Supplemental Digital Content 1

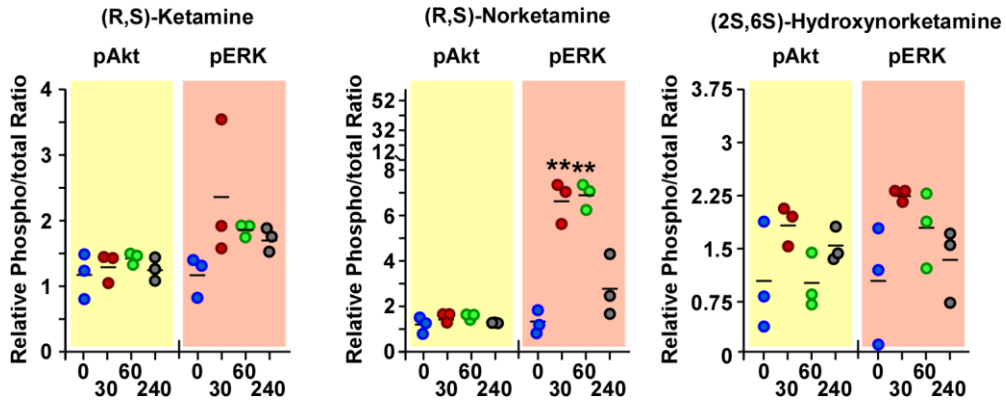

Figure S1. Levels of phospho-active forms of ERK1/2 and Akt in rat brain (cortex) tissues at different time intervals (0 – 240 min) after administration of either (*R,S*)-ketamine, (*R,S*)-norketamine or (2*S,6S*)-hydroxynorketamine. Representative immunoblots are found in Figure 3. Scatter plots illustrating the relative levels of phosphorylated and total forms of ERK1/2 and Akt in response to (*R,S*)-ketamine, (*R,S*)-norketamine and (*2S,6S*)-hydroxynorketamine are shown (n= 3 independent experiments). **, *P< 0.01* (ANOVA) compared with controls.

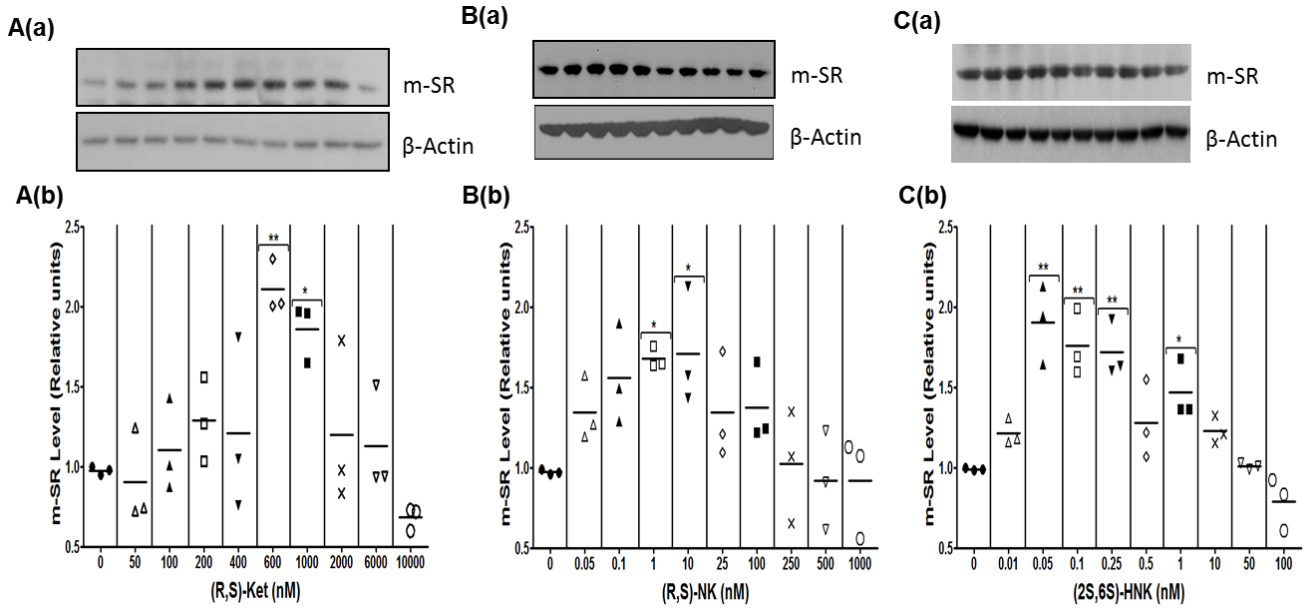

Figure S2. Expression of monomeric serine racemase (m-SR) protein in PC-12 cells after 36 h incubation with different concentrations of (*R,S*)-ketamine (0 – 10 µM) (A), (*R,S*)-norketamine (0 – 1 µM) (B), and (2*S,6S*)-hydroxynorketamine (0 – 0.1 µM) (C); where figure A(a), B(a), C(a) present Western blot analysis with anti-serine racemase antibody, and A(b), B(b), C(b) represent relative levels of m-SR after quantification and normalization with β-actin. Scatter plots illustrating the relative levels of m-SR in response to (*R,S*)-ketamine (Ket), (*R,S*)-norketamine (NK) and (*2S,6S*)-hydroxynorketamine (HNK) after quantification and normalization with β-actin are shown (n= 3 independent experiments). * indicates $p<0.05$ and ** indicates $p<0.01$ (ANOVA) compared with the control

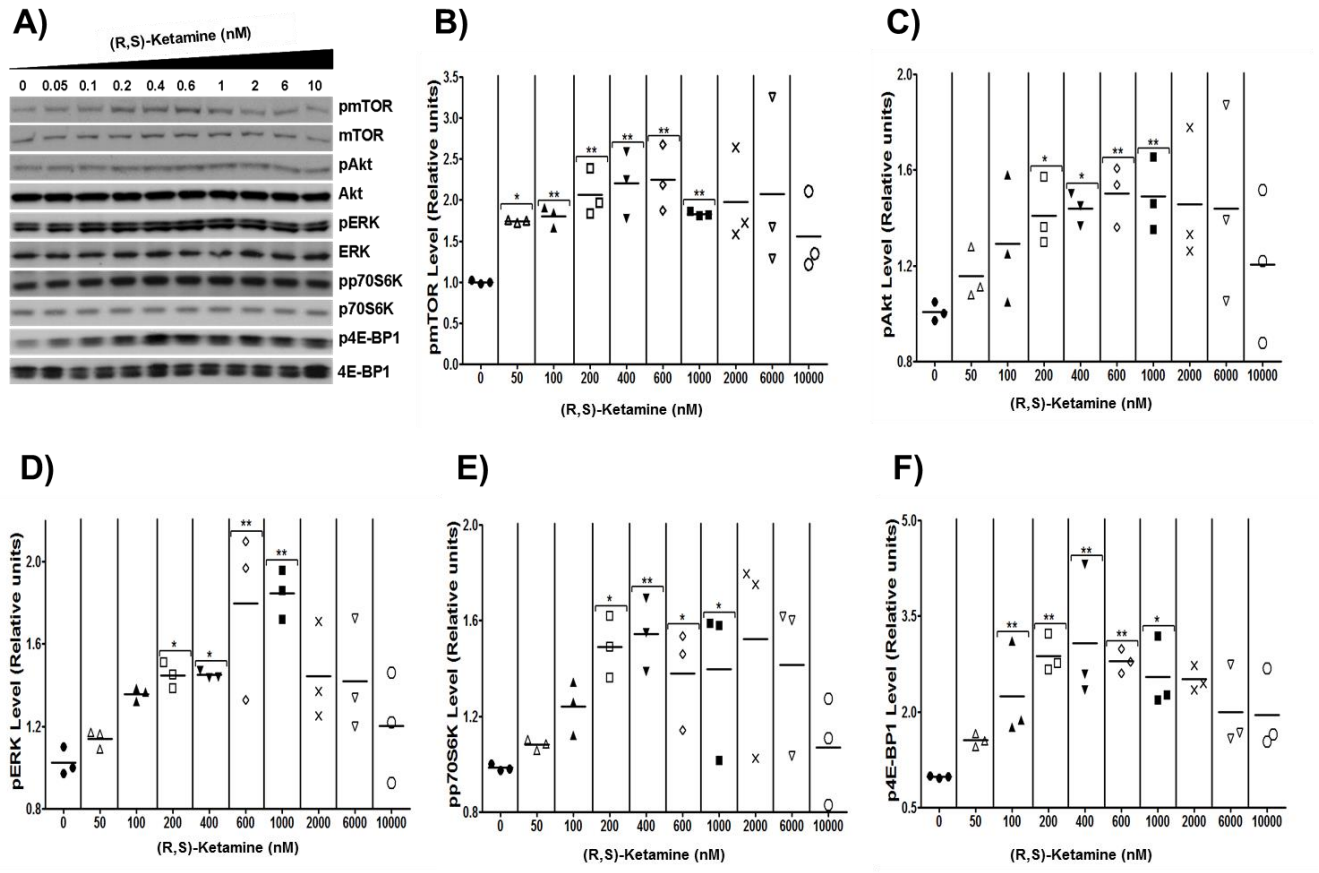

Figure S3. Effect of (*R,S*)-ketamine on the levels of phospho-active forms of mTOR, Akt, ERK1/2, p70S6K and 4E-BP1 in PC-12 cells. A, Cells were treated with different concentrations of (*R,S*)-ketamine (0 – 10 μM) for 1 h and processed for Western blot analysis. Representative immunoblots are presented. Scatter plots illustrating the relative ratio of phosphorylated versus total forms of mTOR (B), Akt (C), ERK1/2 (D), p70S6K (E), and 4E-BP1 (F) in response to (*R,S*)-ketamine are shown (n = 3 independent experiments). * indicates $p<0.05$ and ** indicates $p<0.01$ (ANOVA) compared with the control

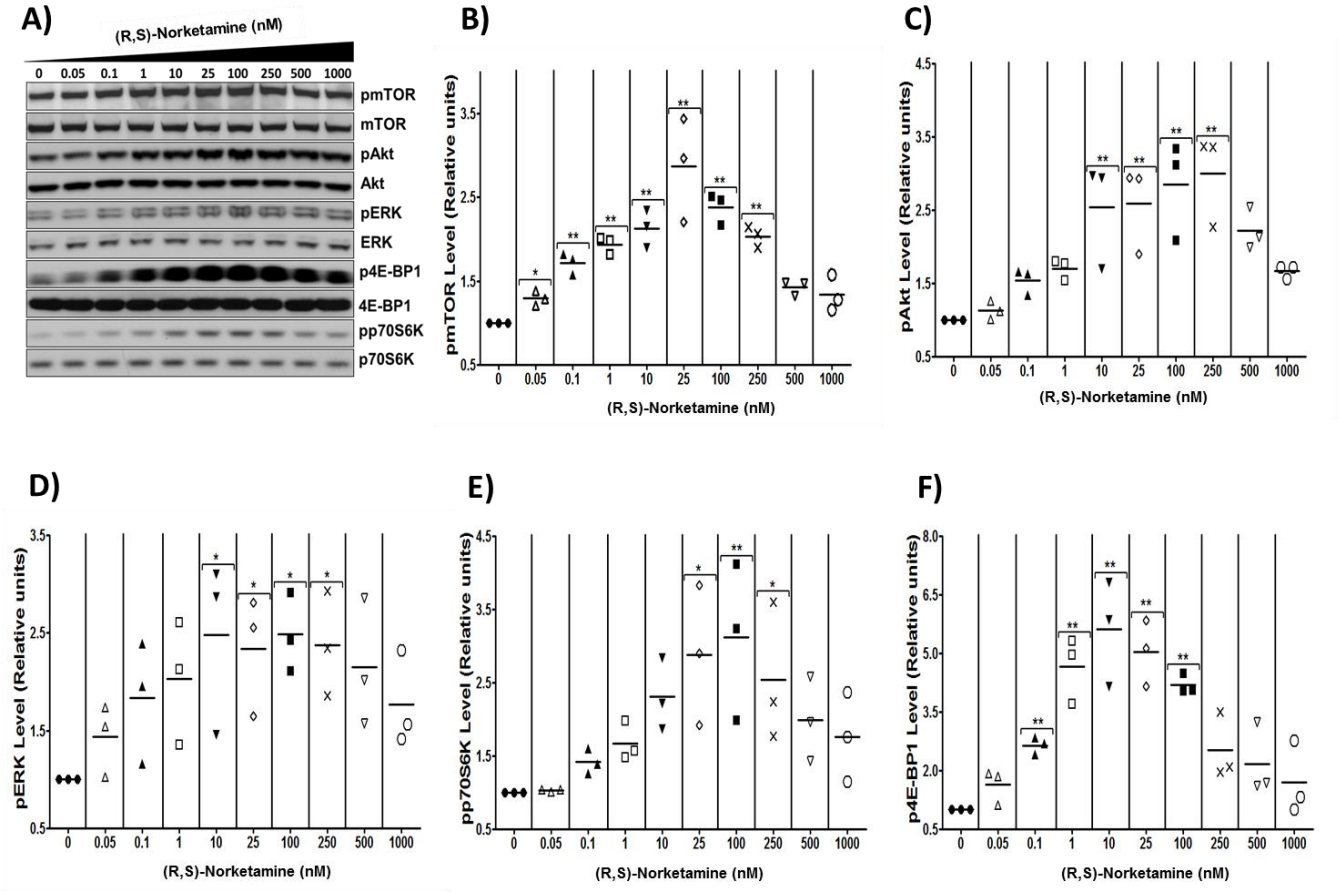

Figure S4. Effect of (*R,S*)-norketamine on the levels of phospho-active forms of mTOR, Akt, ERK1/2, p70S6K and 4E-BP1 in PC-12 cells. A, Cells were treated with different concentrations of (*R,S*)-norketamine (0 – 1 μM) for 1 h and processed for Western blot analysis. Representative immunoblots are presented. Scatter plots illustrating the relative ratio of phosphorylated versus total forms of mTOR (B), Akt (C), ERK1/2 (D), p70S6K (E), and 4E-BP1 (F) in response to (*R,S*)-norketamine are shown (n = 3 independent experiments). * indicates $p<0.05$ and ** indicates $p<0.01$ (ANOVA) compared with the control.

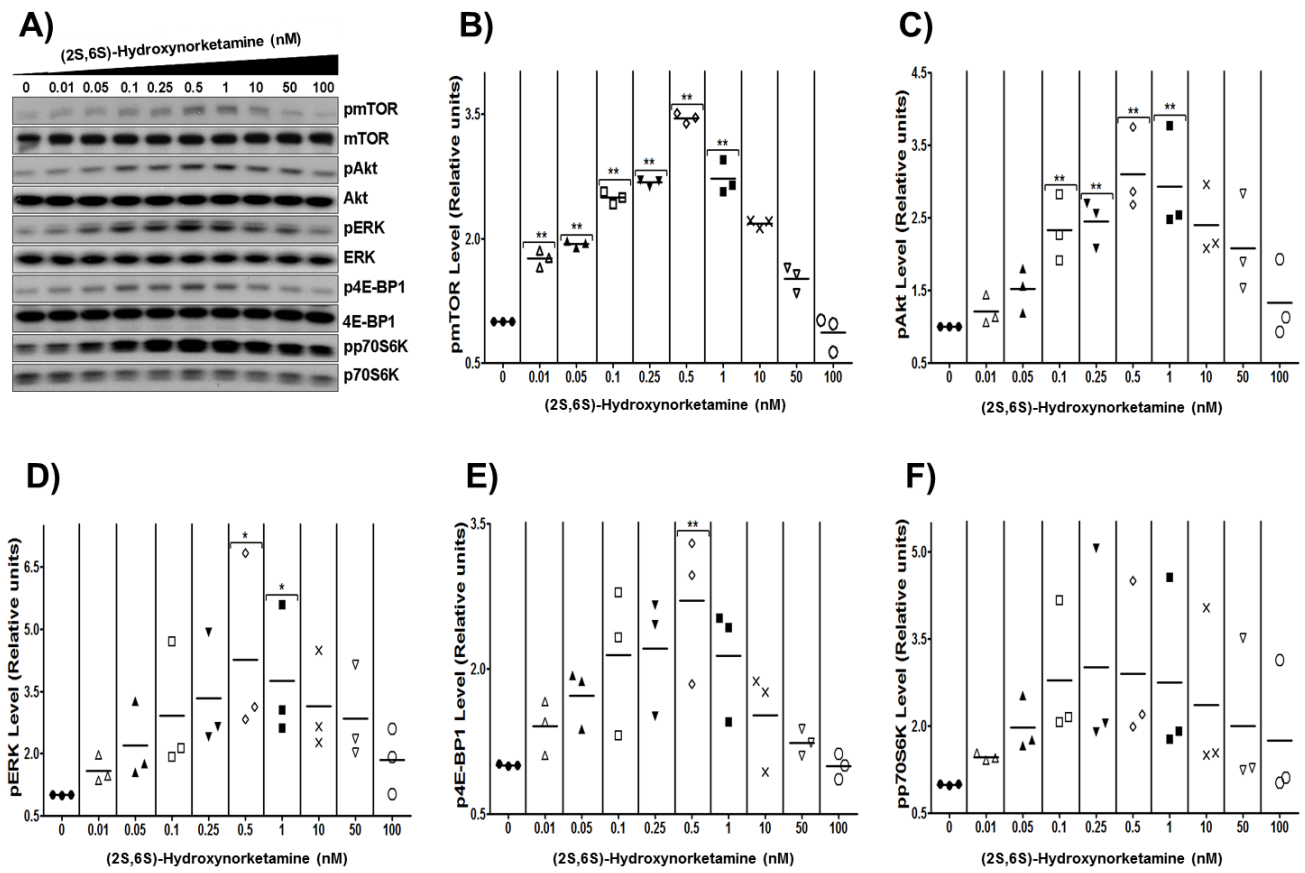

Figure S5. Effect of (*2S,6S*)-hydroxynorketamine on the levels of phospho-active forms of mTOR, Akt, ERK1/2, p70S6K and 4E-BP1 in PC-12 cells. A, Cells were treated with different concentrations of (*2S,6S*)-hydroxynorketamine (0 – 0.1 µM) for 1 h and processed for Western blot analysis. Representative immunoblots are presented. Scatter plots illustrating the relative ratio of phosphorylated versus total forms of mTOR (B), Akt (C), ERK1/2 (D), p70S6K (E), and 4E-BP1 (F) in response to (*2S,6S*)-hydroxynorketamine are shown (n = 3 independent experiments). * indicates $p<0.05$ and ** indicates $p<0.01$ (ANOVA) compared with the control.