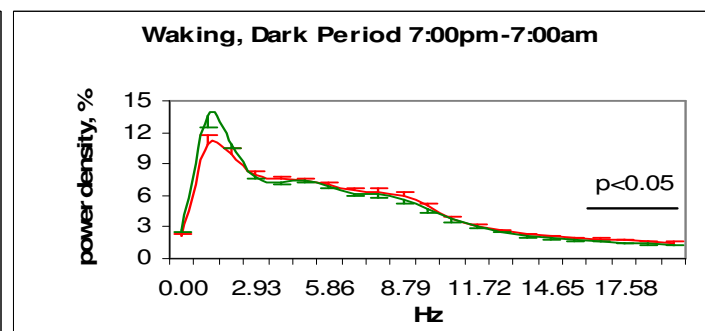
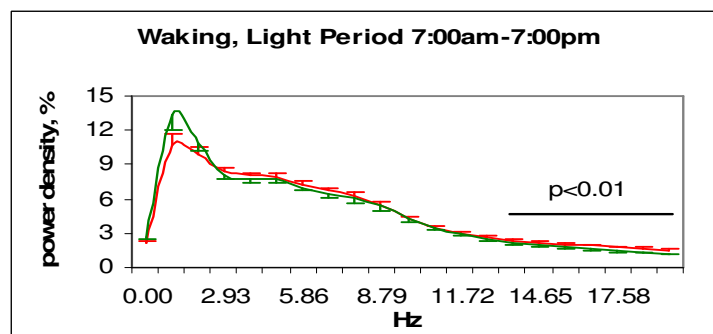
CSNK1E KO Mice Are Active Throughout Subjective Day



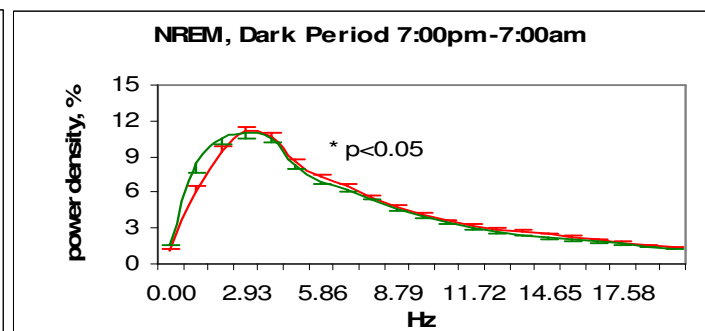
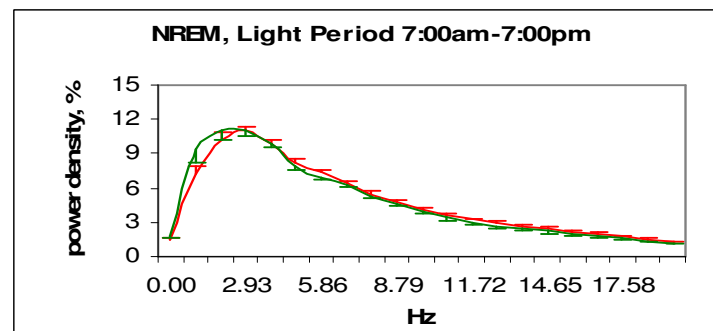
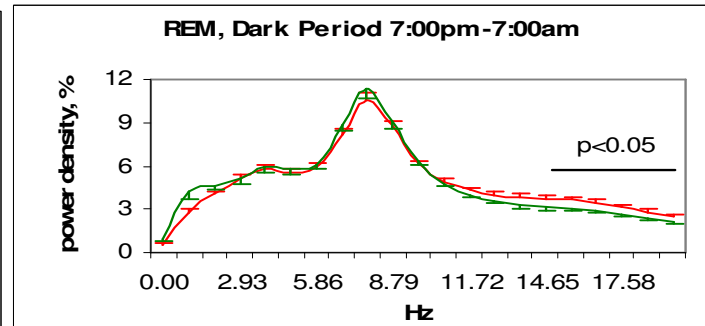
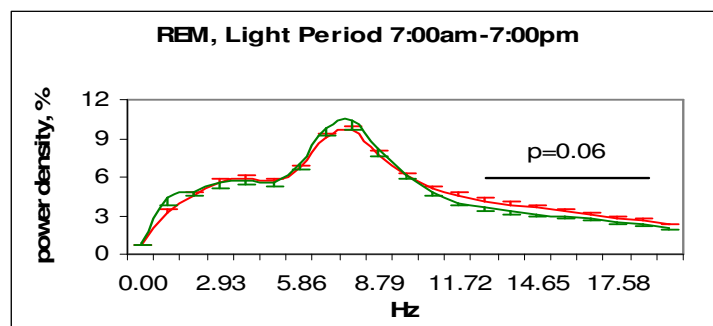
CSNK1E KO Mice Exhibit Longer Waking Time in Subjective Day & Fall Asleep Faster in Subjective Night



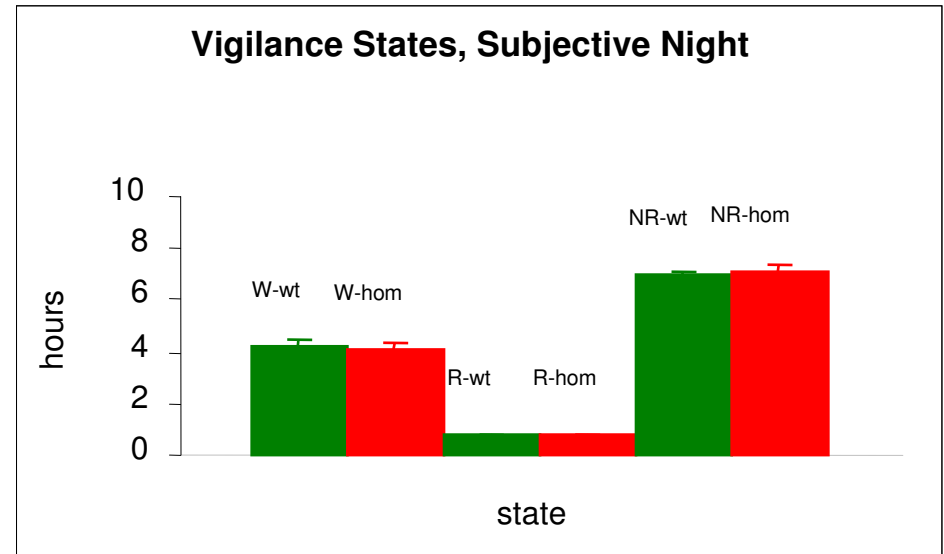
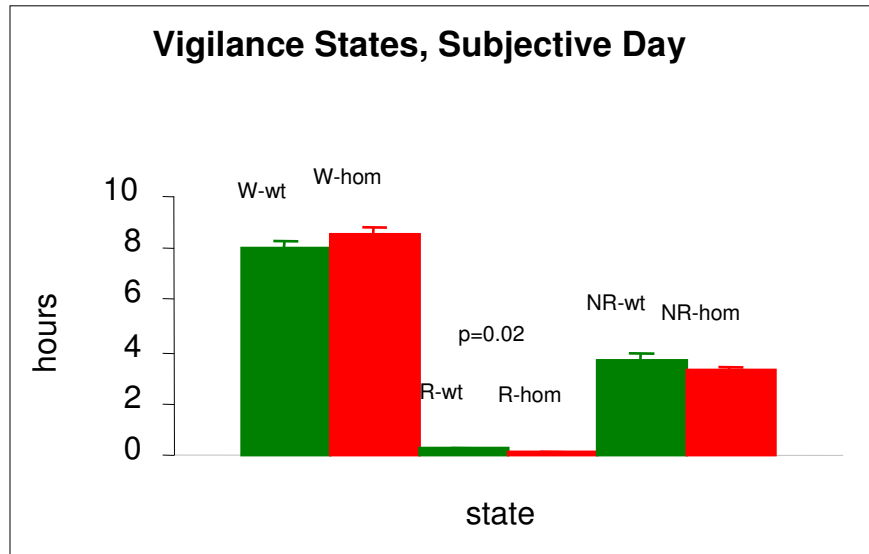
CSNK1E KO Mice Exhibit Higher EEG Power at Beta Frequency During Waking & REM States



Beta frequency EEG associated with active wakefulness

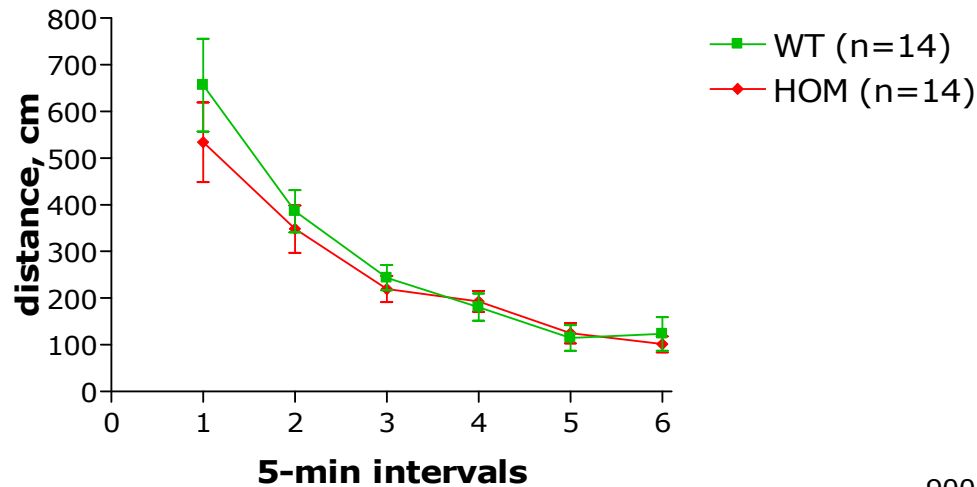


CSNK1E KO Mice Exhibit Smaller Amount of REM Time in Subjective Day, but Normal NREM Time

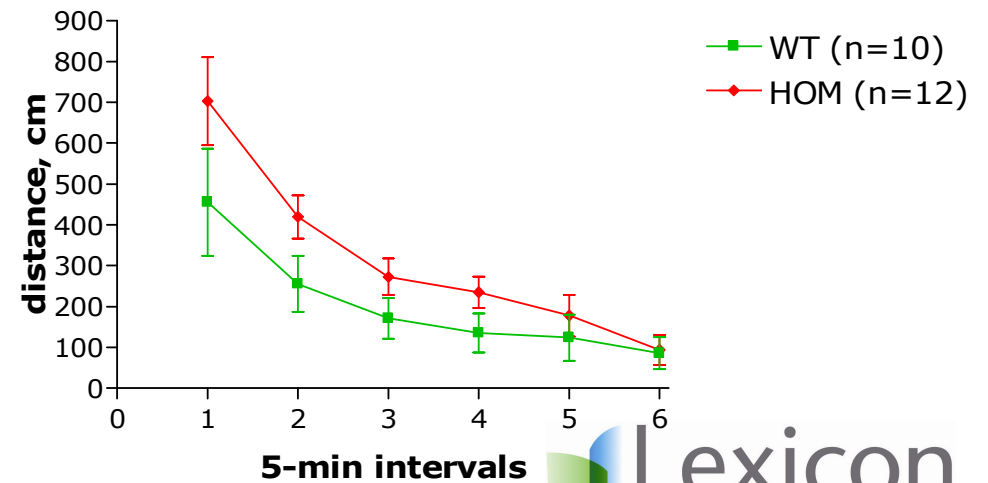


CSNK1E KO Mice – No Difference in Locomotor Activity in Novel Open-field

**Total distance
Male**

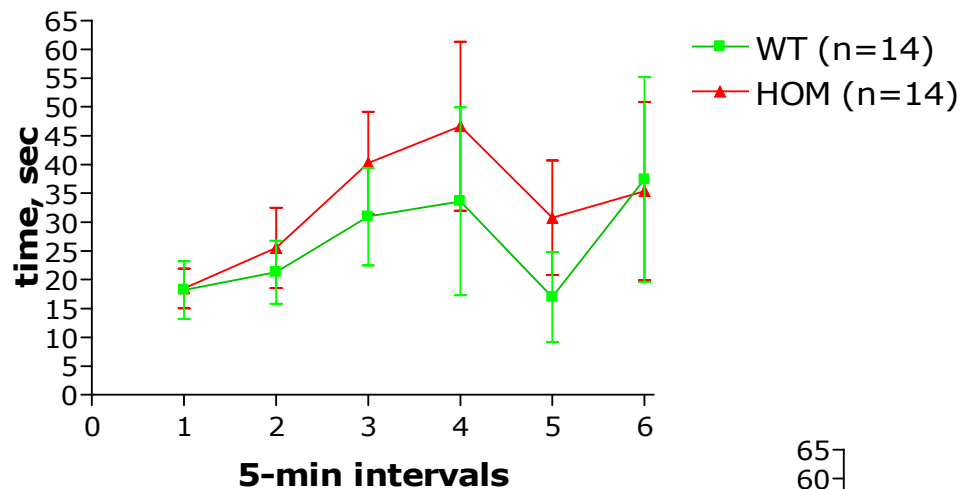


**Total distance
Female**

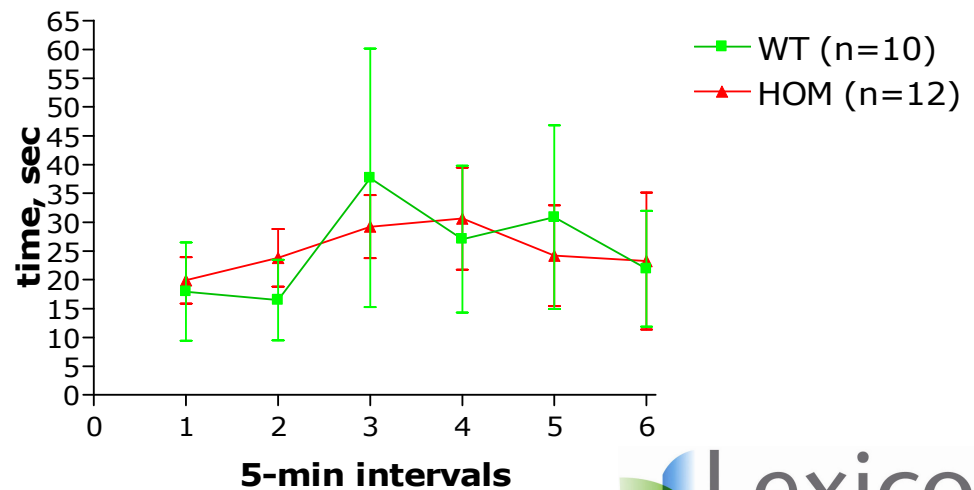


CSNK1E KO mice - No Difference in Anxiety-related Exploratory Pattern

Time in Center Male

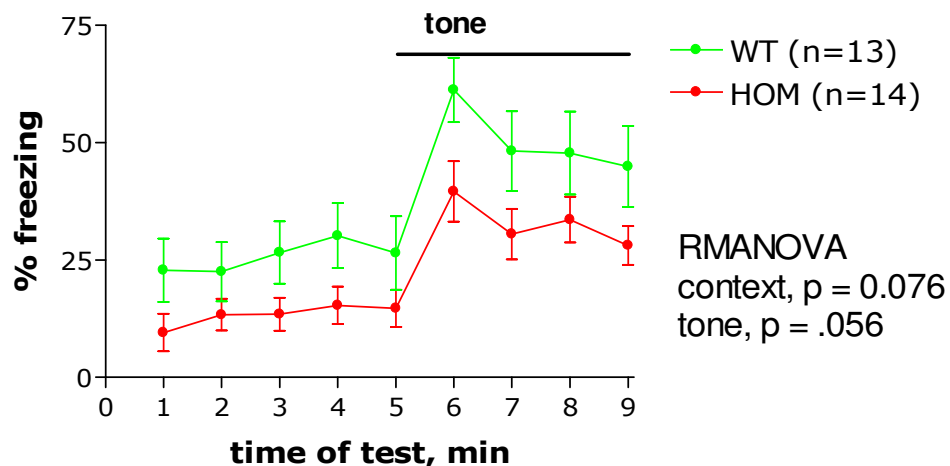


Time in Center Female

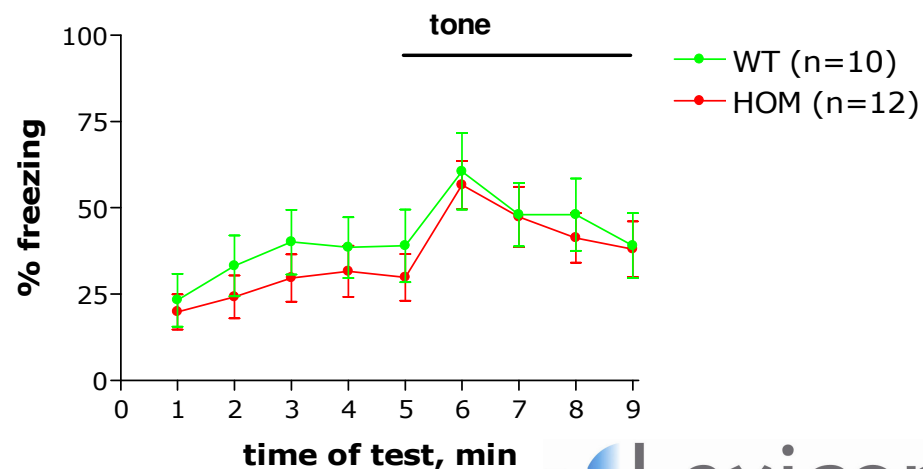


CSNK1E KO Mice – Trend Toward Lower Learning & Memory; Only Evident in Males

**Context + Tone
Freezing Male**



**Context + Tone
Freezing Female**



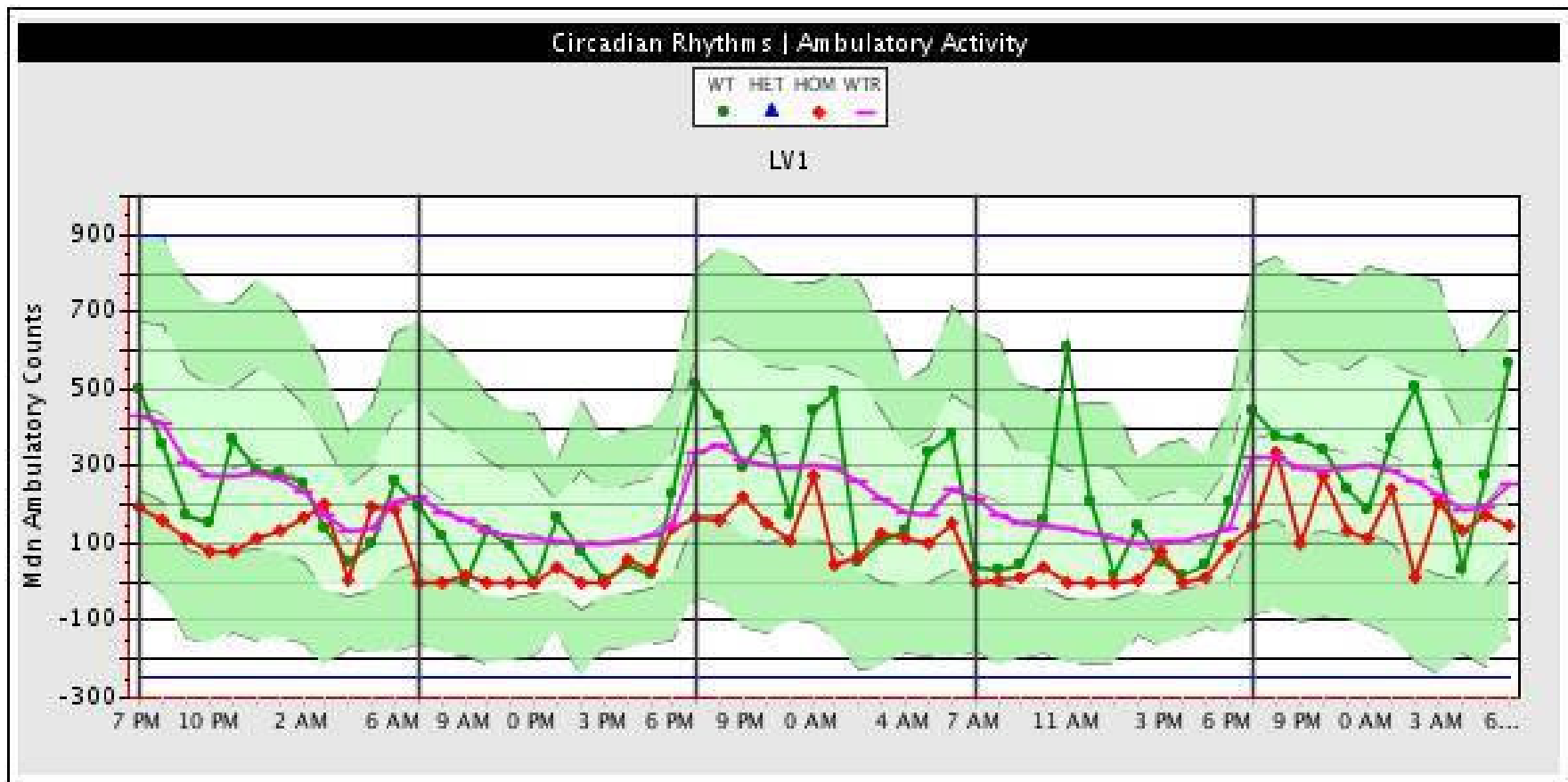
Summary of Evaluation of Lexicon KO Mice – CSNK1E

- Under a standard light–dark cycle, CSNK1E KO mice exhibit overall normal behavior, in particular locomotor activity
 - Under a standard light–dark cycle, CSNK1E KO mice exhibit more prolonged wakefulness (activity & EEG) than WT mice
 - Under a standard light–dark cycle, CSNK1E KO mice exhibit a slight increase in power of beta–frequency EEG. Beta activity is generally associated with active wakefulness
-
- The data suggest that inhibitors of CSNK1E may prolong wakefulness without affecting locomotor activity *per se*
 - This clock gene has been only moderately investigated by pharmaceutical companies

Task 2: GABRA1

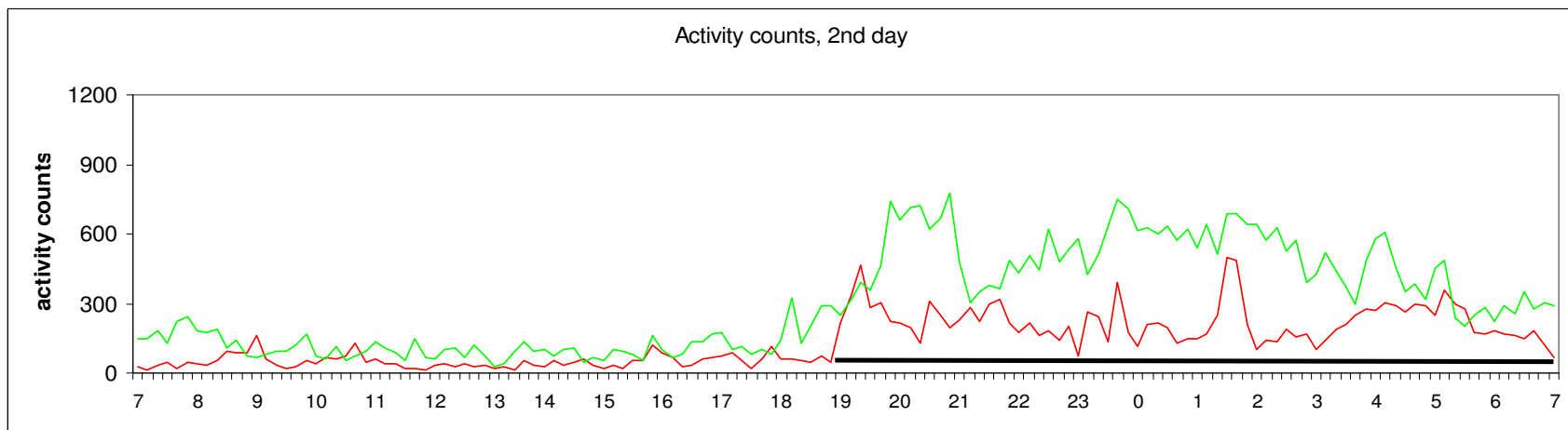
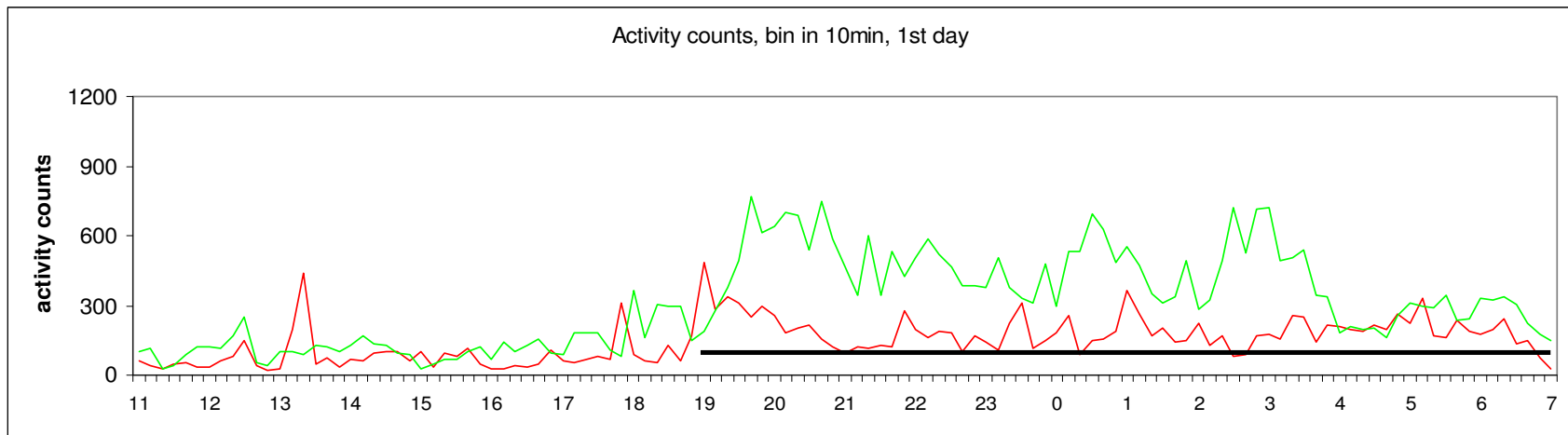
- GABRA1 is the alpha 1 subunit of GABA-A receptor
 - GABRA1 is primarily expressed in the brain and responsible for neuronal hyperpolarization upon GABA receptor activation
 - Benzodiazepines and barbiturates bind to GABA-A receptors and are used as sedatives and hypnotics
-
- In general, KO mice had reduced locomotor activity in EEG cage during the 5 days of recording; more significant during subjective day
 - In OFA and TAC tests, KO mice mice exhibited increased anxiety and decreased locomotor activity, but comparable learning & memory, to that of WT mice
 - KO mice spent significantly more time in NREM and less time in waking & REM states in both subjective night & day
 - KO mice showed significantly higher EEG power at 4-7Hz and >10Hz, especially during waking and REM states

GABRA1 KO Mice Exhibit Reduced Locomotion in Home-Cages



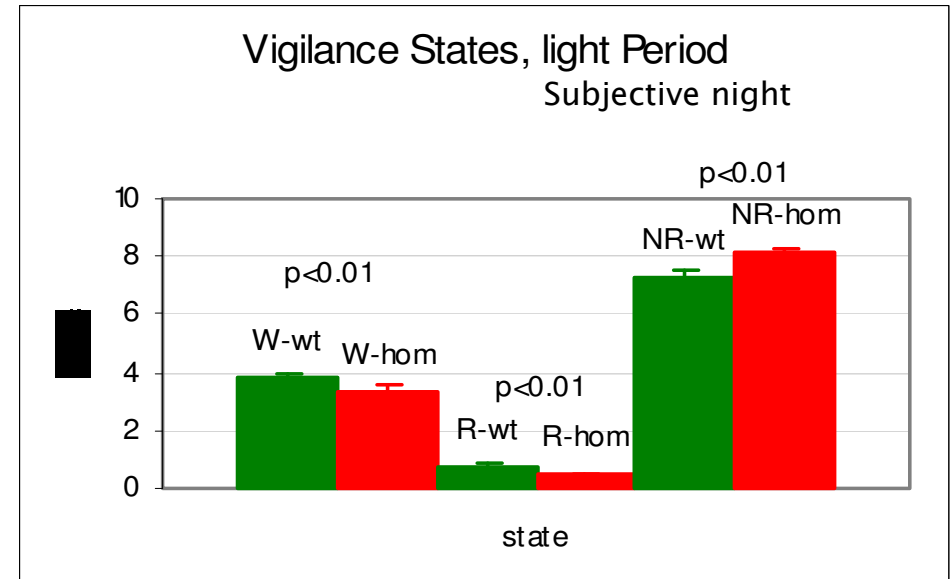
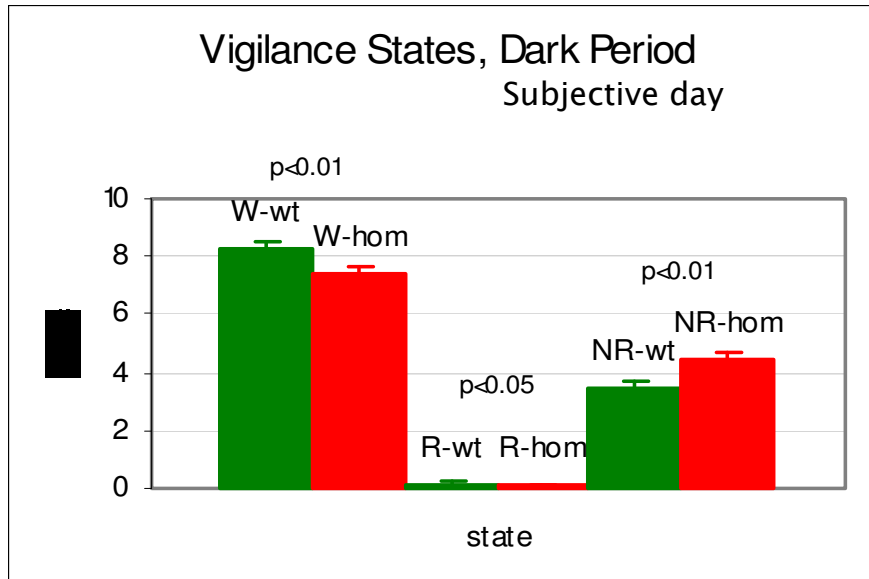
Locomotor Activity of GABRA1 KO mice is reduced as measured in EEG recording cages (10 min bins)

- consistent with home-cage circadian activity phenotype

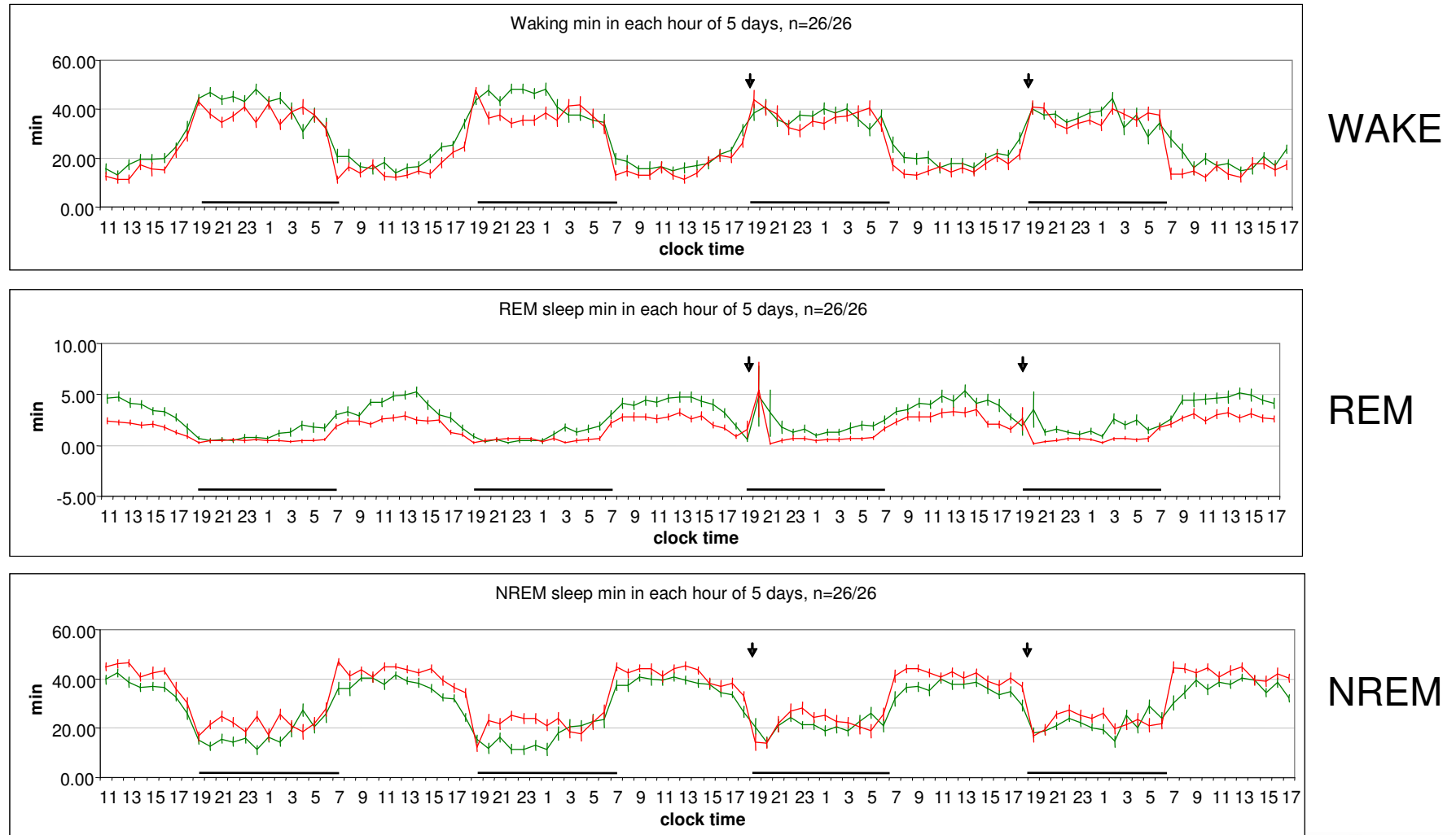


GABRA1 KO's spend significantly less time in waking & REM, but more time in NREM, in both subjective day & night

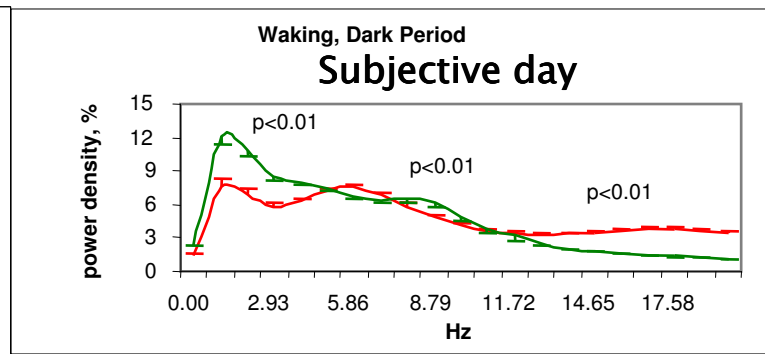
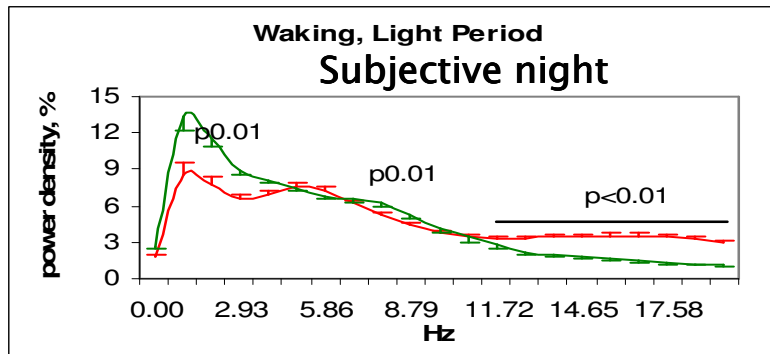
Vigilance States Distribution



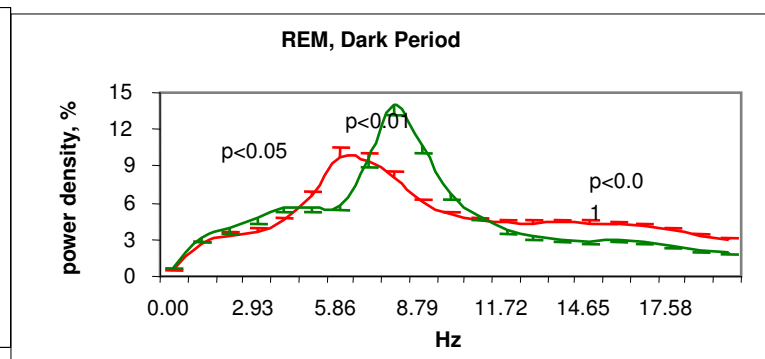
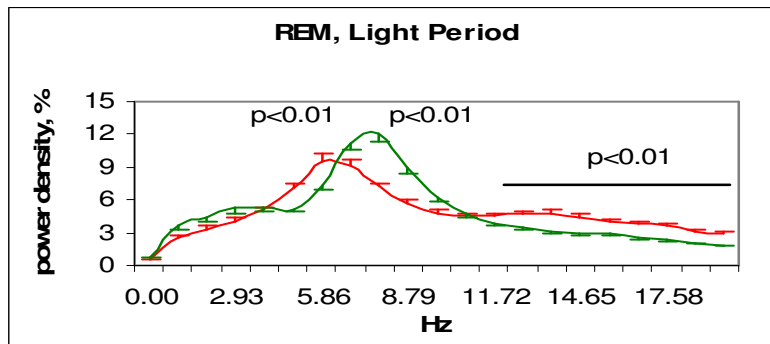
GABRA1 KO mice spent less time in waking and REM, & more time in NREM



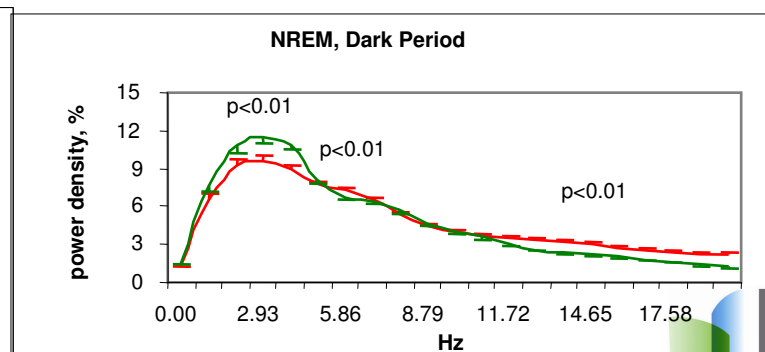
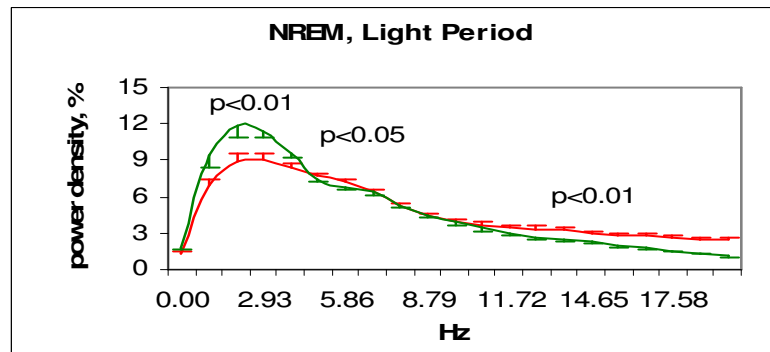
GABRA1 KO mice exhibit changes in the power of some EEG frequencies ranges



Increased beta frequencies;
Decreased delta



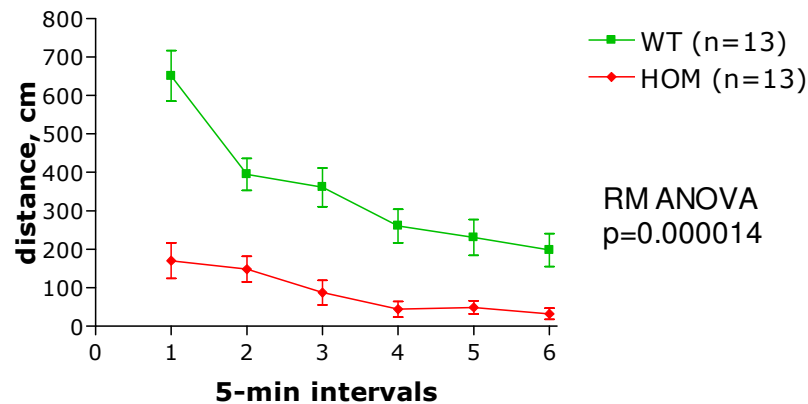
Increased beta frequencies;
Theta shifted to slower frequencies



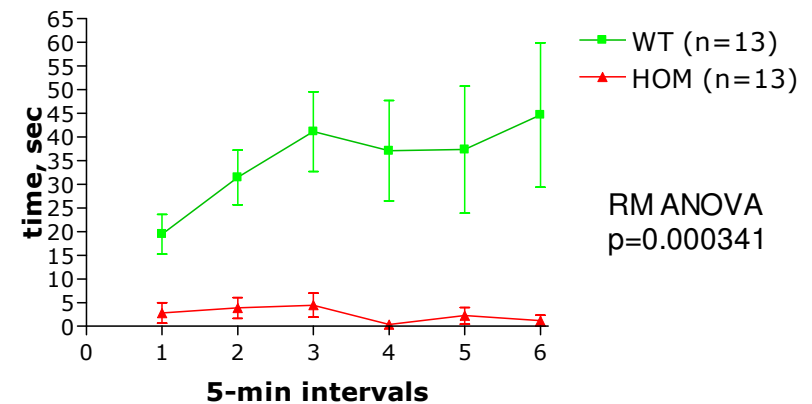
Increased beta frequencies
Decreased delta

Male GABRA1 KO Mice Exhibit Decreased Locomotion and Increased Anxiety (decreased time-in-center) in OFA

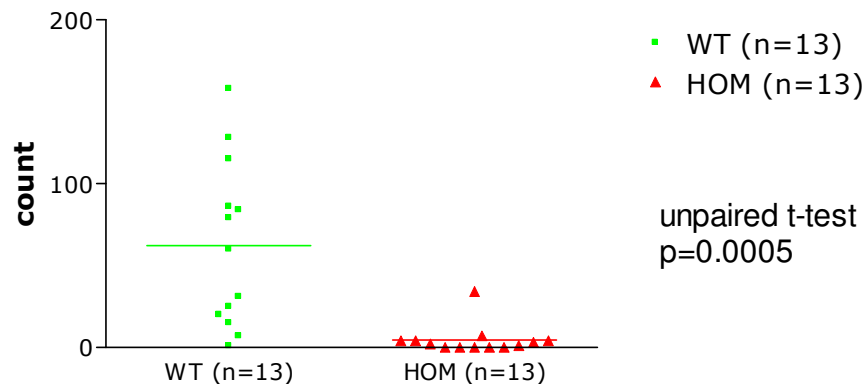
Total distance-M



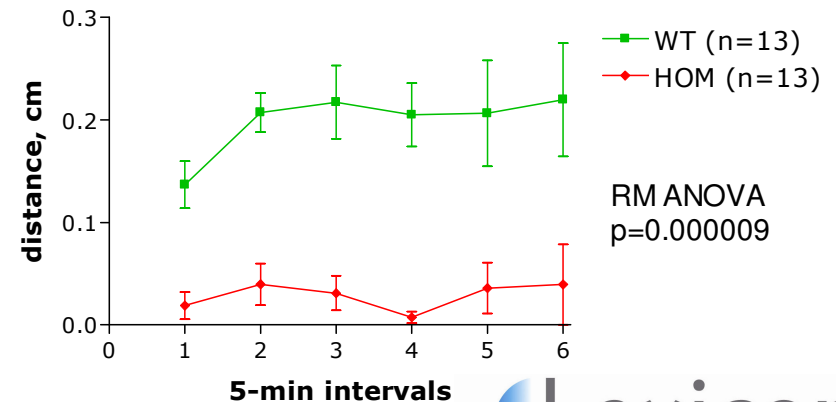
Time in Center-M



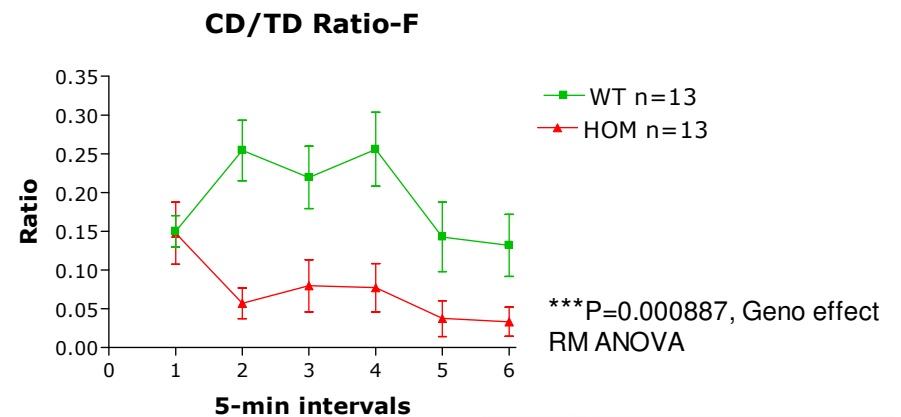
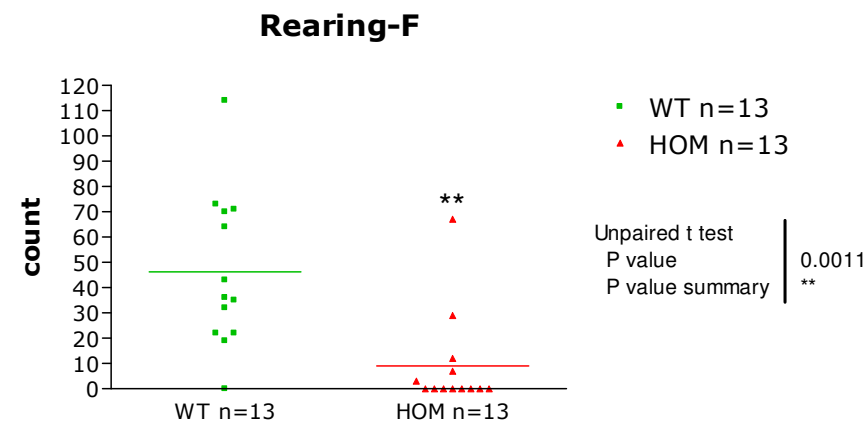
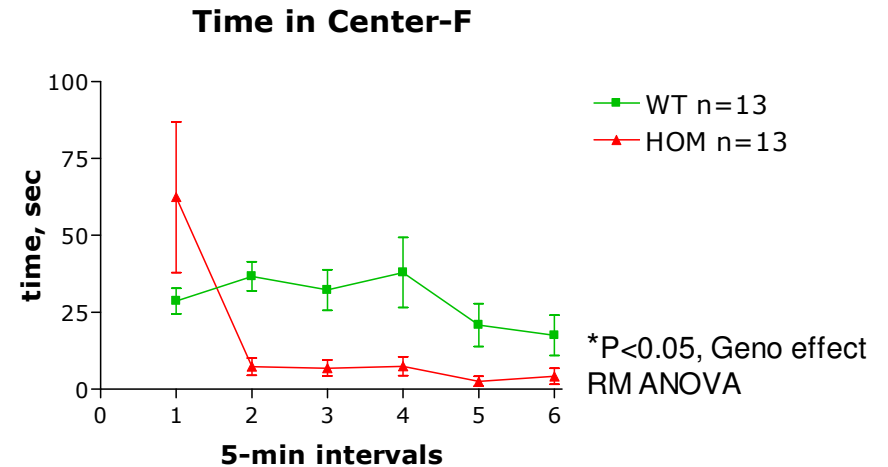
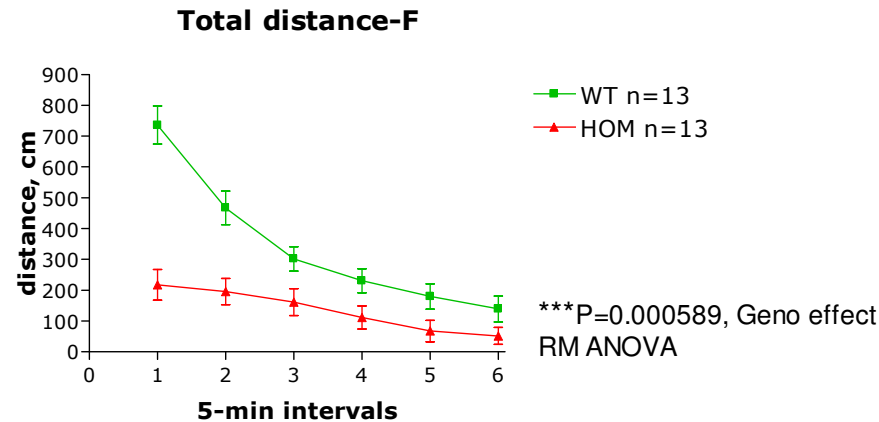
Rearing-M



CD/TD Ratio-M

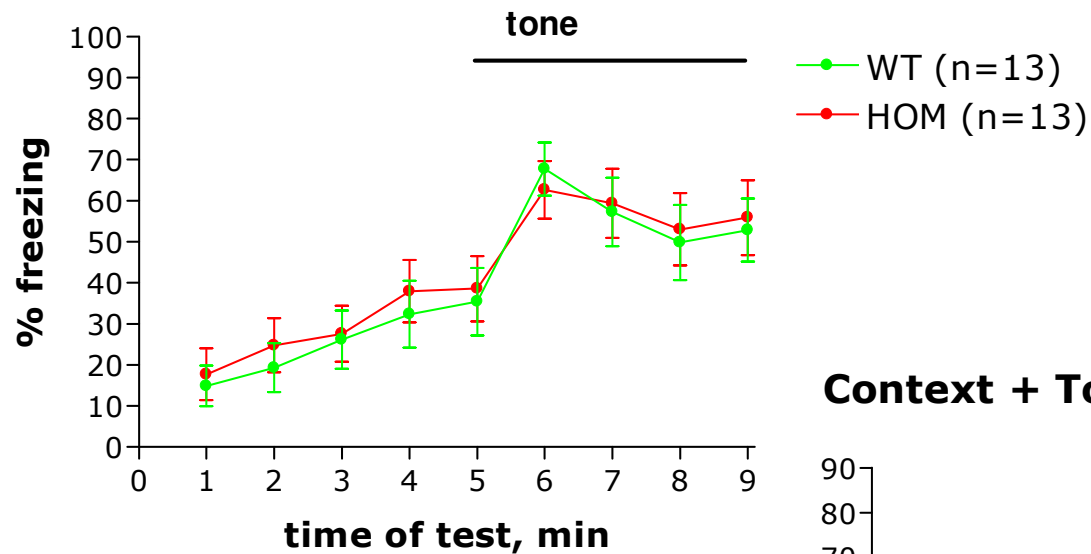


Female GABRA1KO mice exhibit same pattern of activity & anxiety-related behavior as males (OFA)

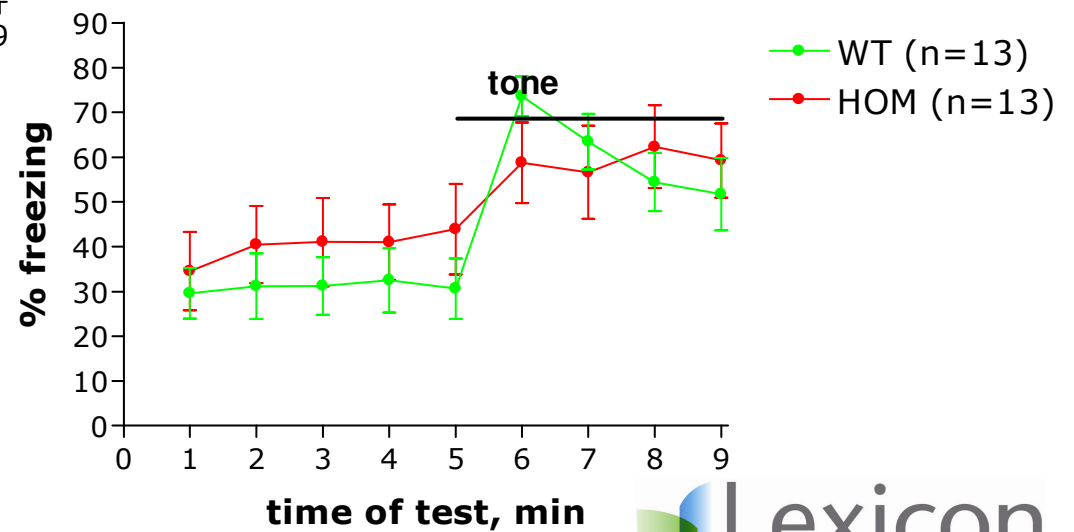


Both Genotypes of GABRA1 mice exhibit comparable learning and memory in delay conditioning task

Context + Tone Freezing Female



Context + Tone freezing - Males



Summary of evaluation of Lexicon KO mice – GABRA1

- GABRA1 KO mice exhibit numerous and substantial changes in behavior and EEG
 - This target is the focus of many sleep aids. It does not require additional efforts to develop pharmacological agents
-
- Although this target and KO's of this target are well-known, we have, as far as we are aware, the first EEG recordings from KO mice. This, along with results from some of the novel anxiety tests we employ, may be the subject of a future publication.

Task 3: Evaluate Lexicon KO's

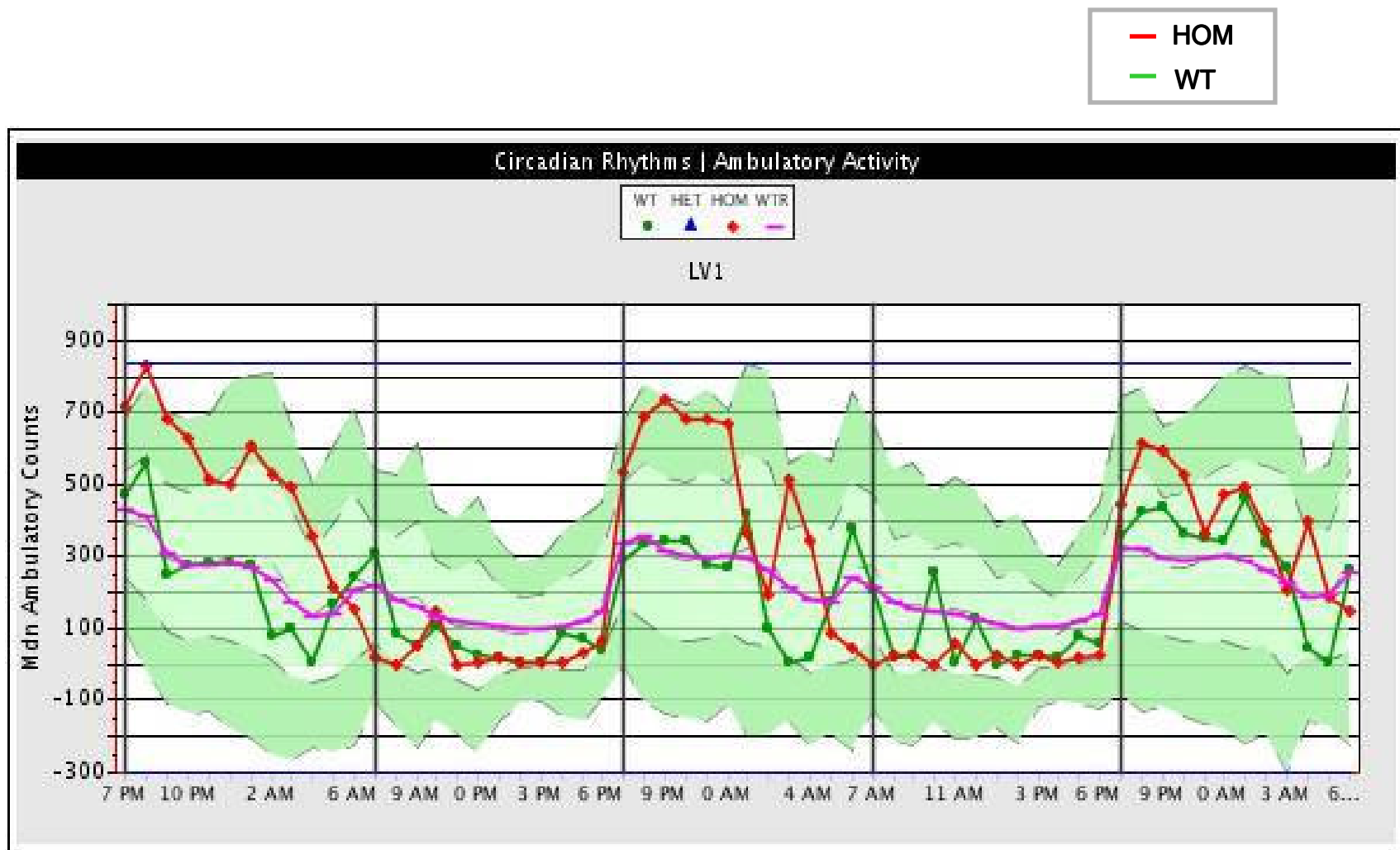
- PRT282T1
- PRT282C1
- GPR710N1

Task 3: Evaluate Lexicon KO's _ PRT282T1 / PRT282C1

- Initial observation - decreased locomotion during subjective night and increased locomotion during subjective day in circadian test- sleep better and get up ready for action; and increased locomotion in novel open field test
 - Phenotype repeated in 4 different alleles or related gene KO's
-
- Both genotypes appeared similar locomotion but KO mice exhibited reduced exploratory activity and increased anxiety level in OFA
 - KO mice showed comparable amount of sleep/wake time across light and dark cycles.
 - KO mice had higher EEG power spectral in all vigilance states, but the overall variation is big. EEG power density may reveal if there is true difference.

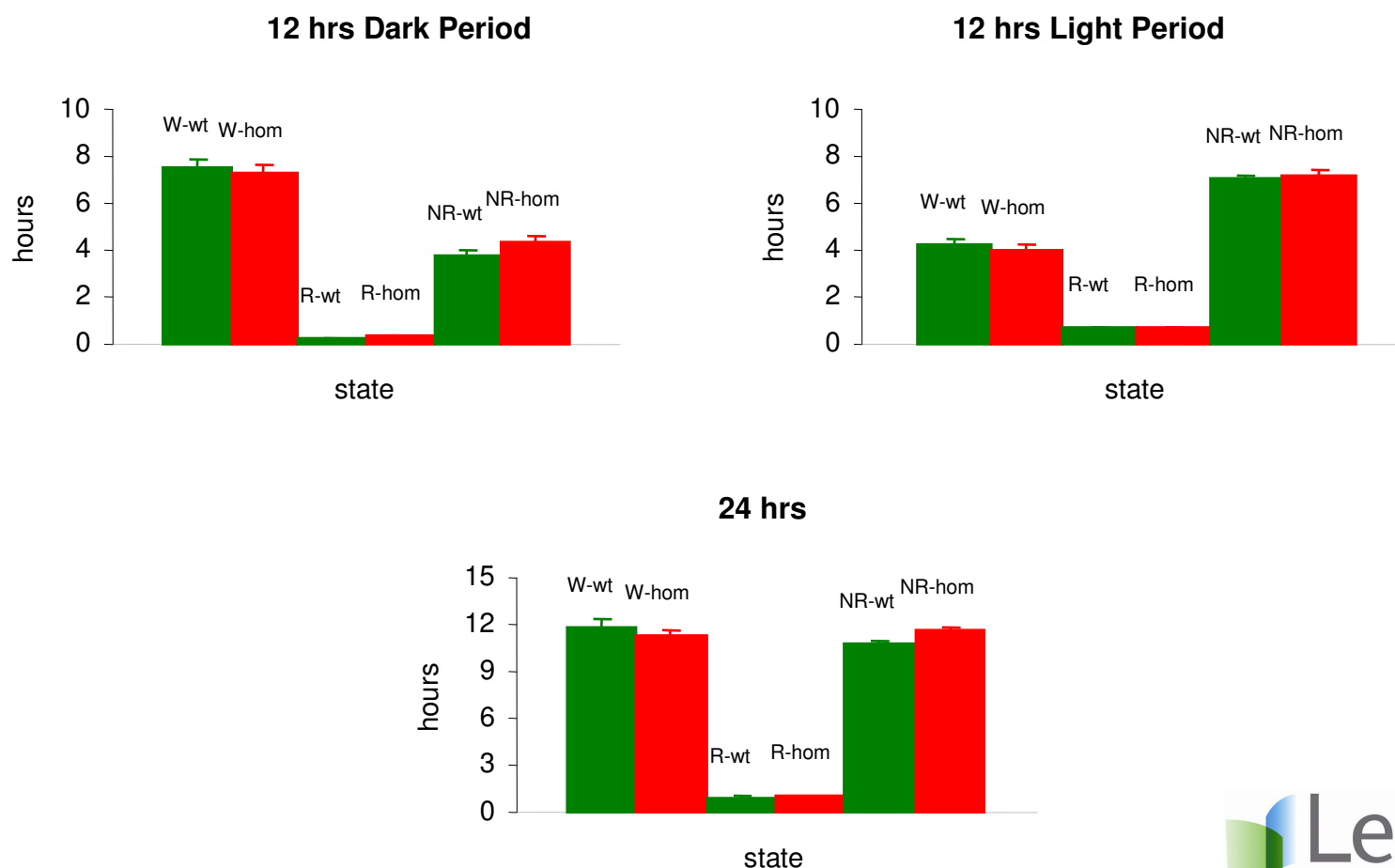
Original Phenotype

Locomotor activity in home-cage is increased in subjective day

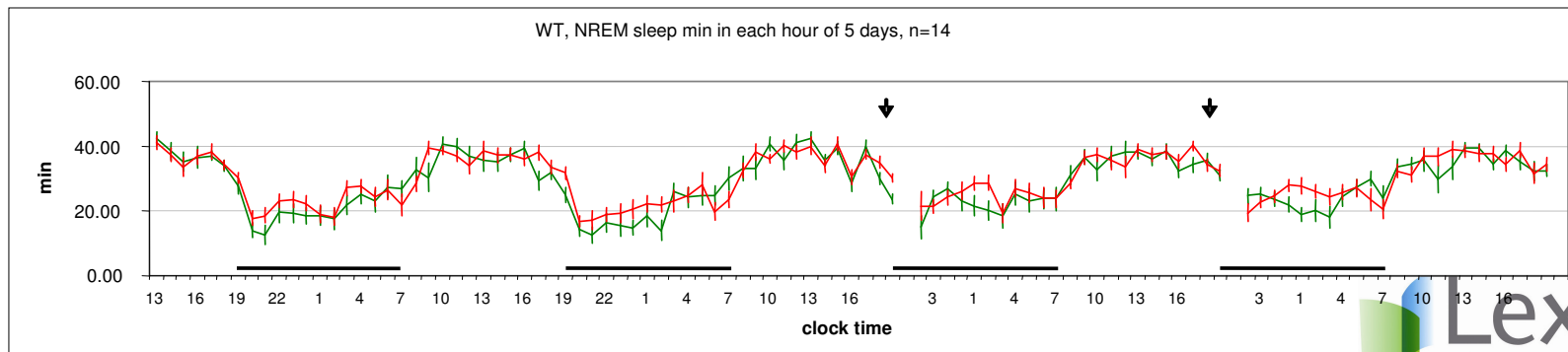
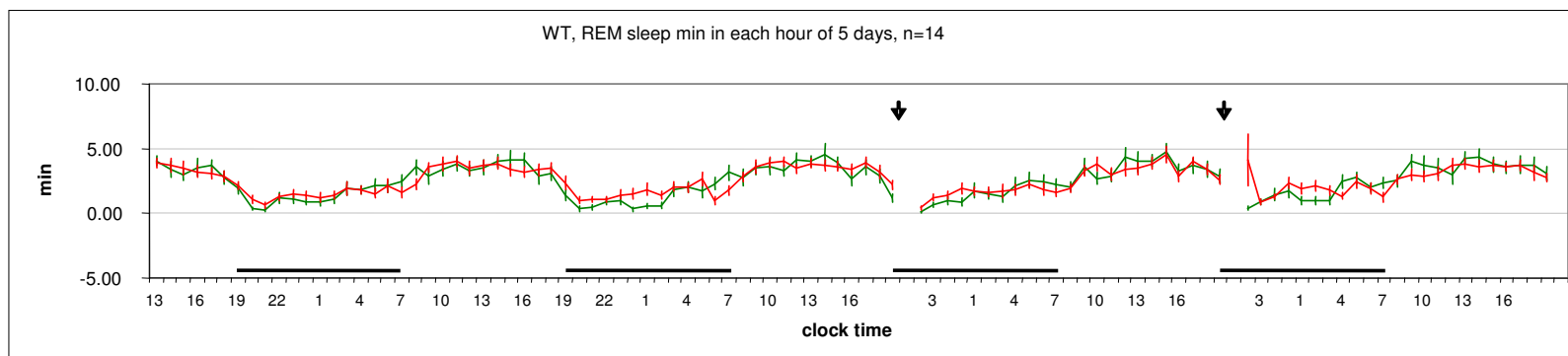
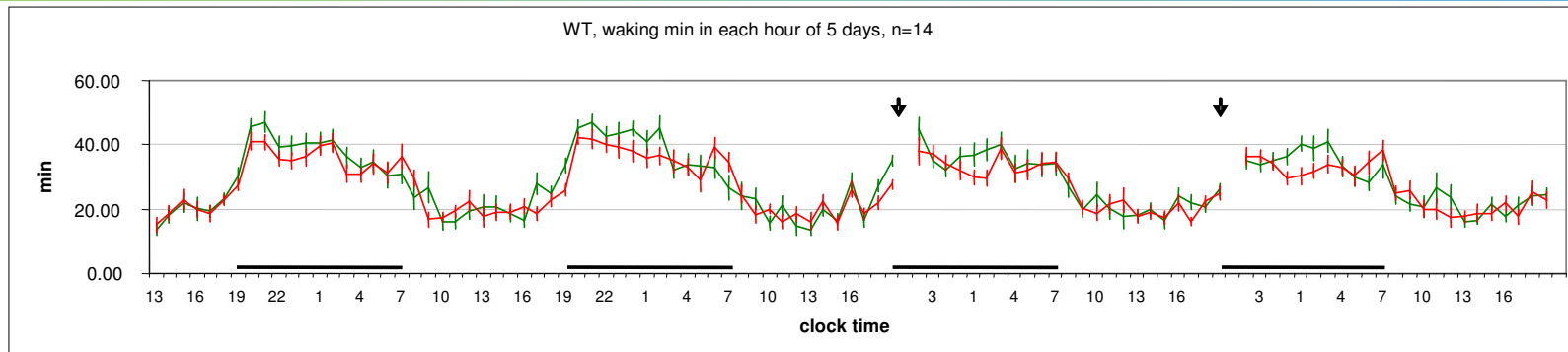


Distribution across, and time within, vigilance states appears very similar for KO & WT mice

Vigilance states distribution not as expected given original dramatic differences in locomotor activity

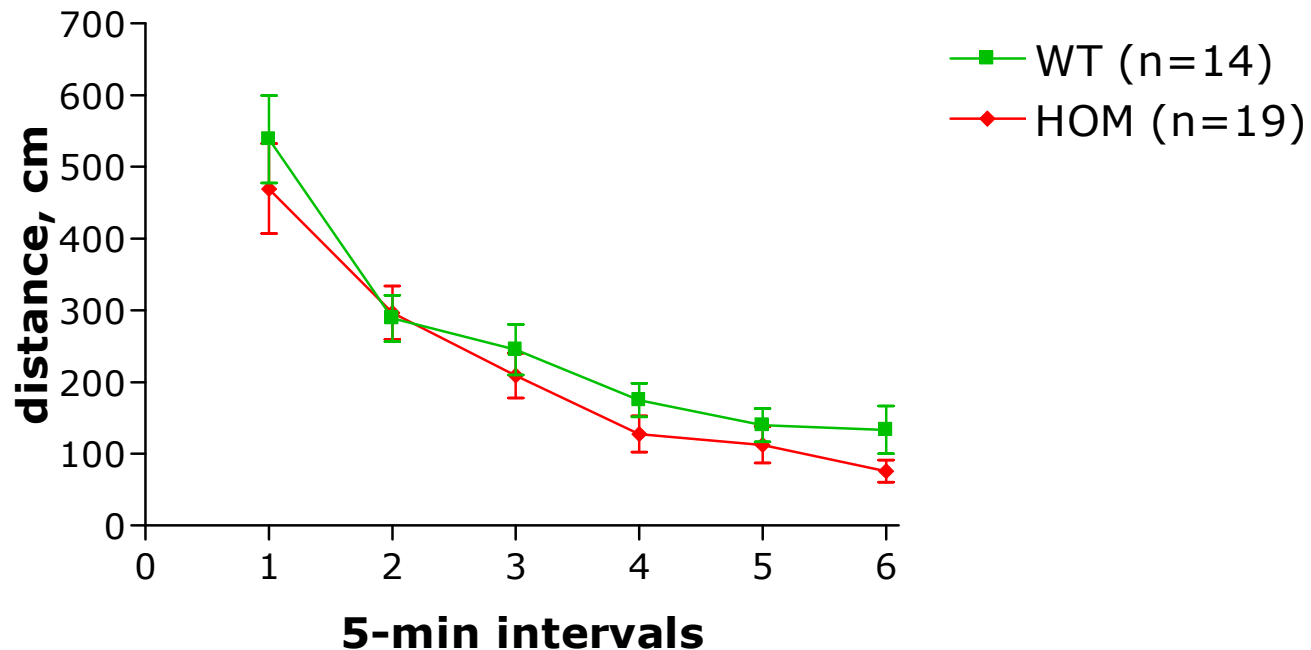


Amount of W, REM, and NREM across Light/Dark Cycles – both genotypes appear similar, not as expected



PRT282T1 KO – no differences in total distance traveled in novel open field (7pm)

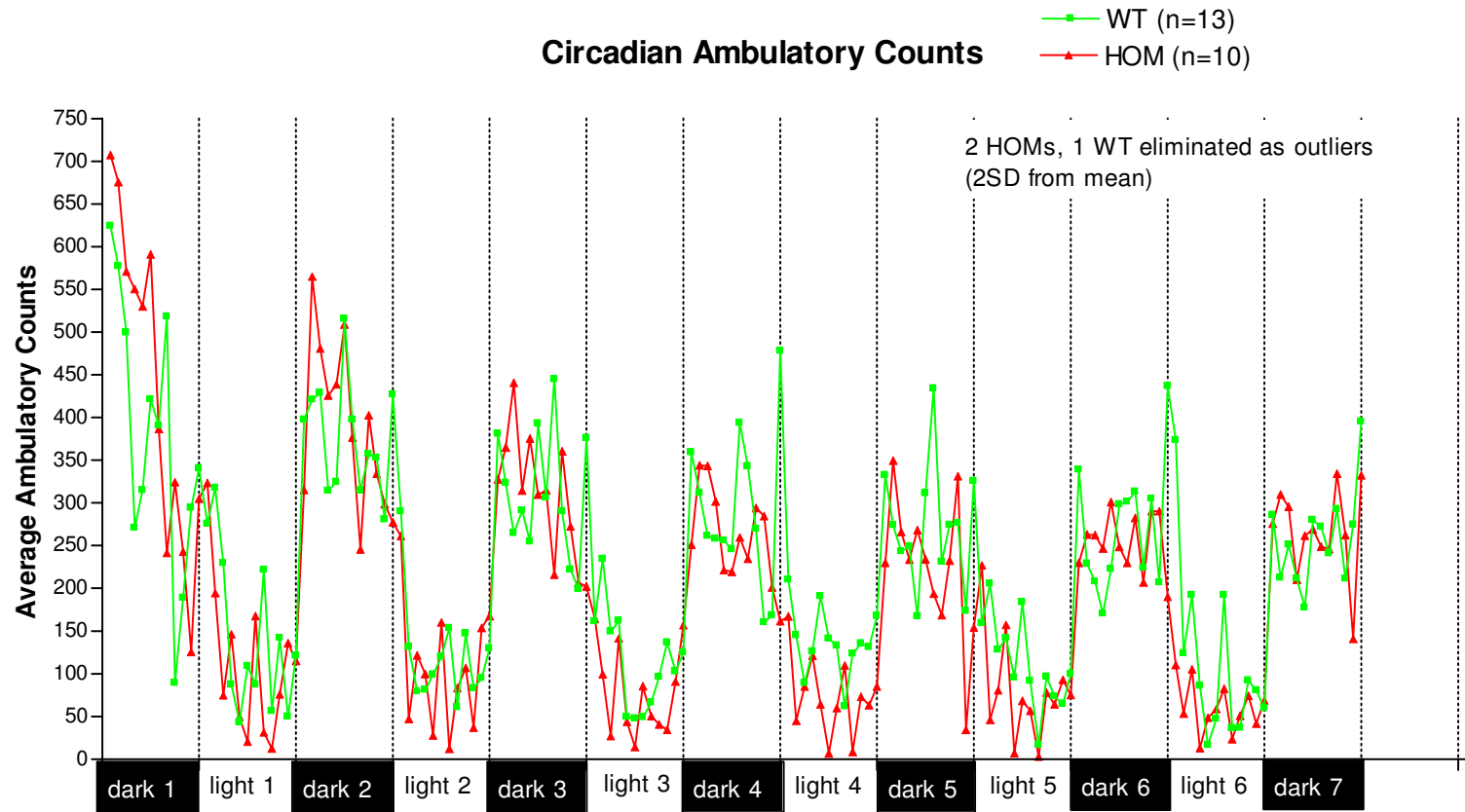
Total distance-All



1 M-WT excluded, very low values of TD

Taken together, this data suggested that the phenotype had dramatically weakened or disappeared

Task 3: PRT282C1 – KO phenotype has disappeared during subsequent breeding – genetic background shift?

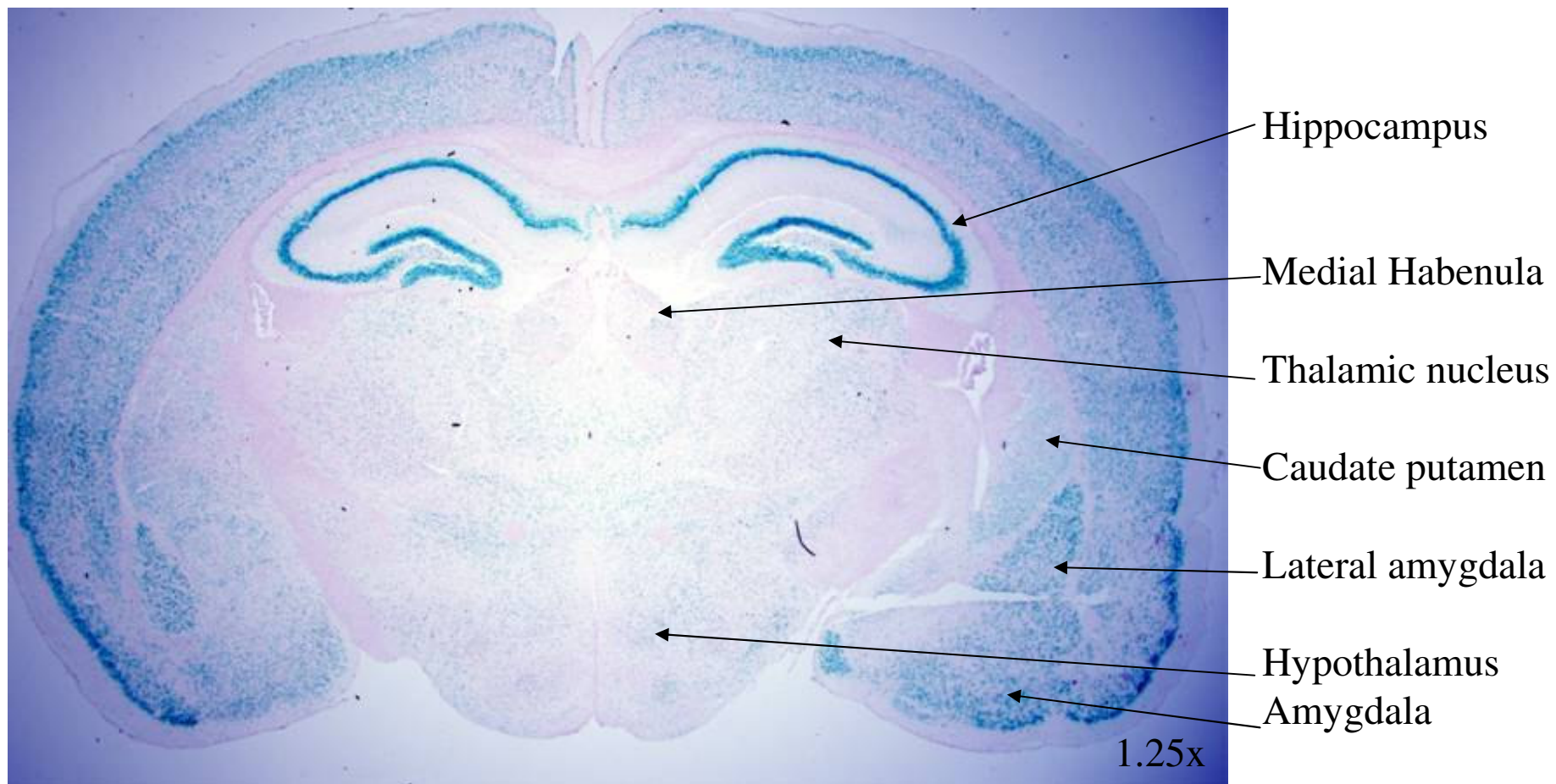


Back-cross breeding is ongoing to try to re-establish phenotype

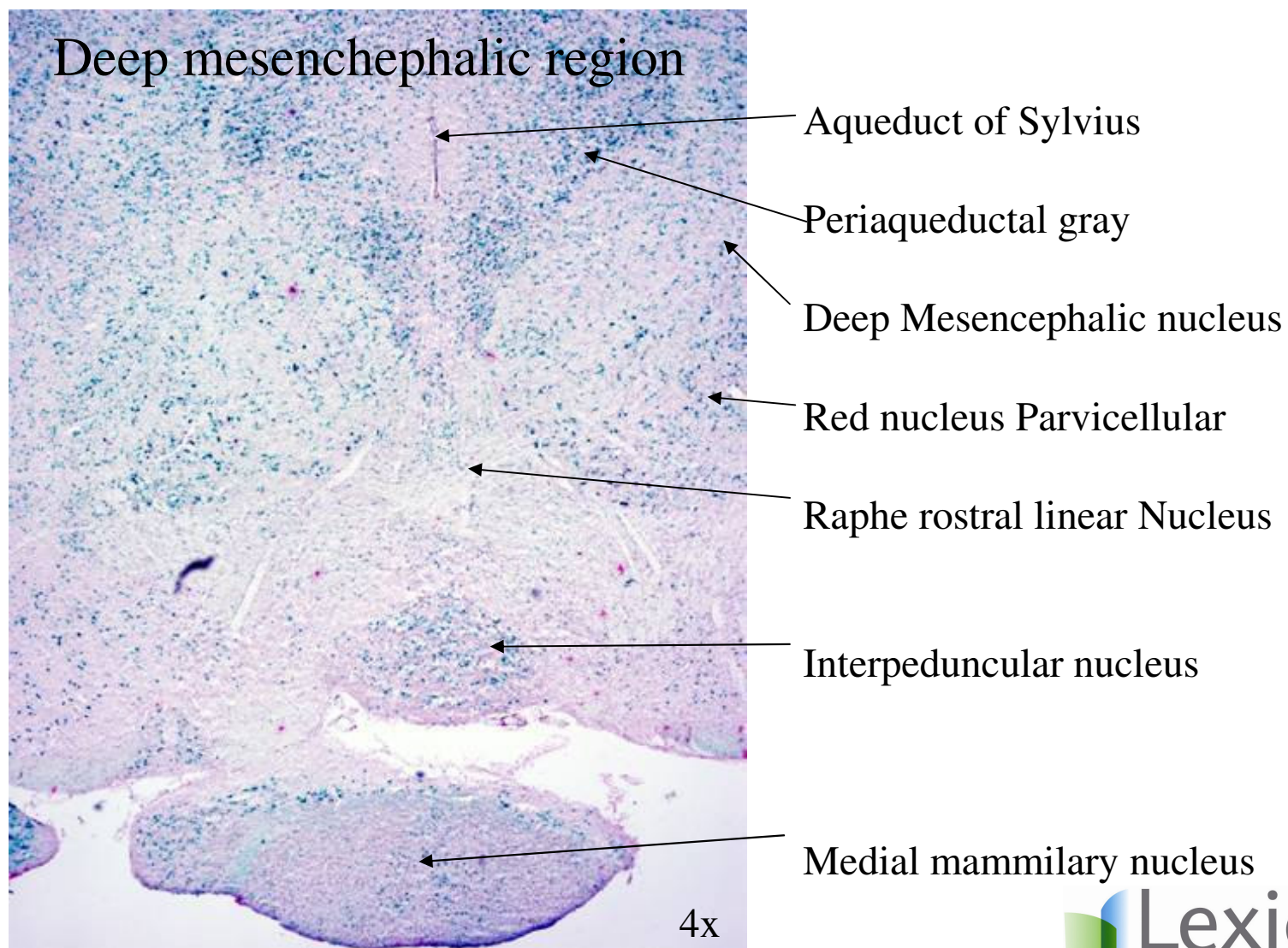
Task 3: Evaluate Lexicon KO's _ GPR710

- Receptor
 - Primarily expressed in CNS
 - Initial observation - decreased locomotion during subjective night
-
- 1st confirmation study
 - KO mice spent more time in NREM at beginning of subjective night
 - KO mice were more active at the beginning of subjective day
 - KO mice habituated more quickly in novel open field
-
- 2nd confirmation study
 - All phenotypes observed from 1st cohort study replicated
 - KO mice exhibited more NREM sleep during sleep deprivation challenge - greater responsiveness to sleep pressure?

GPR710 Gene Expression (LacZ) in Adult Mouse Brain

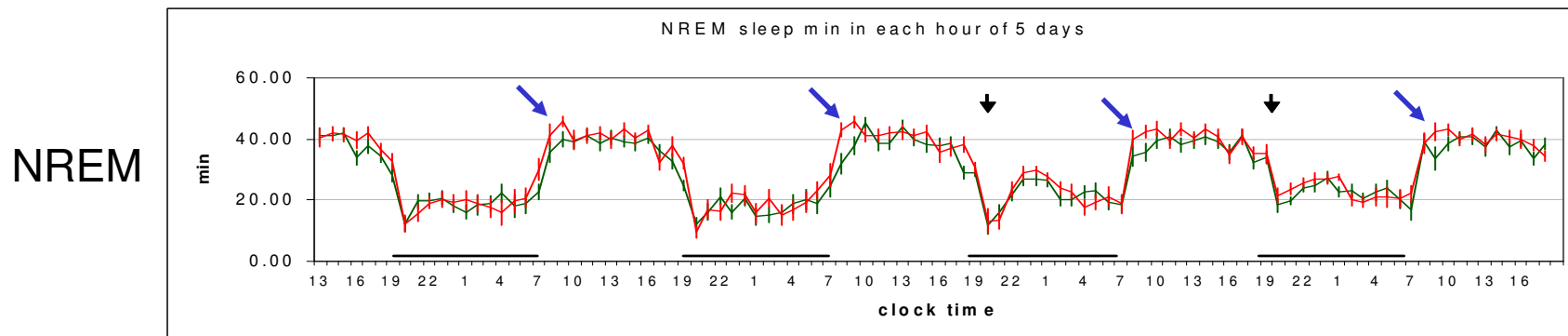
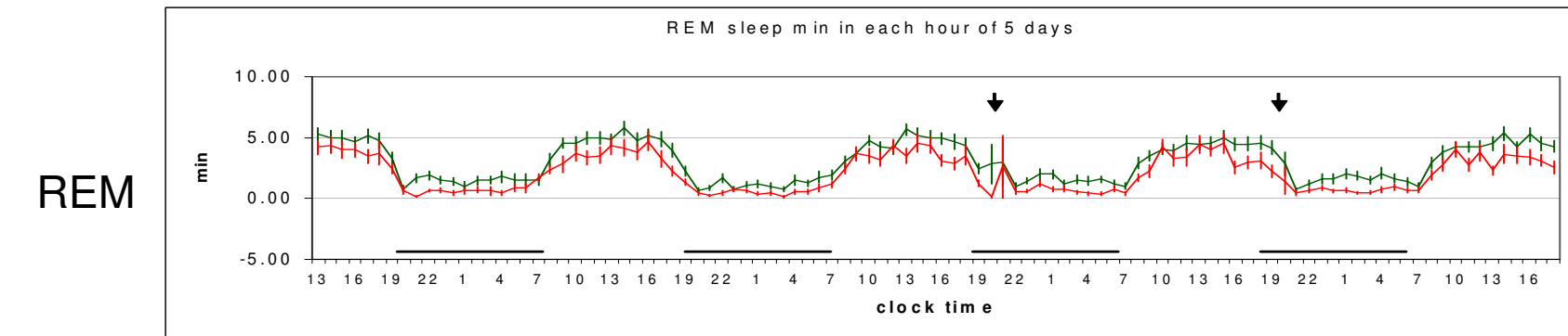
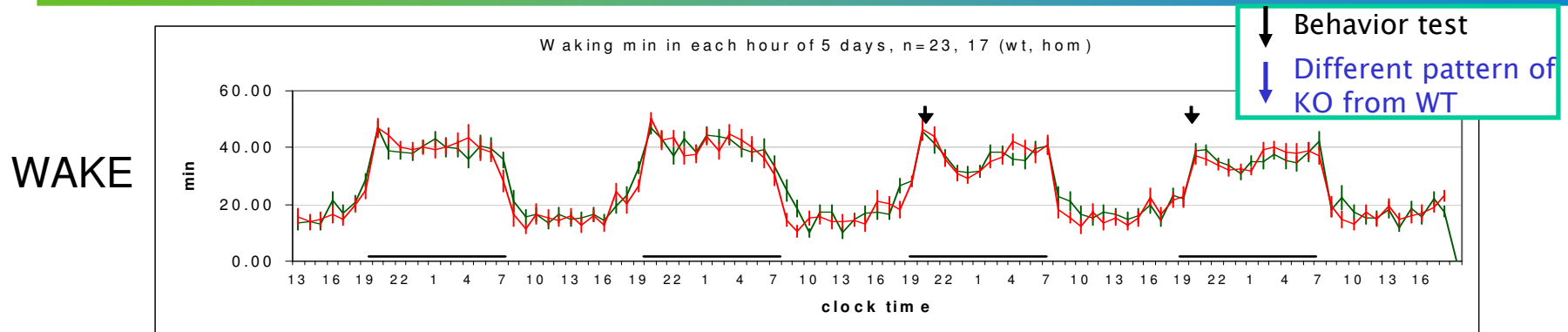


GPR710 – Expressed in Some Sleep Centers in Brain



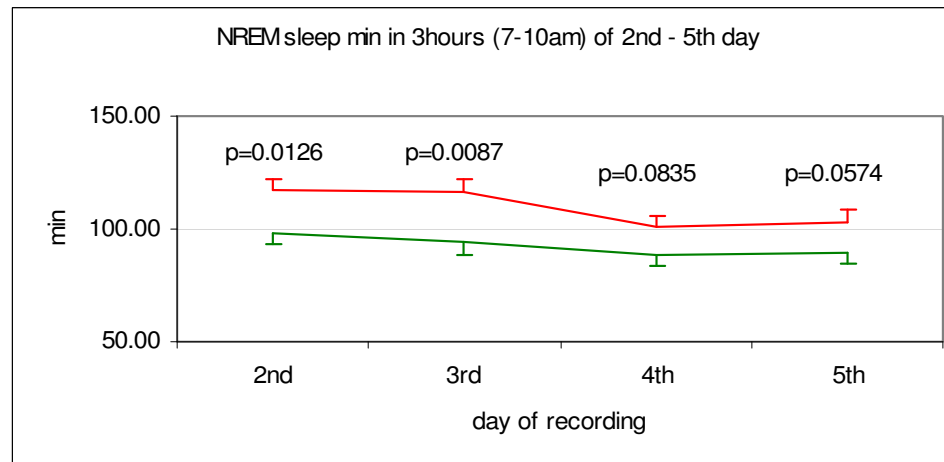
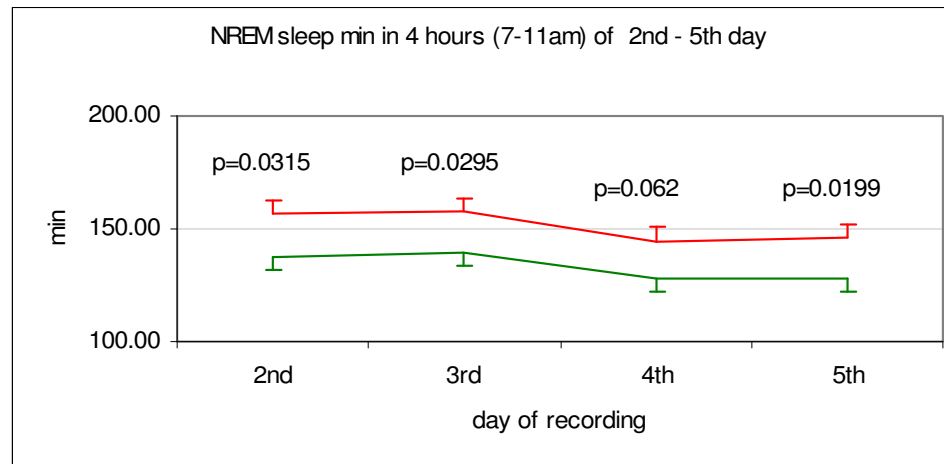
GPR710 KO mice appear to fall asleep faster

- amount of Wake, REM, & NREM across Light/Dark Cycles

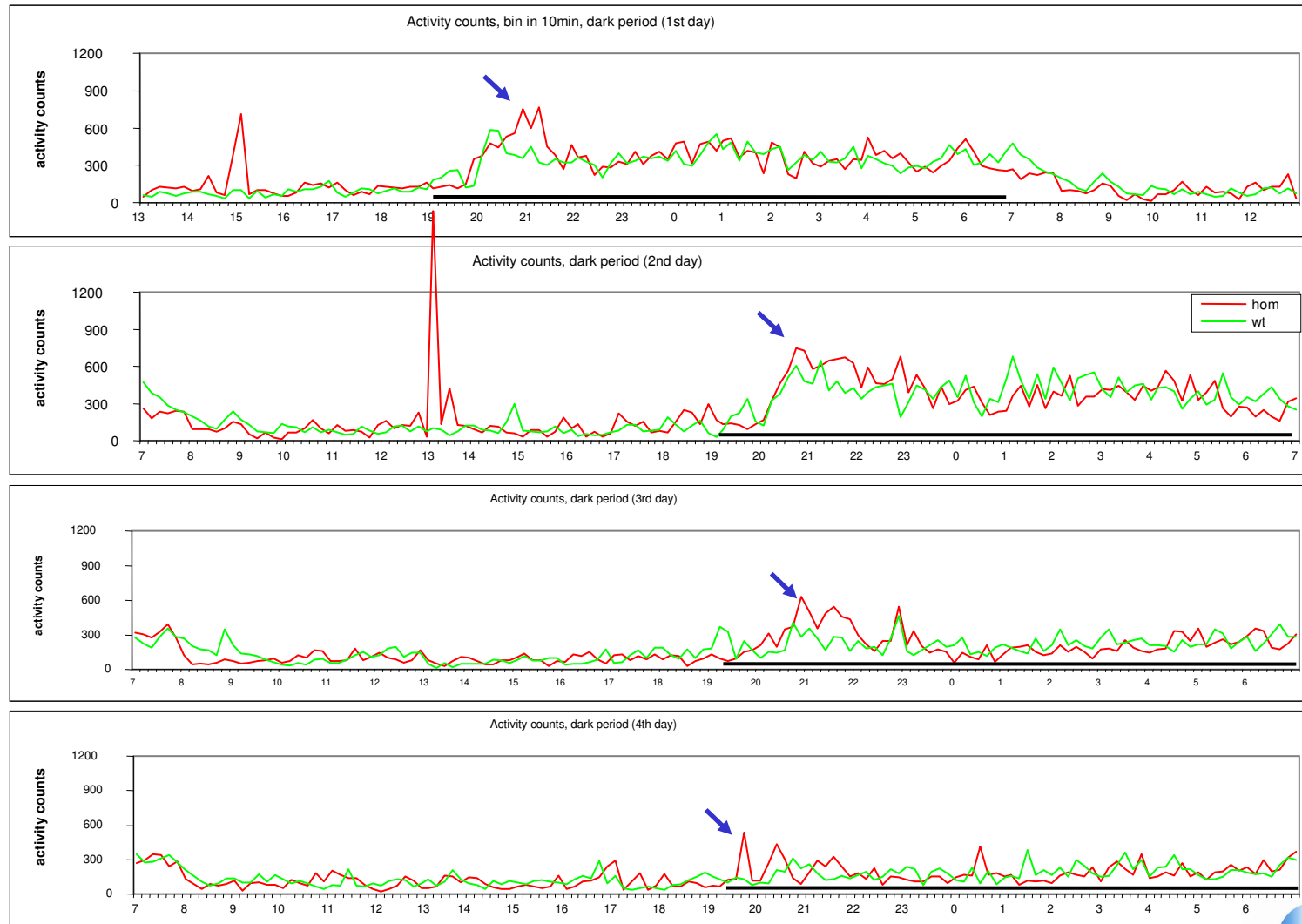


GPR710 KO Mice Spend More Time in NREM at Onset of Subjective Night

KO's fall asleep faster and/or have more efficient sleep at the onset of subjective night (The 3rd day may have the most dependable data as it comes after habituation to the recording situation, and before behavioral testing begins).

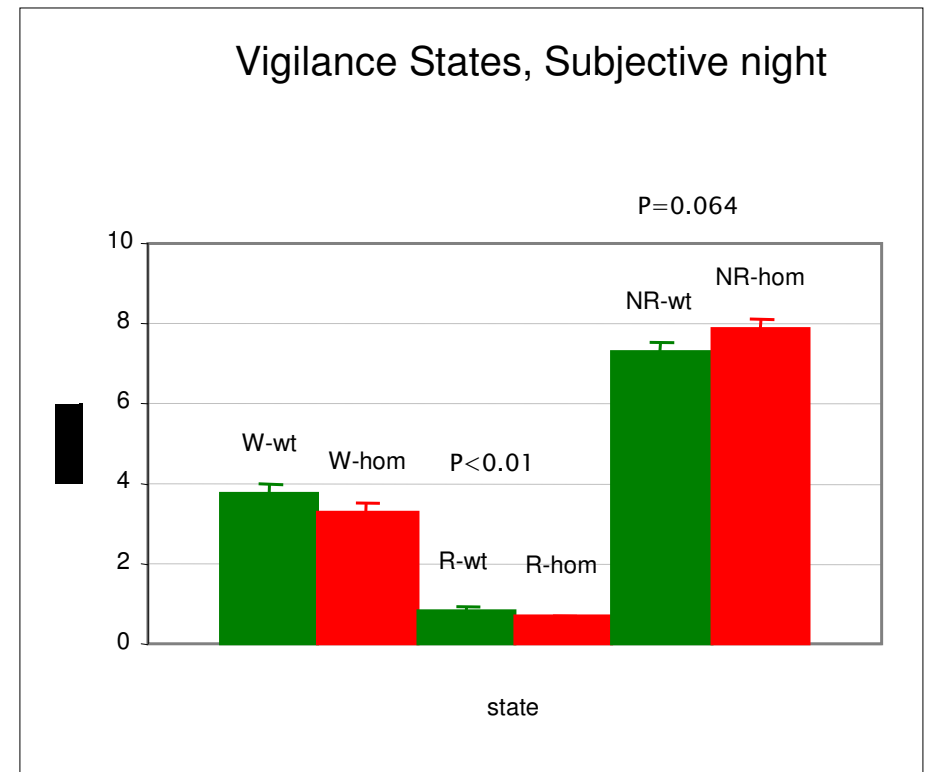
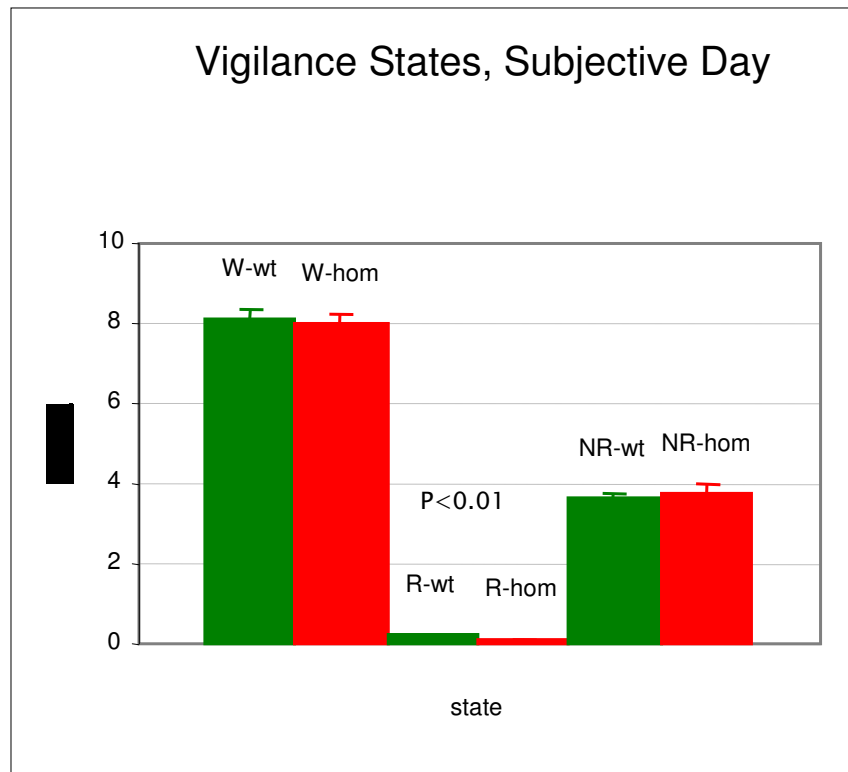


GPR710N1 KO Mice Also Wake Up/Move Around more at the onset of subjective day

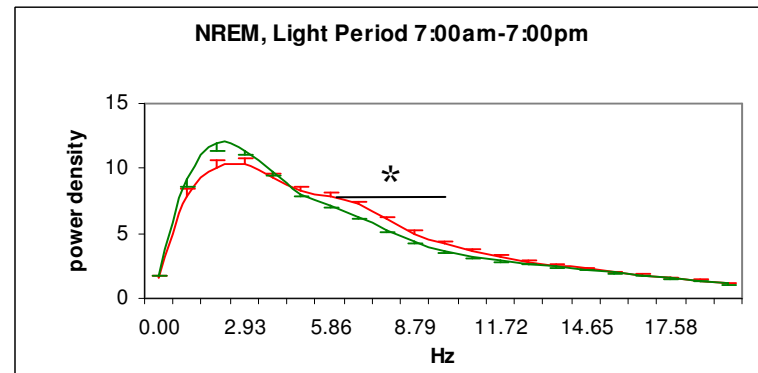
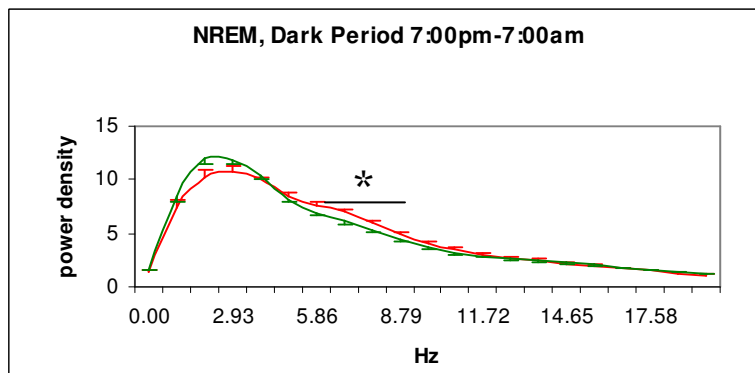
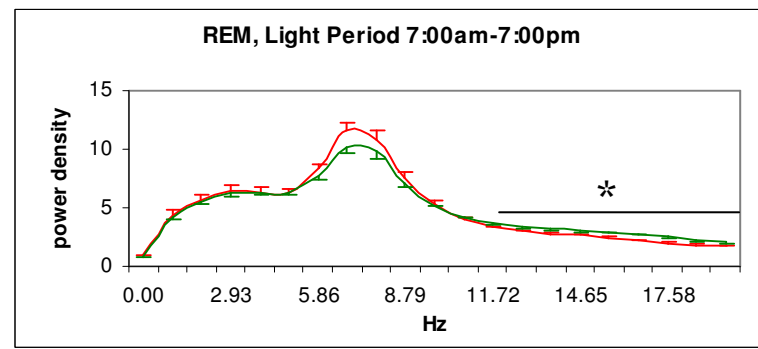
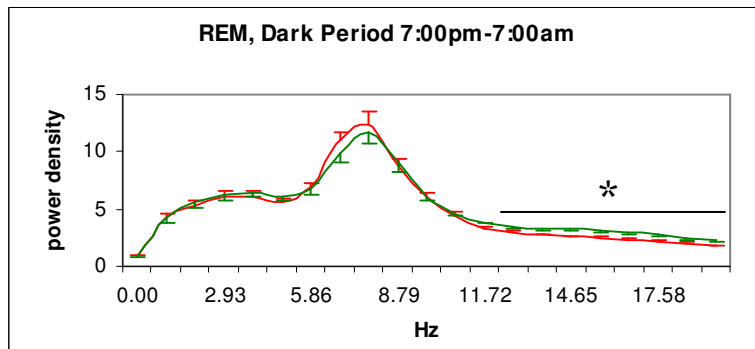
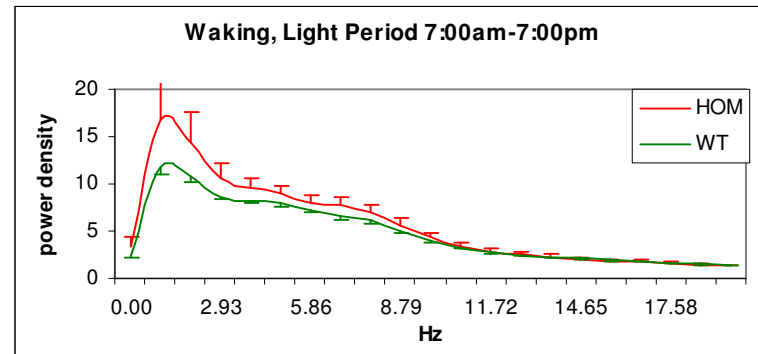
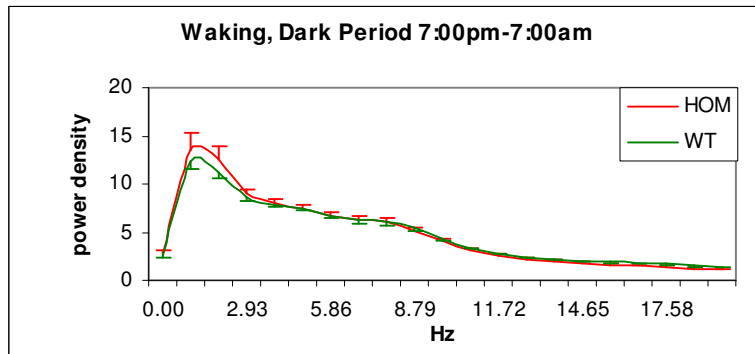


GPR710 KO mice spend less time in REM state in both subjective day & night, & more time in NREM in subjective night

Distribution of Vigilance States over 24 Hrs



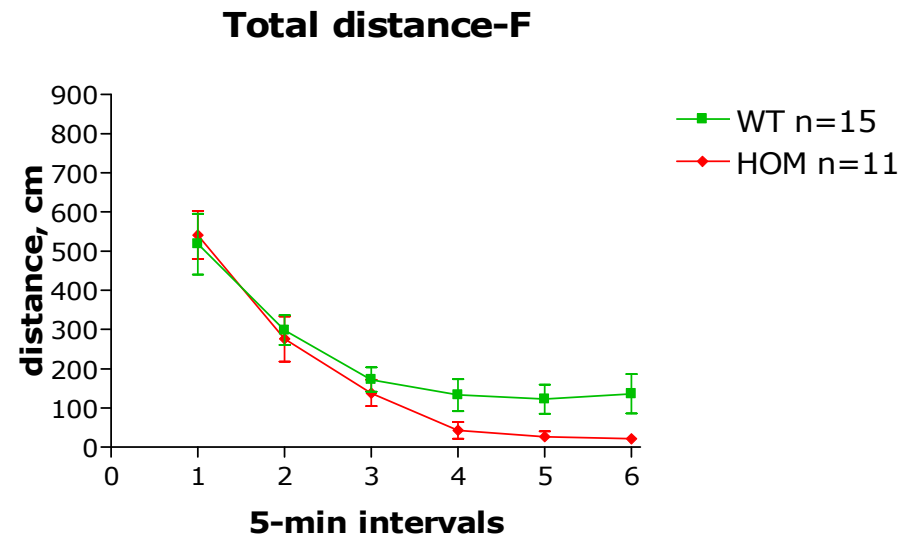
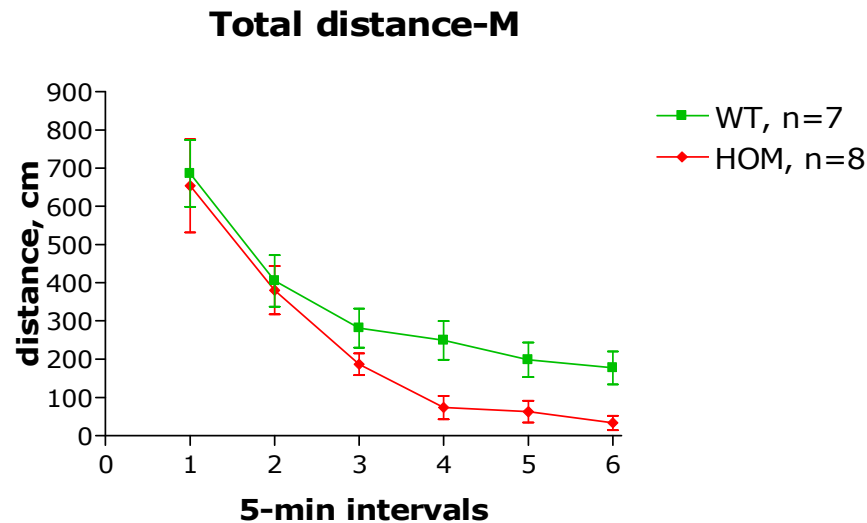
GPR710 KO – Increased theta rhythm in KO mice, prominent in NREM



Open Field, 7 p.m.

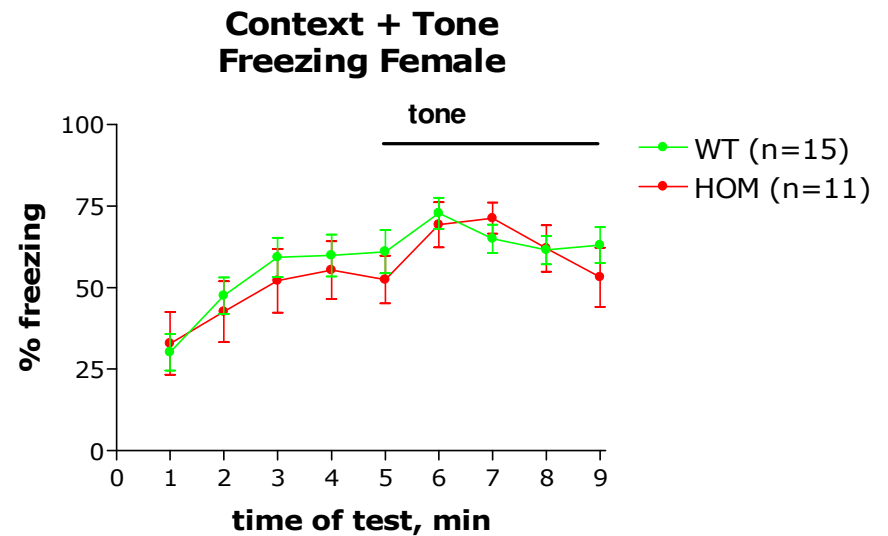
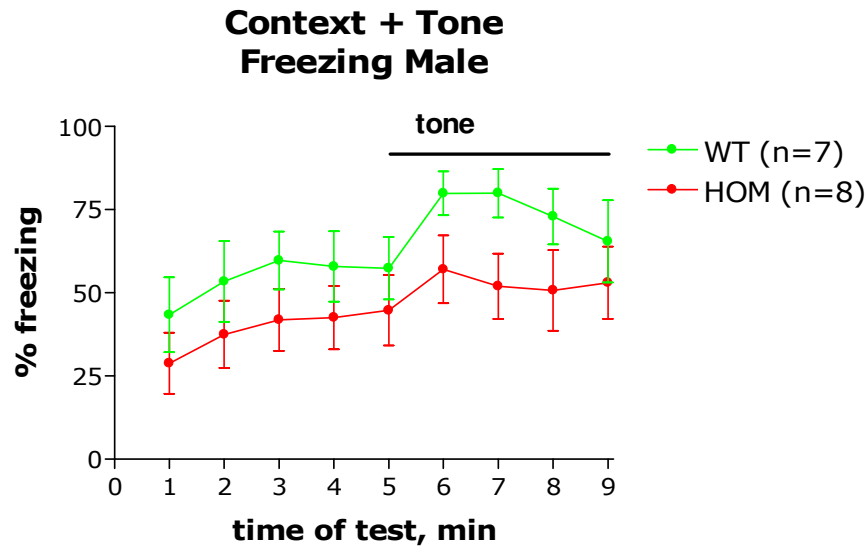
Decreased activity in the Homs towards the end of testing—faster habituation?

If the first interval excluded from RM ANOVA the genotype effect becomes significant ($p=0.03$), if exclude the first two intervals it is even more significant ($p<0.01$)



Delay FC Test, 7 p.m.

No difference between genotypes

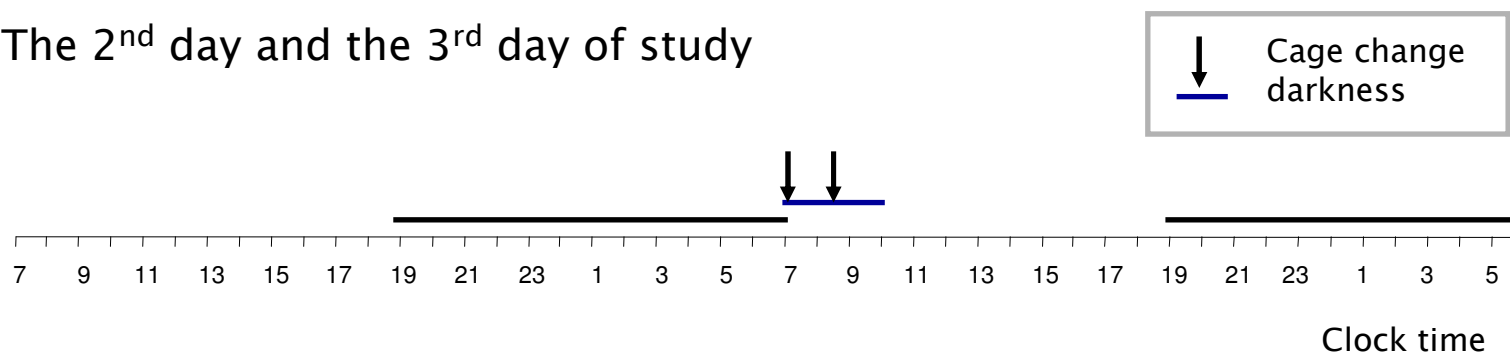


GPR710N1 – 2nd Cohort Confirmation Study in July

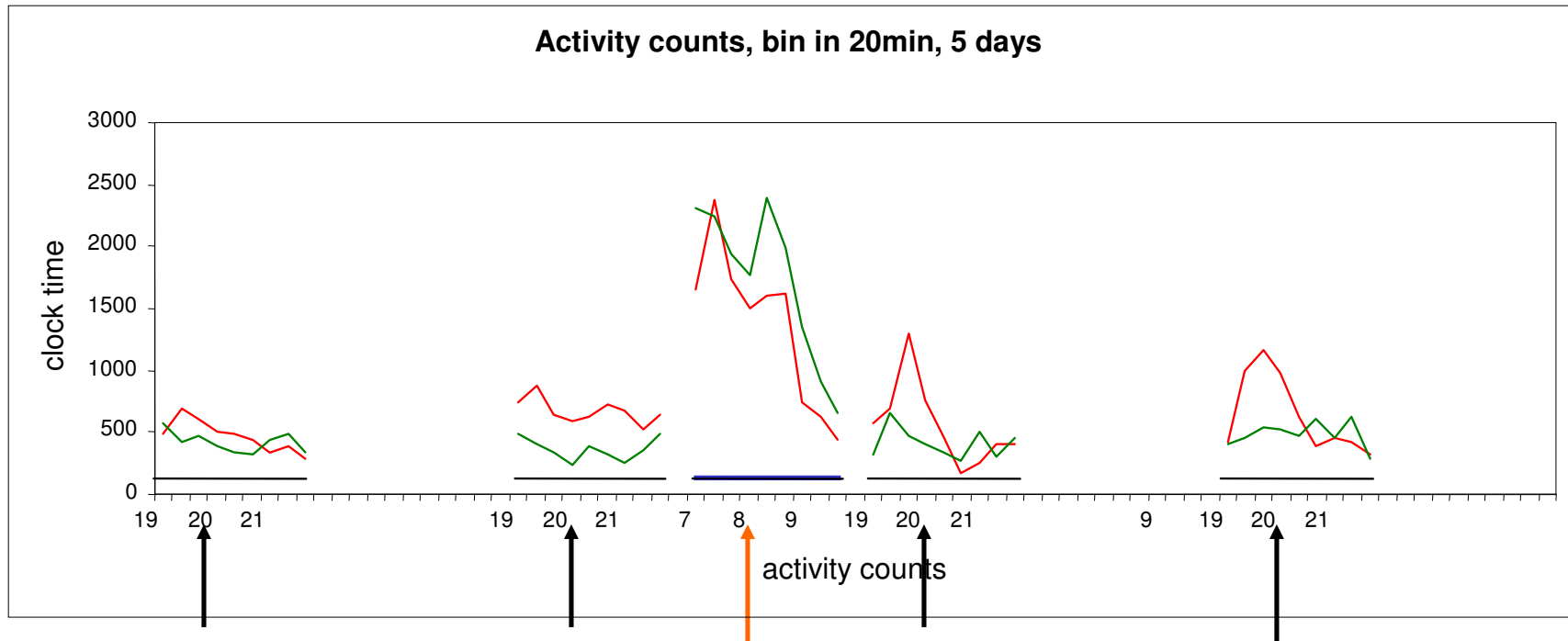
On the third day of sleep study, 3hrs “sleep deprivation” was implemented by:

- 1) changing the subjects' cages twice, at 7:00 & 8:30am, and
 - 2) continuing to leave the mice in darkness (normally a cue for wakefulness) from 7:00-10:00am instead of having the lights come on at 7:00am
- Since this came at the end of subjective day, the mice should have a significant amount of 'sleep pressure'

The 2nd day and the 3rd day of study

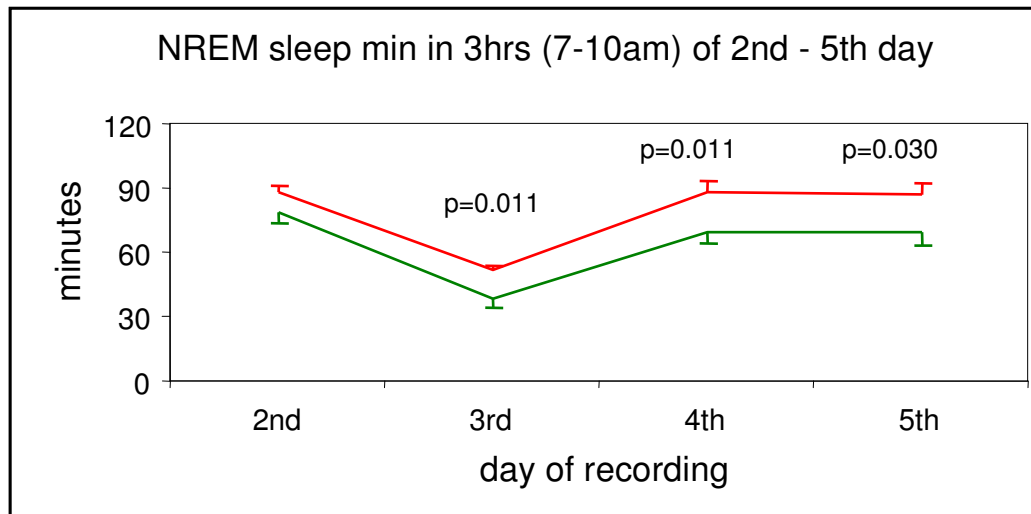


As Seen in the Earlier Cohort, GPR710 KO Mice More Active at the Beginning of subjective day (All Days)

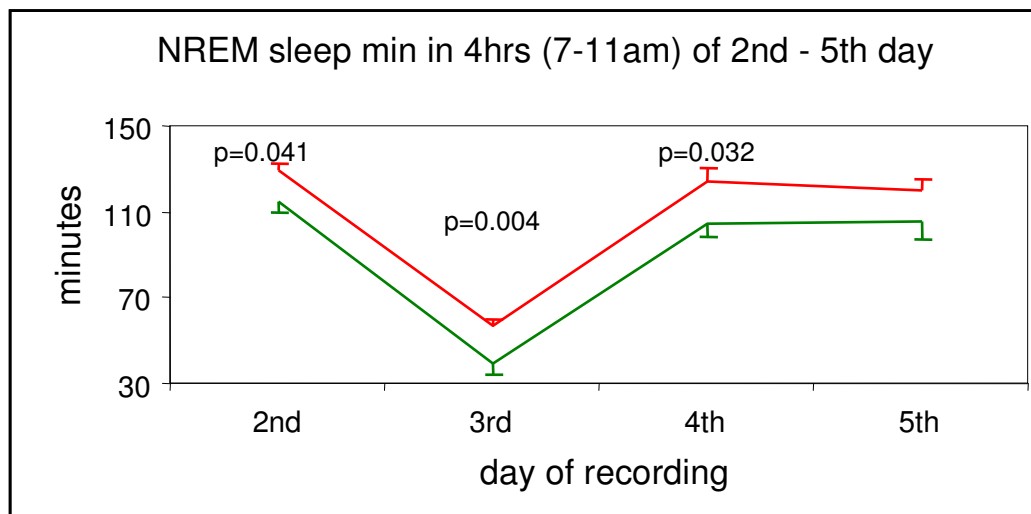


KO mice also appear less active during 3hrs “sleep deprivation” induced by cage changes and continued darkness

KO Mice Exhibit More NREM Time in the First Hours of Subjective Night

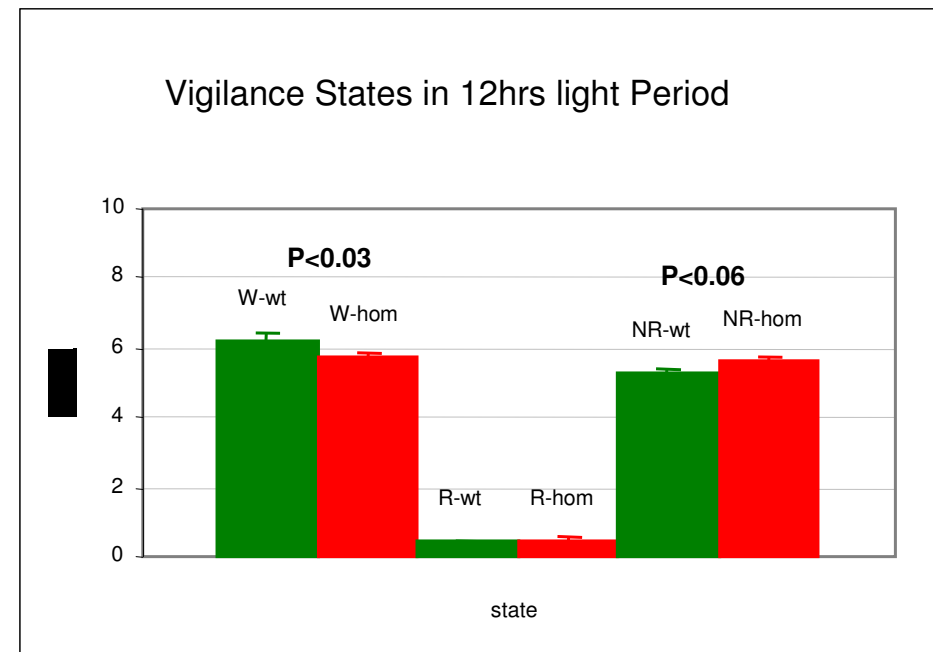
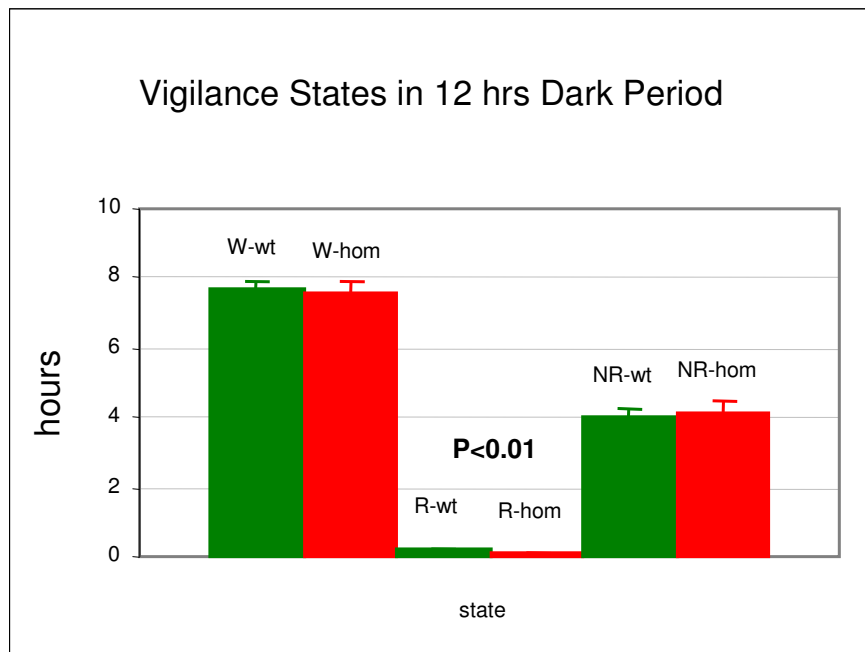


First 3 hrs

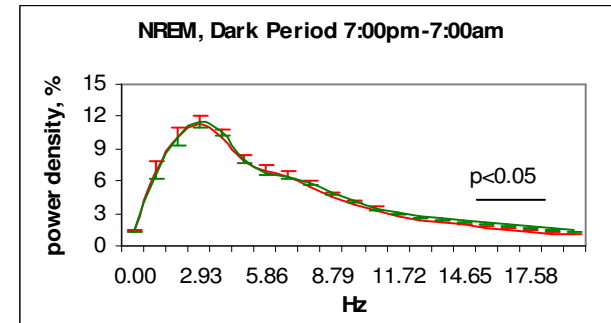
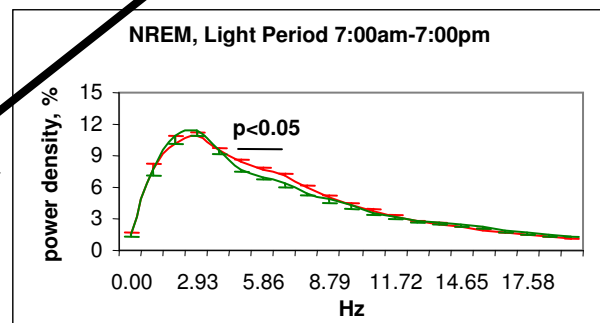
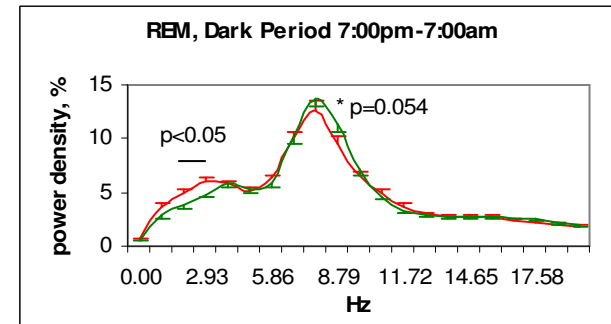
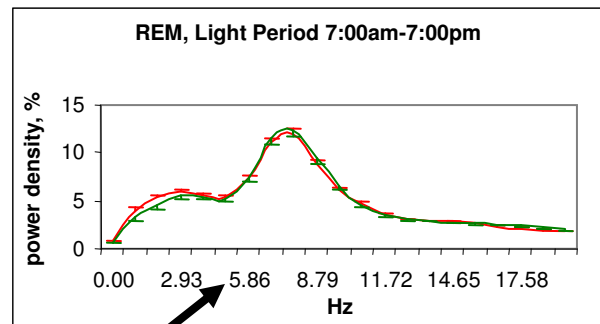
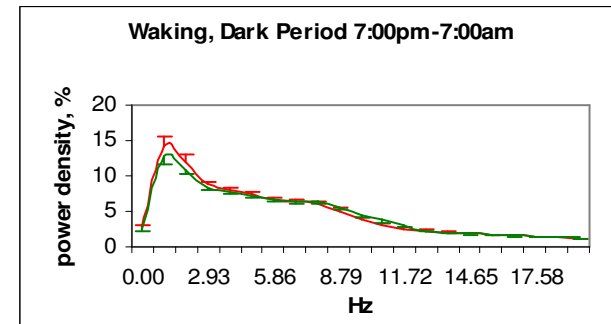
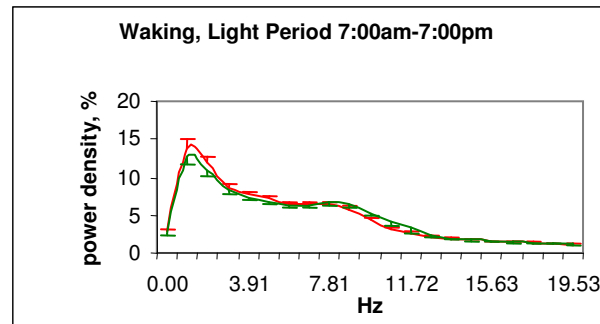


First 4 hrs

Mice Repeat the Phenotype From Previous Cohort -- more NREM & Less Waking EEG during subjective night

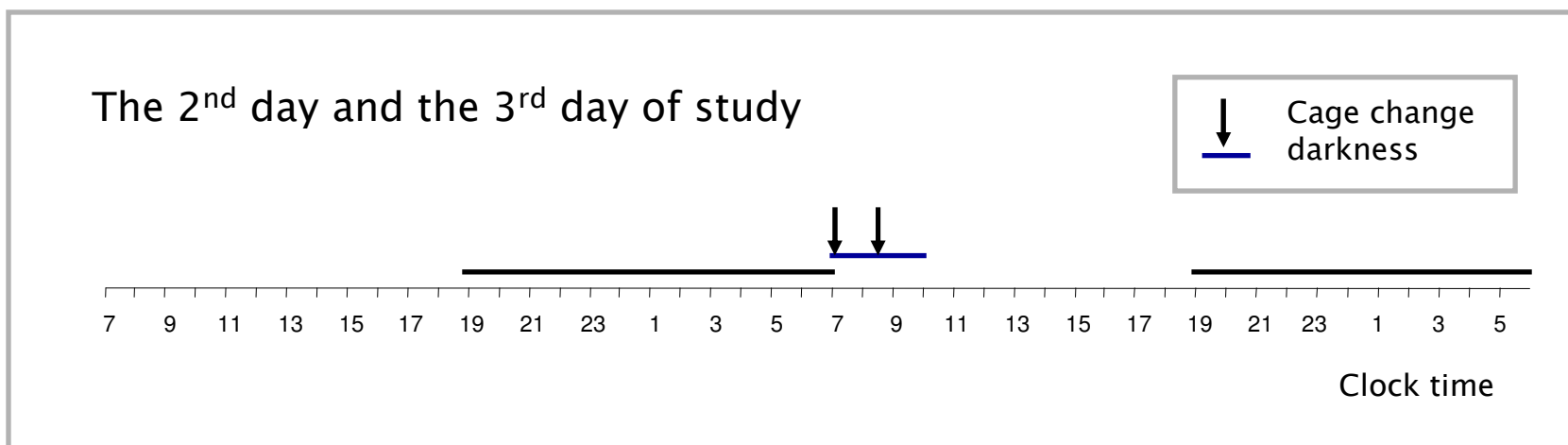


GPR710 KO Repeat Phenotype From Previous Cohort – Greater 5–7 Hz EEG power in subjective night NREM

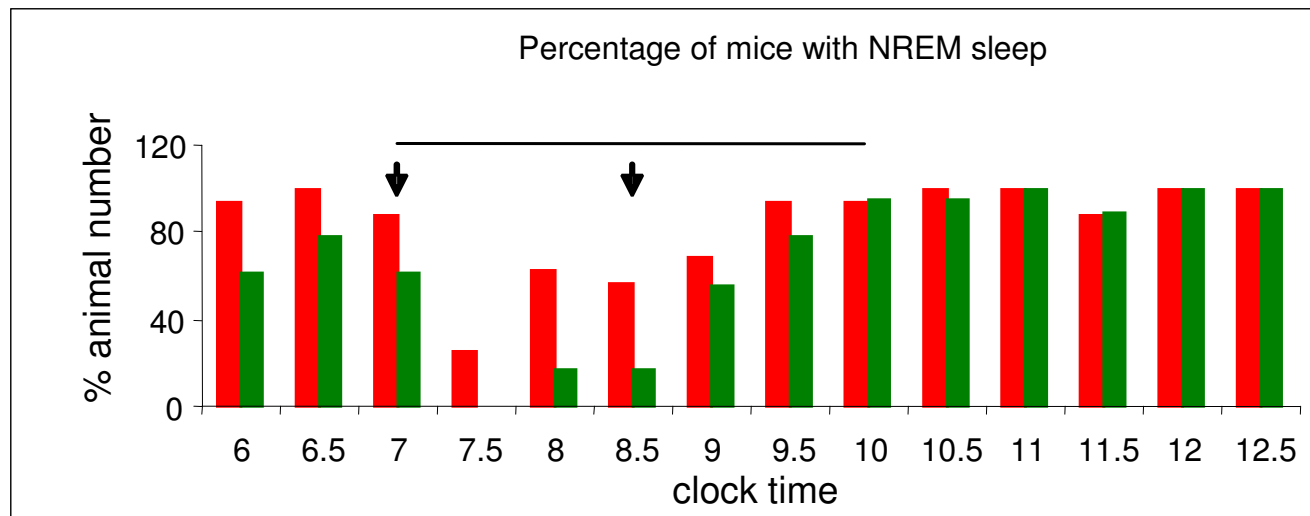


This frequency (theta) is typical of REM sleep

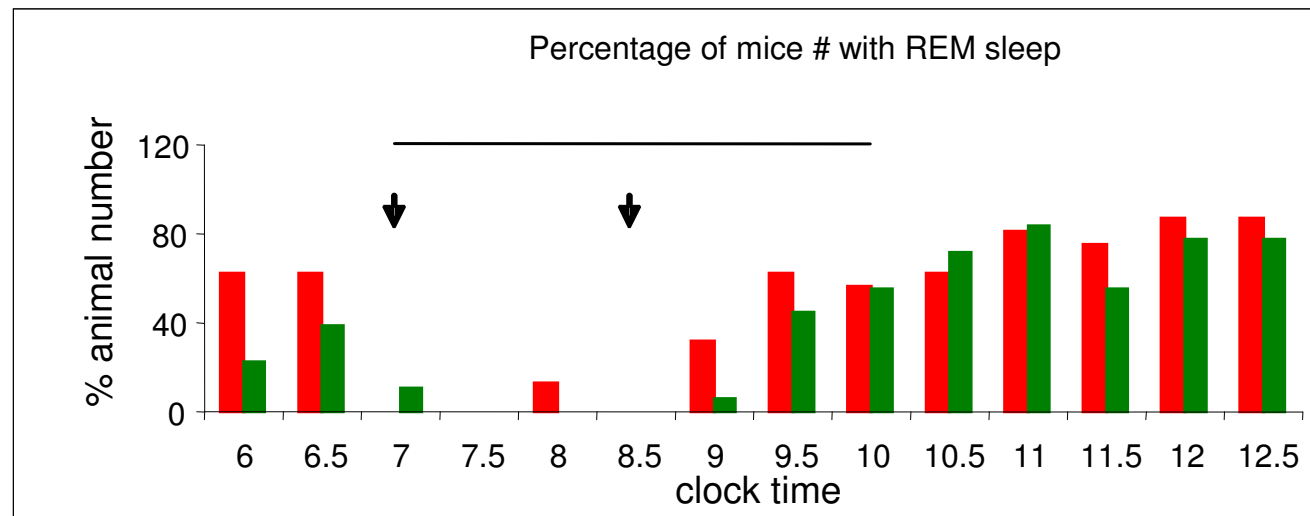
GPR710 – Reaction to Sleep Deprivation Challenge



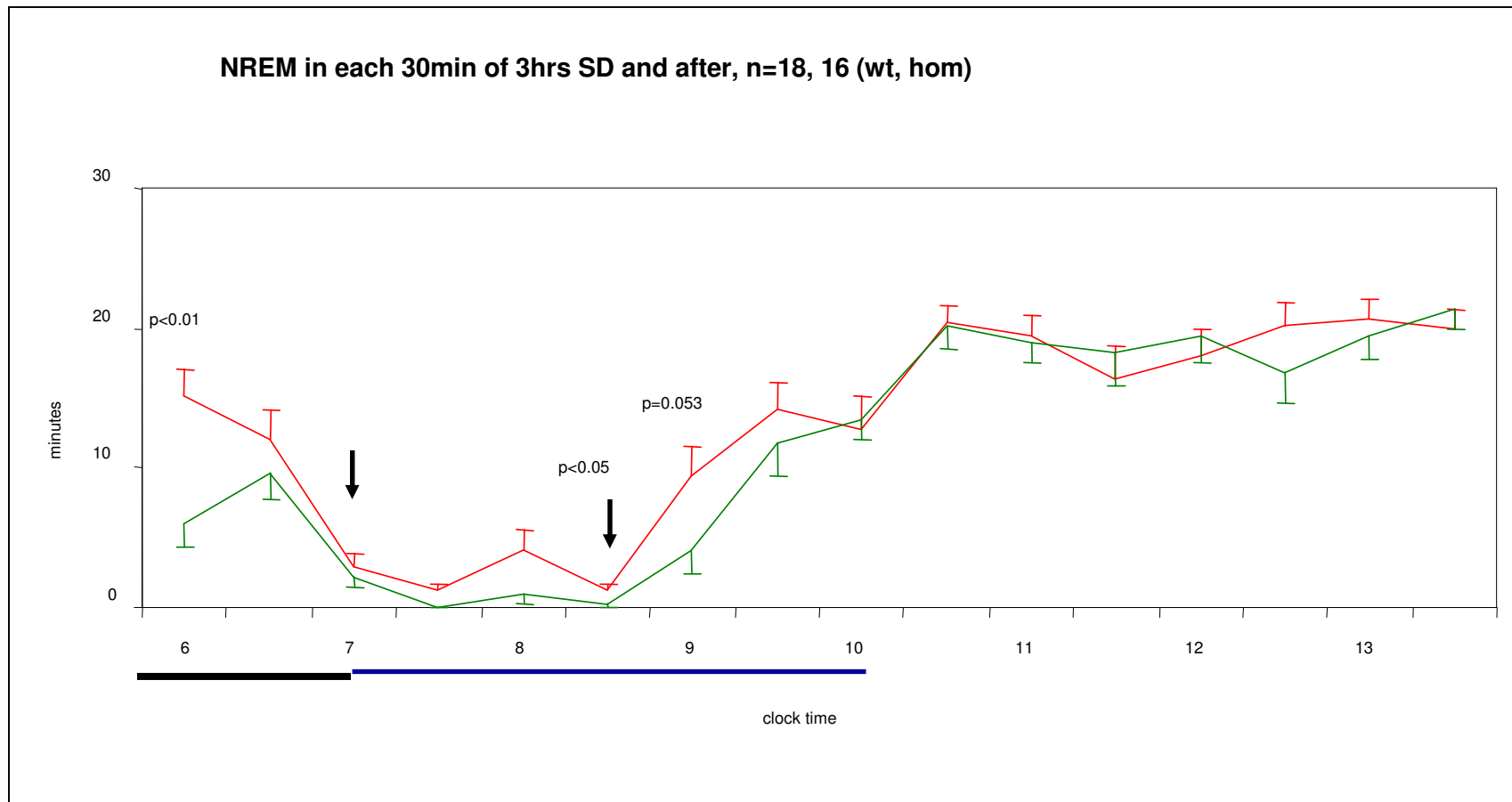
Greater Percentage of GPR710 KO Mice Exhibit NREM & REM during Sleep Deprivation Challenge



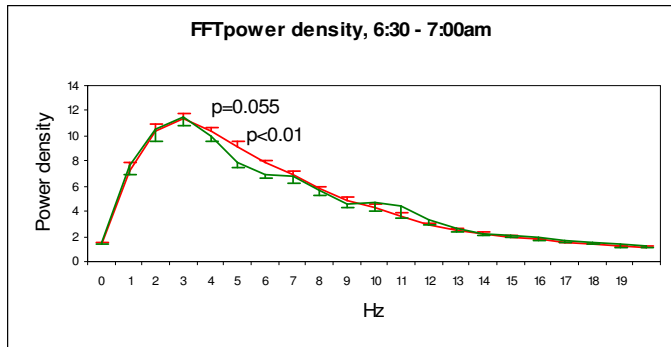
Arrows indicate cage changes



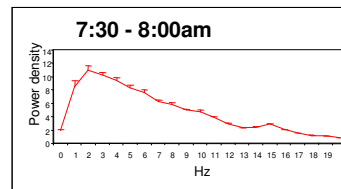
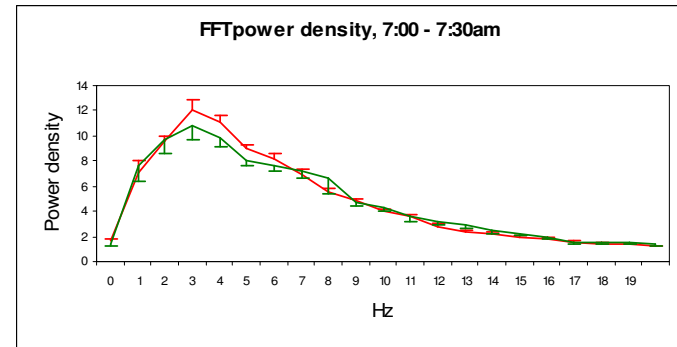
GPR710 KO Mice Exhibit More NREM During SD Challenge



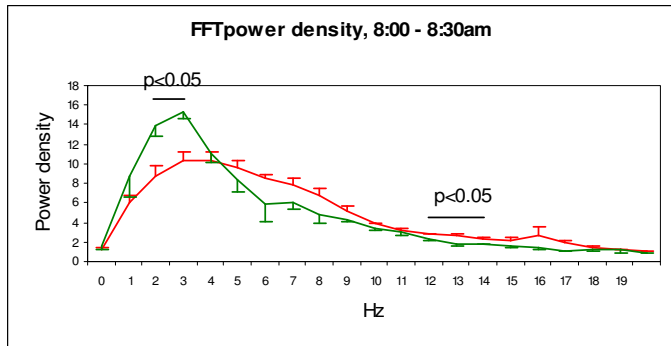
GPR710 – Sleep deprivation challenge: WT Mice May Exhibit Delta Rebound (middle, left-hand graph) KO Mice Exhibit Higher (normal) Delta Power Earlier



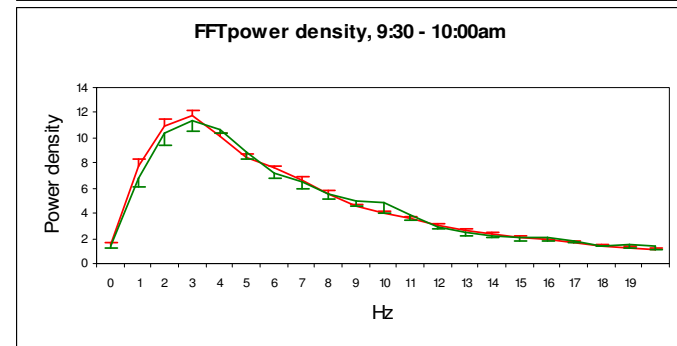
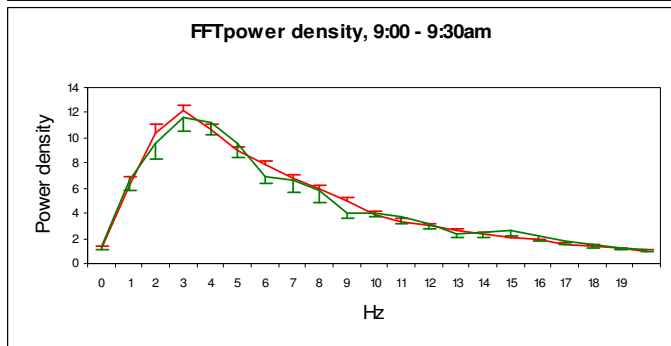
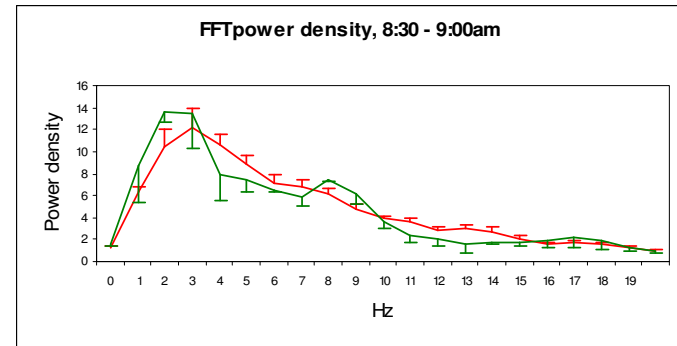
1st cage change



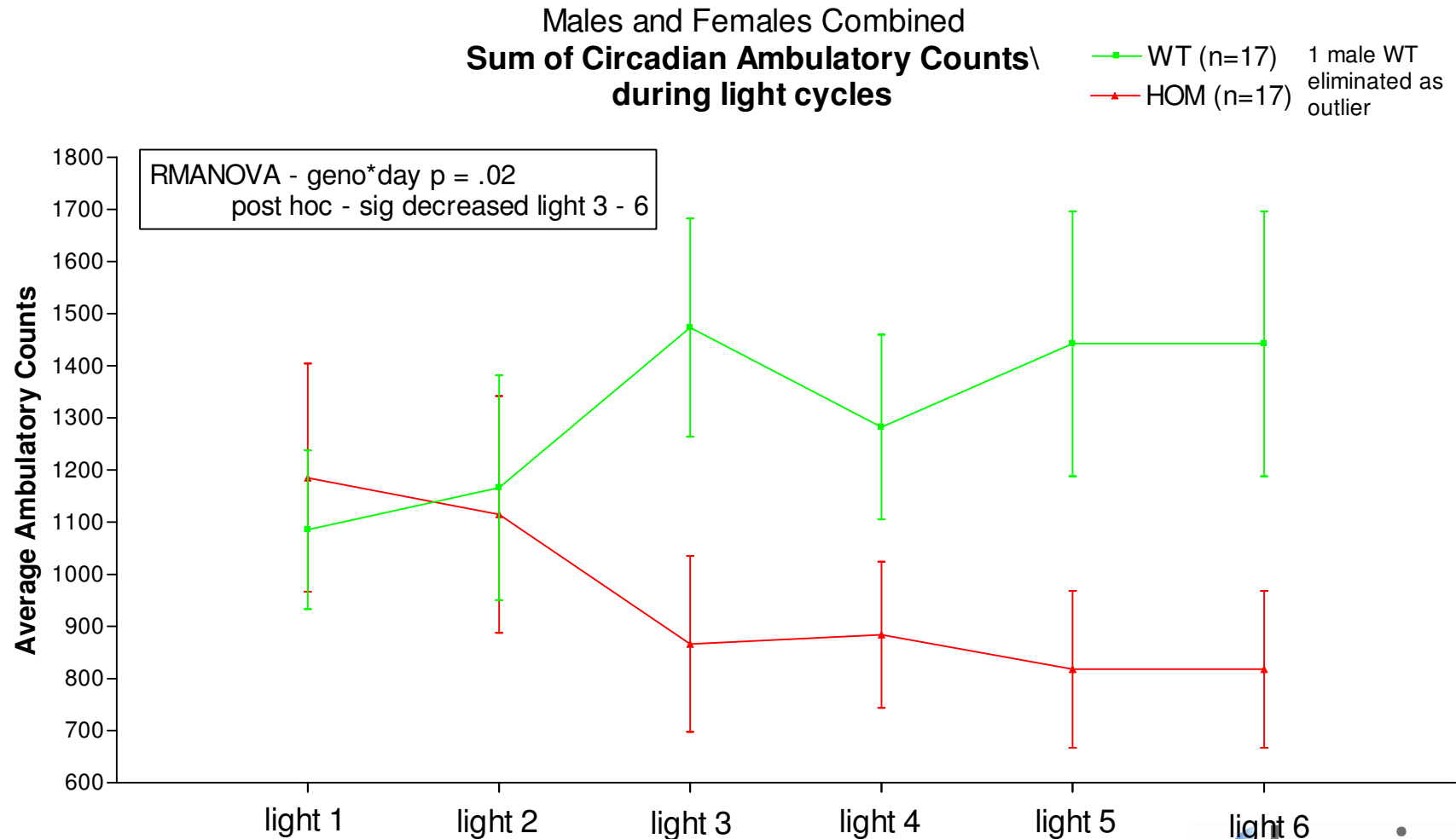
No WT exhibit NREM just after cage change



2nd cage change



KO Mice Showed Decreased Locomotion in Circadian Chamber during subjective night



Summary of evaluation of Lexicon KO's - GPR710

- Genetic inhibition of GPR710 results in few overall behavioral and EEG changes
 - Genetic inhibition of GPR710 leads to a consistent increase in NREM sleep and decreased locomotor activity during subjective night
 - Genetic inhibition of GPR710 results in increased NREM sleep during sleep challenges (novel open field assay & extended dark period plus cage changes)
 - Genetic inhibition of GPR710 leads to a consistent, small increase in locomotor activity at the onset of subjective day
-
- GPR710 is an orphan GPCR.
 - as a GPCR, one can imagine both small molecule agonists and antagonists leading to multiple ways to modulate its activity
 - as an orphan, pharmaceutical interrogation is needed to determine the actual tractability of this target

Conclusion

Task 1

Characterized Sleep/wake pattern of Lexicon C57Bl6/sv129 (F2) mice

Task 2

- CSNK1E: proposing as a therapeutic target for treatment of distorted circadian rhythms, sleep, and jet lag, as well as other physiologic and metabolic processes under circadian regulation
- CHA372N1: EEG/EMG phenotype is revealed for the first time in GABAR1 KO mice, the physiological and the pathophysiological events associated with the discovered EEG power spectral feature need to be further studied

Task 3

- GPR710N1: proposed as a therapeutic target for treatment of sleep disorders
- PRT282T/C1: repeat experiments upon C1 mice when available



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