

**Table S1. Brain tissue subject information, related to Figures 1-4**

Information from subjects who were the source of brain homogenate samples used in this study.

**Table S1**

	<b>Control</b>	<b>Bipolar disorder with psychosis</b>	<b>Bipolar disorder without psychosis</b>	<b>Schizophrenia</b>
Sex (male, female)	26, 9	8, 12	7, 5	26, 9
Age at death (years +/- sem)	44.14 +/- 1.31	45.4 +/- 2.12	45.5 +/- 3.92	42.6 +/- 1.44
Age of diagnosis (years +/- sem)	NA	24.2 +/- 1.50	27.0 +/- 3.68	21.29 +/- 1.03
Illness duration (years +/- sem)	NA	21.2 +/- 2.04	18.5 +/- 3.24	21.29 +/- 1.72
Postmortem interval (hours +/- sem)	29.37 +/- 2.18	38.15 +/- 3.76	39.58 +/- 6.51	31.4 +/- 2.63
Brain pH (+/- sem)	6.61 +/- 0.05	6.32 +/- 0.07	6.57 +/- 0.08	6.47 +/- 0.04
Lifetime antipsychotic (mg +/- sem)	0	15685 +/- 6332.73	2791.67 +/- 2048.15	85004.29 +/- 16959.77

**Figure S1. Additional DLPFC Western blots of PI3K-Akt-mTOR, related to Figure 1**

A-C. Additional Western blots showing phospho and total levels of PI3K, Akt, and mTOR in the DLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane (U=psychosis status unknown). One subject had CADASIL syndrome and was not included in the analysis.



**Figure S2. Additional DLPFC Western blots of ULK1-p70S6K, and 4E-BP1, related to Figure 2**

A-C. Additional Western blots showing phospho and total levels of ULK1, p70S6K, and 4E-BP1 in DLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane (U=psychosis status unknown). One subject had CADASIL syndrome and was not included in the analysis.



### Figure S3. GSK3 in the DLPFC, related to Figure 3

A-E. Western blots showing phosphorylated levels of GSK3 $\alpha$  and GSK3 $\beta$  in DLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane (U=psychosis status unknown). One subject had CADASIL syndrome and was not included in the analysis.

F. Quantification of levels of p-GSK3 $\alpha$  (S21) in control, bipolar disorder-no psychosis (BP-NP), bipolar disorder-psychosis (BP-P), and schizophrenia (schiz) DLPFC homogenate, separated by sex. One-way ANOVA for male and female subjects, with Bonferroni correction for multiple comparisons.

\* $p < 0.05$  with multiple comparison correction. See Table S2 for statistical details.

G. Quantification of levels of p-GSK3 $\beta$  (S9) in control, bipolar disorder-no psychosis (BP-NP), bipolar disorder-psychosis (BP-P), and schizophrenia (schiz) DLPFC homogenate, separated by sex. One-way ANOVA for male and female subjects, with Bonferroni correction for multiple comparisons.

\* $p < 0.05$  with multiple comparison correction. See Table S2 for statistical details.

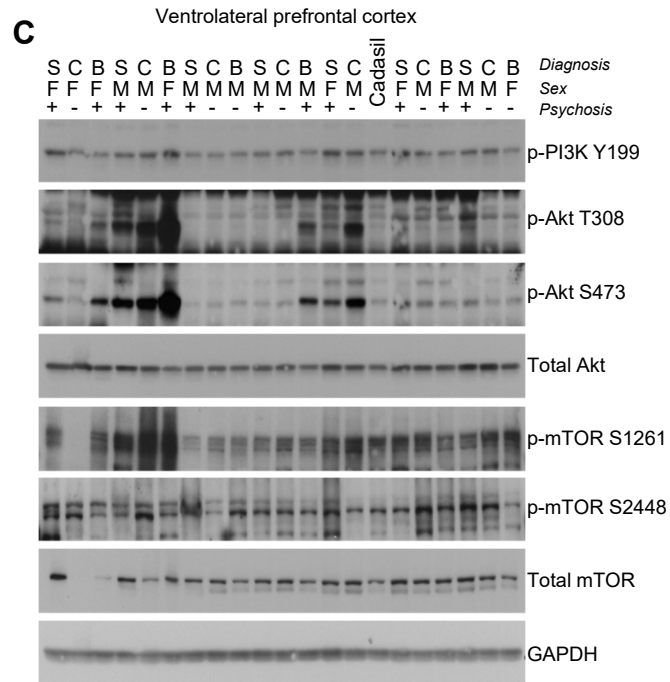
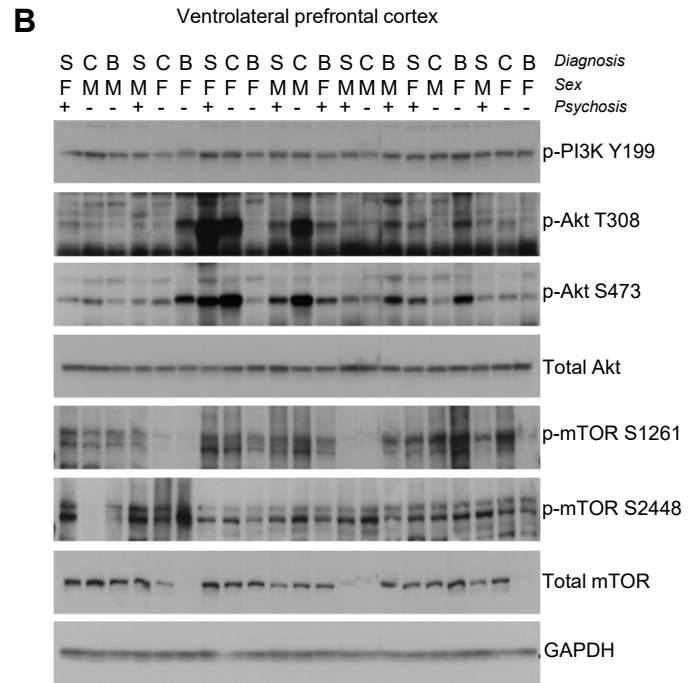
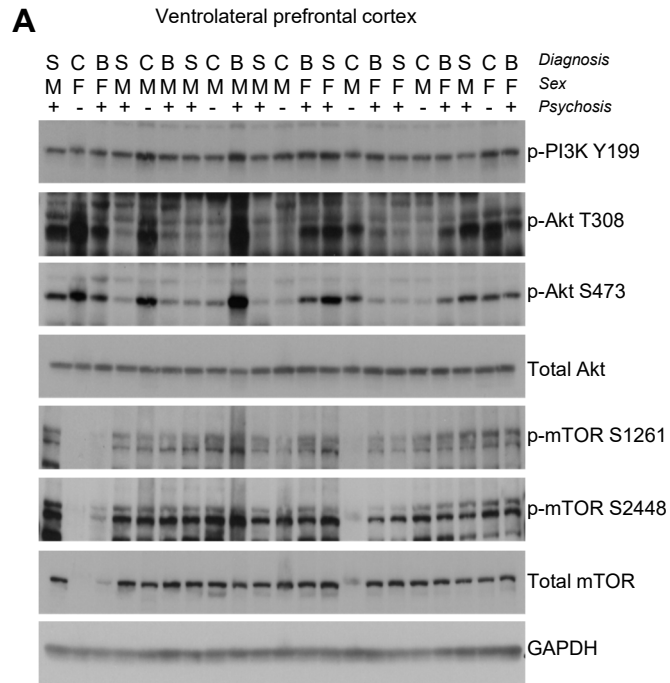
Summary data are the mean+SEM. n=35 control (26 male, 9 female), 12 BP-no psychosis (7 male, 5 female), 20 BP-psychosis (8 male, 12 female), 35 schizophrenia (26 male, 9 female)





**Figure S4. Additional VLPFC Western blots of PI3K-Akt-mTOR, related to Figure 3**

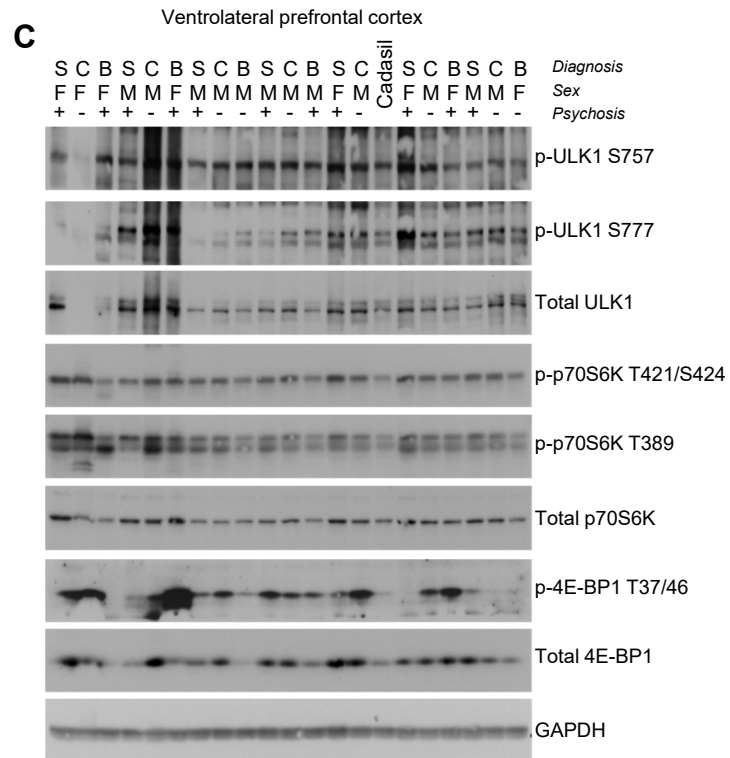
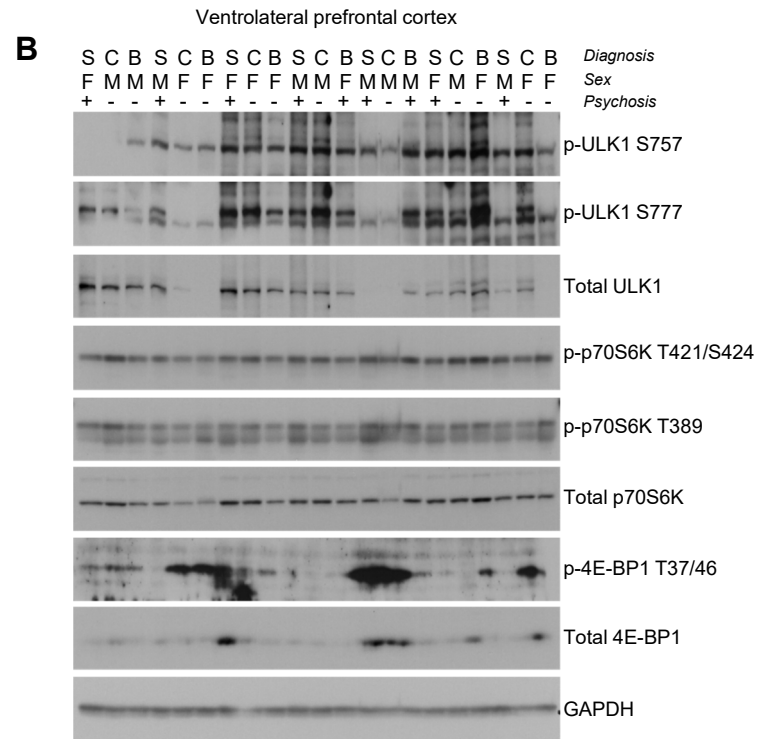
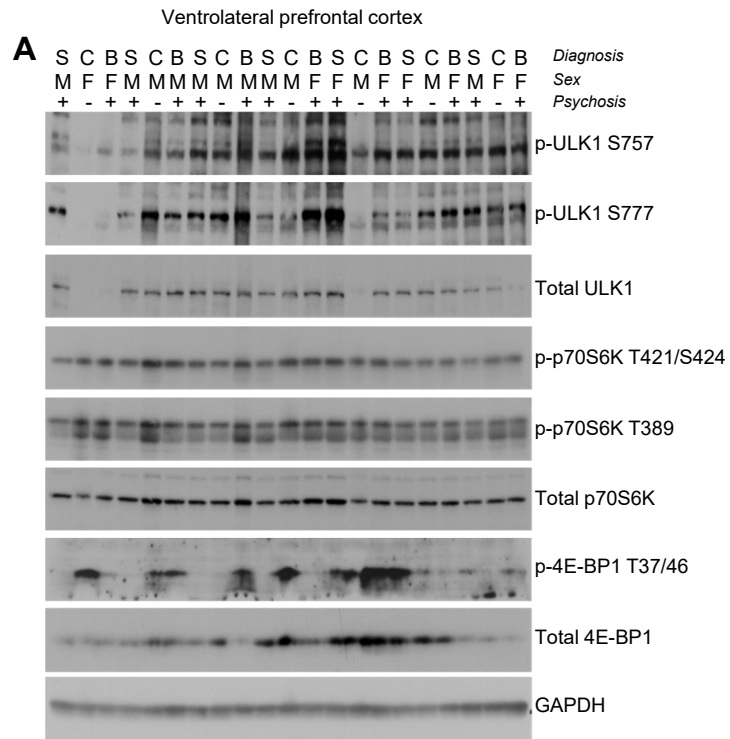
A-C. Additional Western blots showing phospho and total levels of PI3K, Akt, and mTOR in the VLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane. One subject had CADASIL syndrome and was not included in the analysis.

**Figure S4**

**Figure S5. Additional VLPFC Western blot of ULK1-p70S6K, and 4E-BP1, related to Figure 4**

A-C. Additional Western blots showing phospho and total levels of ULK1, p70S6K, and 4E-BP1 in VLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane. One subject had CADASIL syndrome and was not included in the analysis.

**Figure S5**



## Figure S6. GSK3 in the DLPFC, related to Figure 4

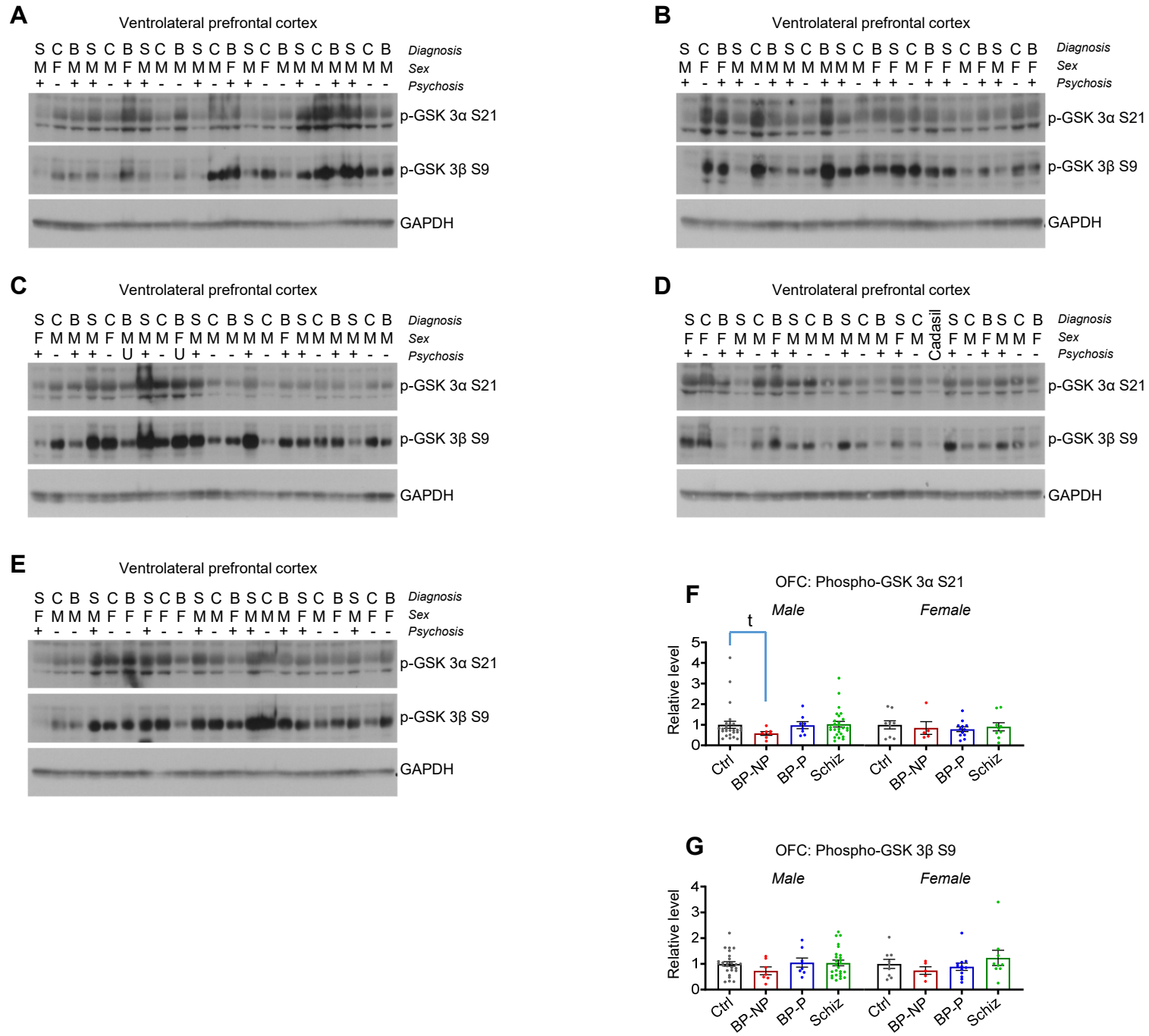
A-E Western blots showing phosphorylated levels of GSK3 $\alpha$  and GSK3 $\beta$  in VLPFC of control, bipolar disorder, and schizophrenia subjects. Diagnosis (S=schizophrenia, C=control, B=bipolar disorder), sex (M=male, F=female), and absence (-) or presence (+) of psychosis indicated above each lane. One subject had CADASIL syndrome and was not included in the analysis.

F. Quantification of levels of p-GSK3 $\alpha$  (S21) in control, bipolar disorder-no psychosis (BP-NP), bipolar disorder-psychosis (BP-P), and schizophrenia (schiz) VLPFC homogenate, separated by sex. One-way ANOVA for male and female subjects, with Bonferroni correction for multiple comparisons.  $t=p<0.05$  with direct comparison. See Table S2 for statistical details.

G. Quantification of levels of p-GSK3 $\beta$  (S9) in control, bipolar disorder-no psychosis (BP-NP), bipolar disorder-psychosis (BP-P), and schizophrenia (schiz) VLPFC homogenate, separated by sex. One-way ANOVA for male and female subjects, with Bonferroni correction for multiple comparisons. No significant differences between groups were detected. See Table S2 for statistical details.

Summary data are the mean+SEM. n=35 control (26 male, 9 female), 12 BP-no psychosis (7 male, 5 female), 20 BP-psychosis (8 male, 12 female), 35 schizophrenia (26 male, 9 female)

**Figure S6**



**Figure S7. Raw object testing time data and Y-maze performance for male DN-Akt experiments, related to Figures 5 and 6**

A. Pertaining to the object-in place task, graph depicts the trial 2 investigation time of the object pair whose location is constant between trials (fixed location) and the object pair that swaps location between trials (novel location) for the GFP and DN-Akt groups. A main effect of the swapped objects in increasing investigation time across the 7 minute assessment period was found for the GFP group [ $F(1, 40)=31.31, p<0.0001$ ] and not for the DN-Akt group [ $F(1, 35)=1.262, p=0.2689$ ]. Analysis performed using 2-way repeated measures ANOVA.

B. Pertaining to the object-context task, the graph depicts the trial 3 investigation time of the object not previously encountered in the test arena (novel location) and that for the object previously encountered in the test arena (fixed location) for the GFP and DN-Akt groups. A main effect of novel location in increasing investigation time across the 10 minute assessment period was found for the GFP group [ $F(1, 64)=17.97, p<0.0001$ ]. For the DN-Akt group, a main effect of novel location in *decreasing* investigation was found [ $F(1, 56)=29.36, p<0.0001$ ]. Analysis performed using 2-way repeated measures ANOVA.

C. Schematic of Y-maze spontaneous alternation task. Spontaneous alternation behavior was assessed both prior to viral infusion (trial 1) and 4 days post-viral infusion into the mPFC (trial 2).

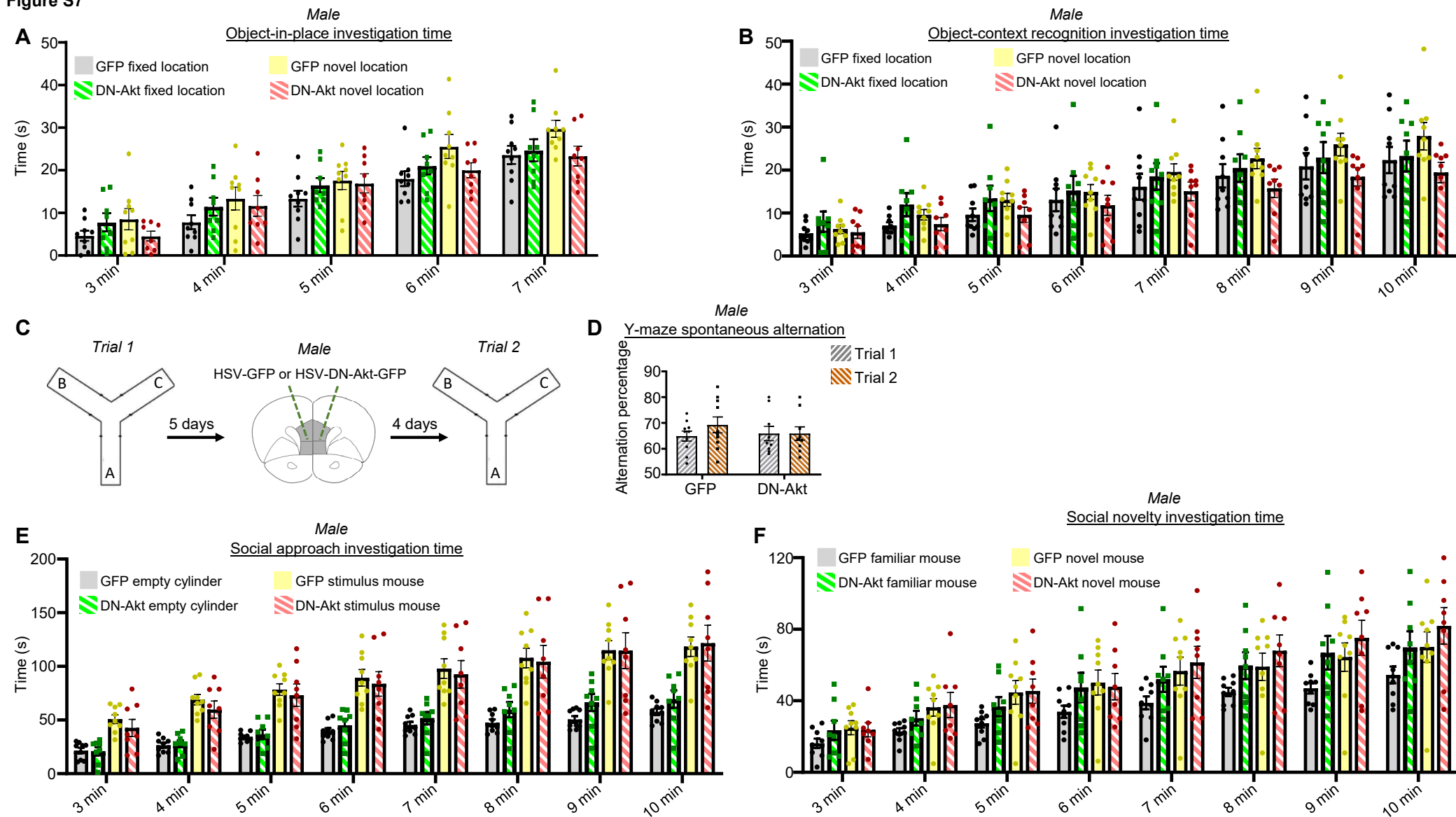
D. Graph depicts spontaneous alternation percentages for GFP and DN-Akt groups at trial 1 and trial 2. 2-way repeated measures ANOVA revealed no differences between groups.  $n=10$  GFP,  $9$  DN-Akt

E. Pertaining to the social approach task, the graph depicts the time the GFP and DN-Akt groups investigate the empty cylinder or the stimulus mouse as a function of time. A main effect of the stimulus mouse in increasing investigation time vs. the inanimate object across the 10 minute assessment period was found for the GFP [ $F(1, 64)=270.6, p<0.0001$ ] and DN-Akt groups [ $F(1, 56)=63.32, p<0.0001$ ]. Analysis performed using 2-way repeated measures ANOVA.

F. Pertaining to the social novelty task, the graph depicts the time the GFP and DN-Akt groups investigate the familiar mouse or the novel mouse as a function of time. A main effect of the novel mouse in increasing investigation time vs. the familiar mouse across the 10 minute assessment period was found for the GFP [ $F(1, 64)=29.61, p<0.0001$ ] and DN-Akt groups [ $F(1, 56)=5.861, p=0.0187$ ]. Analysis performed using 2-way repeated measures ANOVA.

Summary data are the mean+SEM



**Figure S7**

**Figure S8. Effect of DN-Akt on female mouse cognition, related to Figures 5 and 6**

A. Object-in-place testing schematic. Female mice infused with HSV-GFP or HSV-DN-Akt-GFP and 4 days later habituated in the arena, followed 1 day later by assessment in the object-in-place task.

B. Object-in-place discrimination ratios for trial 1 in the GFP and DN-Akt-GFP groups. As expected, no differences between groups in discrimination ratios were present in trial 1. n=10 GFP, 10 DN-Akt

C. Object-in-place discrimination ratios for trail 2 in the GFP and DN-Akt-GFP groups. In trial 2, a significant decrease in discrimination ratio was detected for the DN-Akt group relative to the GFP group at the 3 minute time bin. 2-way repeated measures ANOVA with multiple comparison correction post-hoc (3 min,  $q=0.0018$ ; 4 min  $q=0.1778$ ; 5 min  $q=0.1778$ ; 6 min  $q=0.36341$ ; 7 min  $q=0.5249$  n=10 GFP, 10 DN-Akt

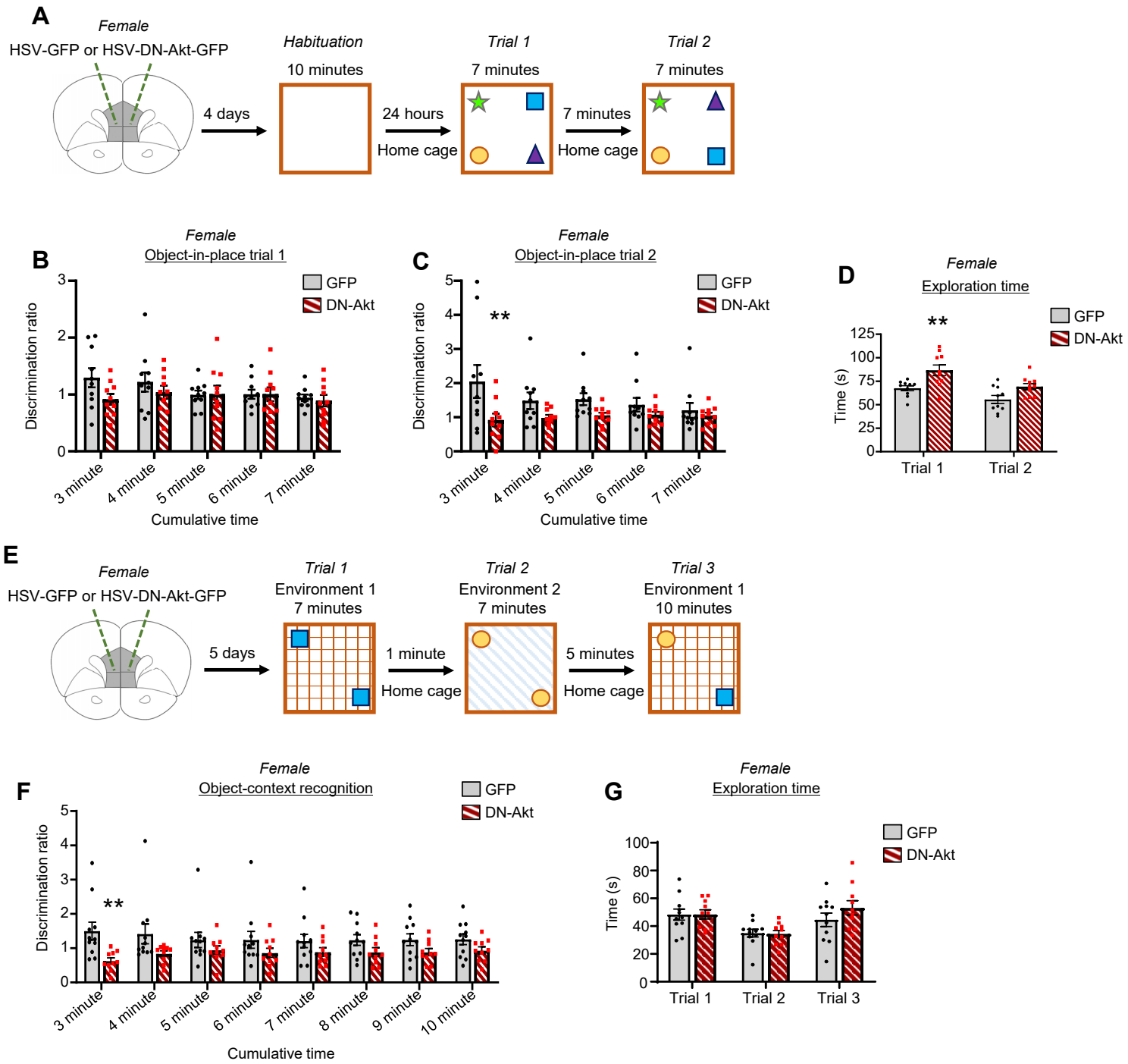
D. Graph depicts total time spent exploring objects during trial 1 and trail 2 of the object-in-place test. DN-Akt mice spent more total time investigating objects during trial 1 relative to the GFP group ( $p=0.0047$ ), with no differences between groups during trial 2 ( $p=0.0506$ ). Analysis performed using 2-way repeated measures ANOVA with Bonferroni post-hoc. n=10 GFP, 10 DN-Akt

E. Object-context recognition schematic. Female mice were infused with HSV-GFP or HSV-DN-Akt-GFP in the mPFC and 5 days later assessed in the object-context recognition task.

F. Object-context discrimination ratios for trial 3 in the GFP and DN-Akt-GFP groups. A significant decrease in discrimination ratio was detected for the DN-Akt group relative to the GFP group at the 3 minute time bin. 2-way repeated measures ANOVA with multiple comparison correction post-hoc (3 min  $q=0.0051$ ; 4 min  $q=0.0893$ ; 5 min  $q=0.2315$ ; 6 min  $q=0.2164$ ; 7 min  $q=0.2164$ ; 8 min  $q=0.0446$ ; 9 min  $q=0.0446$ ; 10 min  $q=0.0446$ ). n=11 GFP, 10 DN-Akt

G. Graph depicts total time spent exploring object during trials 1-3. No differences were detected between the GFP and DN-Akt groups. n=11 GFP, 10 DN-Akt

Summary data are the mean+SEM

**Figure S8**

## Figure S9. Effect of WT-Akt on male mouse cognition, related to Figures 5 and 6

- A. Object-in-place testing schematic. Male mice were infused with HSV-GFP or HSV-WT-Akt-GFP and 4 days later habituated in the testing arena, followed 1 day later by assessment in the object-in-place task.
- B. One mPFC hemisphere was infused with HSV-GFP and the opposite mPFC hemisphere infused with HSV-WT-Akt-GFP; hemisphere receiving each virus was altered between mice. 5 days post-infusion, the mPFC was dissected. Representative Western blot showing levels of total Akt1.
- C. Pair-wise comparison reveals that HSV-WT-Akt-GFP significantly increased levels of Akt (two-tailed paired t-test,  $p=0.0024$ ).  $n=10$  GFP and 10 WT-Akt mPFC hemispheres
- D. Object-in-place discrimination ratios for trial 1 in the GFP and WT-Akt-GFP groups. As expected, no differences between groups in discrimination ratios were present in trial 1.  $n=7$  GFP, 6 WT-Akt
- E. Object-in-place discrimination ratios for trail 2 in the GFP and WT-Akt-GFP groups. No differences were found between the GFP and WT-Akt groups at any time bins. 2-way repeated measures ANOVA with multiple comparison correction post-hoc (3 min,  $q=0.6249$ ; 4 min  $q=0.7590$ ; 5 min  $q=0.6670$ ; 6 min  $q=0.6249$ ; 7 min  $q=0.6249$ ).  $n=7$  GFP, 6 DN-Akt
- F. Graph depicts total time spent exploring objects during trial 1 and trail 2 of the object-in-place test. No differences between GFP and WT-Akt groups were detected.  $n=7$  GFP, 6 DN-Akt
- G. Object-context recognition schematic. Male mice were infused with HSV-GFP or HSV-WT-Akt-GFP in the mPFC and 5 days later assessed in the object-context recognition task.
- H. Object-context discrimination ratios for trial 3 in the GFP and WT-Akt-GFP groups. No difference between the WT-Akt and GFP groups were detected at any time bins. 2-way repeated measures ANOVA with multiple comparison correction post-hoc (3 min  $q=0.9974$ ; 4 min  $q=0.9974$ ; 5 min  $q=0.9974$ ; 6 min  $q=0.9974$ ; 7 min  $q=0.9974$ ; 8 min  $q=0.9974$ ; 9 min  $q=0.9974$ ; 10 min  $q=0.9974$ ).  $n=10$  GFP, 9 WT-Akt

I. Graph depicts total time spent exploring object during trials 1-3. No differences were detected between the GFP and WT-Akt groups. n=10 GFP, 9 WT-Akt

Summary data are the mean+SEM

**Figure S9**

