Supplemental Digital Content 1: Supplemental Results

Fig. 1 presents the normalized symbolic transfer entropy (NSTE) matrix of eight electroencephalographic channels and significant changes of connectivity across six substates of the baseline and ketamine anesthesia states. Fig. 1 (A) presents the mean NSTE matrix over the three substates (B1, B2 and B3) of the baseline state. The feedback dominancy clearly appears in the NSTE matrix. The frontal channels have a larger NSTE (red and yellow colors) compared to the temporal and parietal channels. The feedforward connectivity from the temporal and parietal to the frontal channels has a relatively smaller NSTE (blue color) in Fig. 1 (A). Fig. 1 (B)-(D) present the substates of the ketamine-anesthetized state (A1, A2 and A3), respectively. The A1 stage includes the induction of ketamine. The relative change of NSTE was calculated as follows:

$$\frac{NSTE\left(A(i,j)_{1,2,3}\right)-NSTE\left(\bar{B}(i,j)_{1,2,3}\right)}{NSTE\left(\bar{B}(i,j)_{1,2,3}\right)} \times 100\ (\%),\ i \text{ and } j = 1\sim8 \qquad (1)$$

,where $NSTE\left(\bar{B}(i,j)_{1,2,3}\right)$ is the mean NSTE of the electroencephalographic channel (*i*) and (*j*) over all three substates (B1, B2 and B3) of the baseline state and $NSTE\left(A(i,j)_{1,2,3}\right)$ is the mean NSTE of the electroencephalographic channel (*i*) and (*j*) for each substate (A1, A2 or A3) of the anesthetized state. Each NSTE matrix for a substate is the mean of NSTE matrices over ten 10 s-long small windows. Fig. 1 (E-G) present the relative change (%) of NSTE for each substate (A1, A2 and A3) of the anesthetized state compared to the mean NSTE matrix of baseline state. The figures demonstrate the decrease of the feedback connections (denoted with blue colors) in A2 and A3 after ketamine administration and the increase of some feedforward connections (red colors). For visualization, Fig. 2 demonstrates the increase and decrease of NSTE on a 2-dimensional scalp plot. Only extreme cases are presented in the 2-dimensional scalp plot and we did not test for significance. The figures show the overall decrease of feedback connectivity from frontal to temporal and parietal channels; some channel connections from parietal and temporal to frontal regions increase after ketamine.

The regional differences of the relative power for five frequency bands are presented in Table 1. In particular, the frontal channels (F3 and F4) and the parietal channels (P3 and P4) show significant regional differences during both baseline consciousness and ketamine anesthesia. The organizations of relative powers in the five frequency bands change across states and the temporal patterns depend on the frequency bands in Fig. 1 (A)-(E). The theta, alpha and beta bands have larger relative power in parietal channels (P3 and P4, denoted with black color in the Table 1); in contrast, the delta and gamma powers are larger in the frontal channels (F3 and F4, denoted with red color in the Table 1). The regional difference of relative powers could produce spurious connectivity. However, potentially spurious connectivity from regional differences in the relative power spectrum was controlled for by subtracting surrogate data in equation (4).

Table 1. The Regional Difference of Relative Power Across Frontal and Parietal Regions for Ketamine

Channel Names	Fp3-P3		Fp3-P4		Fp4-P3		Fp4-P4		F3-P3		F3-P4		F4-P3		F4-P4	
(**B**aseline|**A**nesthesia)	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Delta									•	•	•		•		•	
Theta									•	•	•	•	•		•	
Alpha							•		•	•	•	•	•	•	•	•
Beta										•	•			•		
Gamma										•	•			•		

The relative powers of frontal and parietal electroencephalogram channels were tested for five frequency bands. The significance is denoted with "•" as p<0.01 and, otherwise, with "blank" in ANOVA test with Bonferroni correction (α'(0.00025)=α(0.01)/N, N=40 for 5 frequency bands × 8 pairs of electroencephalogram channels) . If the frontal channel has a larger power, it is denoted with red color vs. black color. In most frequency bands, the frontal channels (F3 and F4) and the parietal channels (P3 and P4) show significant regional differences in the relative powers.

Table 2. The Means and Standard Deviations of Feedback and Feedforward Connections Across Six Substates for Three Anesthetics

		B1	B2	B3	A1	A2	A3
Ketamine	**FB**	0.0077±0.0033	0.0073±0.0027	0.0073±0.0031	0.006±0.0025	0.0047±0.0022	0.0057±0.0033
	FF	0.0042±0.0015	0.0041±0.0014	0.0041±0.0015	0.0044±0.0015	0.0045±0.0018	0.0050±0.0022
Propofol	**FB**	0.0058±0.0021	0.0060±0.0024	0.0052±0.0015	0.0055±0.0016	0.0039±0.0011	0.0033±0.0008
	FF	0.0035±0.0017	0.0033±0.0011	0.0032±0.0012	0.0033±0.0017	0.0032±0.0018	0.0031±0.001
Sevoflurane	**FB**	0.007±0.0037	0.0073±0.0045	0.0075±0.0041	0.007±0.0037	0.0049±0.0018	0.004±0.0015
	FF	0.0037±0.0017	0.003±0.0011	0.0037±0.0018	0.0034±0.0013	0.003±0.0013	0.0041±0.0026

The feedback (**FB**) and feedforward (**FF**) connections, $\overline{NSTE}_{f\rightarrow p}\ and\ \overline{NSTE}_{p\rightarrow f}$, between four frontal channels (FP1, FP2, F3 and F4) and two parietal channels (P3 and P4) were calculated for the three anesthetic groups(ketamine: n=30, propofol; n=9, sevoflurane: n=9). The significance test with repeated one-way ANOVA and Tukey's multicomparision test between six substates are described in the Results. B=baseline consciousness (three substates), A=anesthetized (three substates)

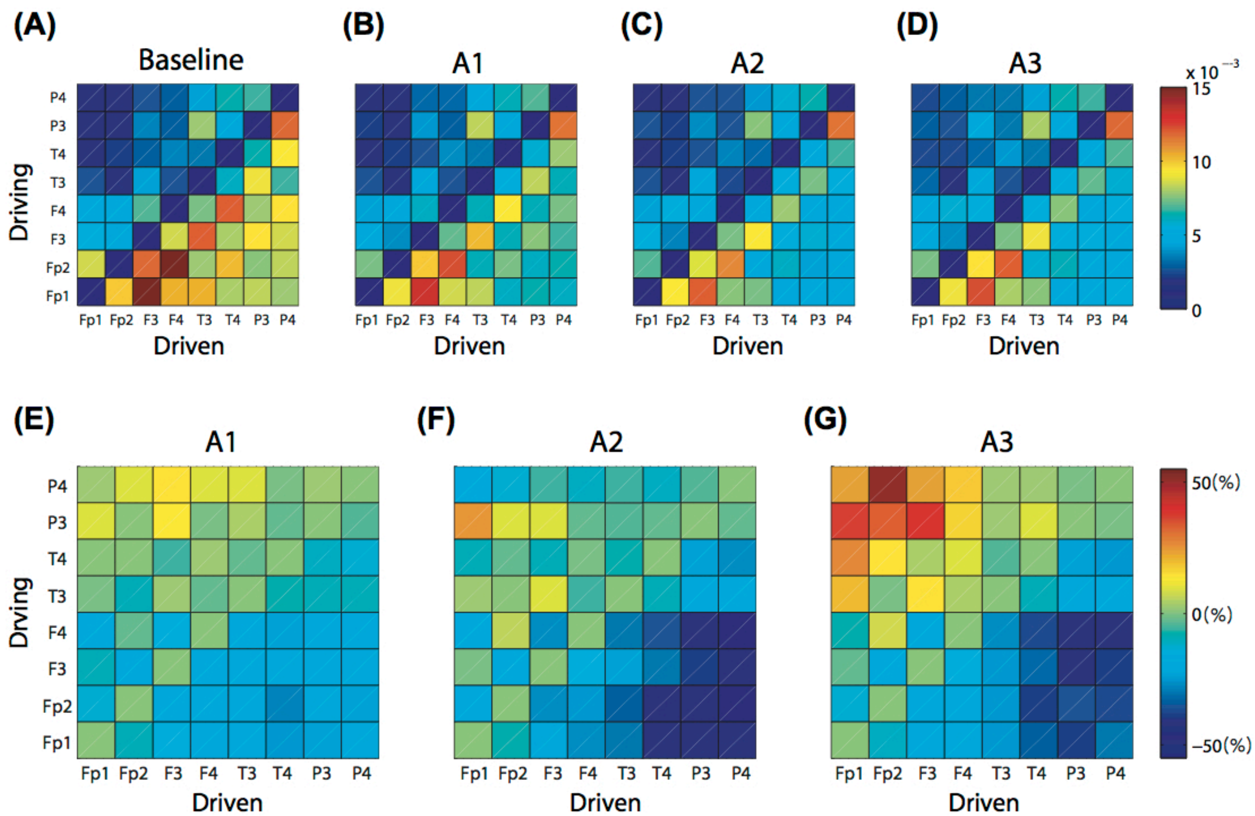

Fig.1. Normalized symbolic transfer entropy (NSTE) matrix for 8 electroencephalographic channels in the six substates of ketamine anesthesia. (A) The NSTE matrix averaged over the three substates of the baseline state (B1, B2 and B3; 100 s-long electroencephalogram epochs). (B-D) The NSTE matrices for the three substates of the anesthetized state (A1, A2 and A3; 100 s-long electroencephalogram epochs). Each NSTE matrix for a substate is the average of NSTE matrices for ten 10 s-long small windows. The relative changes (%) of NSTE matrices of the anesthesized state compared to the NSTE matrix of baseline state are presented for (E) A1, (F) A2 (G) A3 substates. After anesthetic-induced unconsciousness, the feedback connectivity from frontal to temporal and parietal channels decreases (denoted with dark blues).

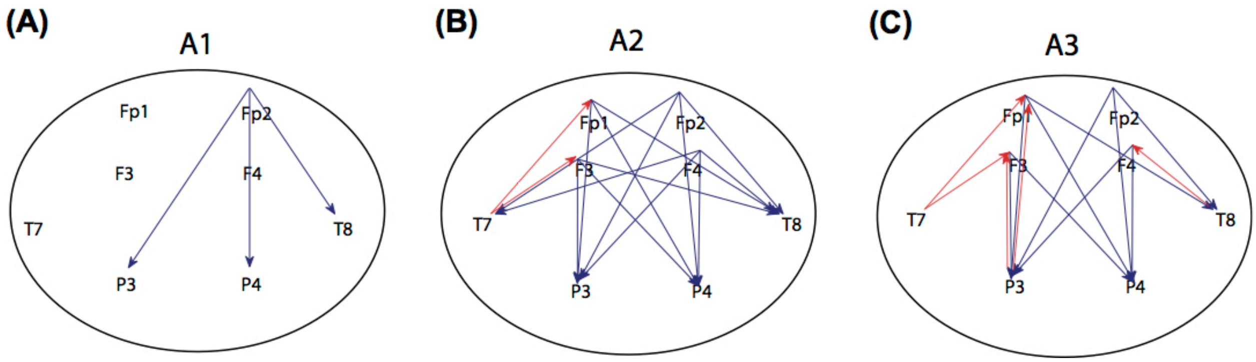

Fig. 2. Graphical representation of the change of connectivity after anesthetic administration. The relative changes of connections in the substates (A1, A2 and A3) during ketamine anesthesia are presented. The large increase and decrease of connection strength against the mean value of baseline state are denoted for each pair of electroencephalographic channels. If Normalized symbolic transfer entropy (NSTE) decreased more than 25%, the connection is denoted with a blue line; if the increased more than 25%, the connection is denoted with a red line.

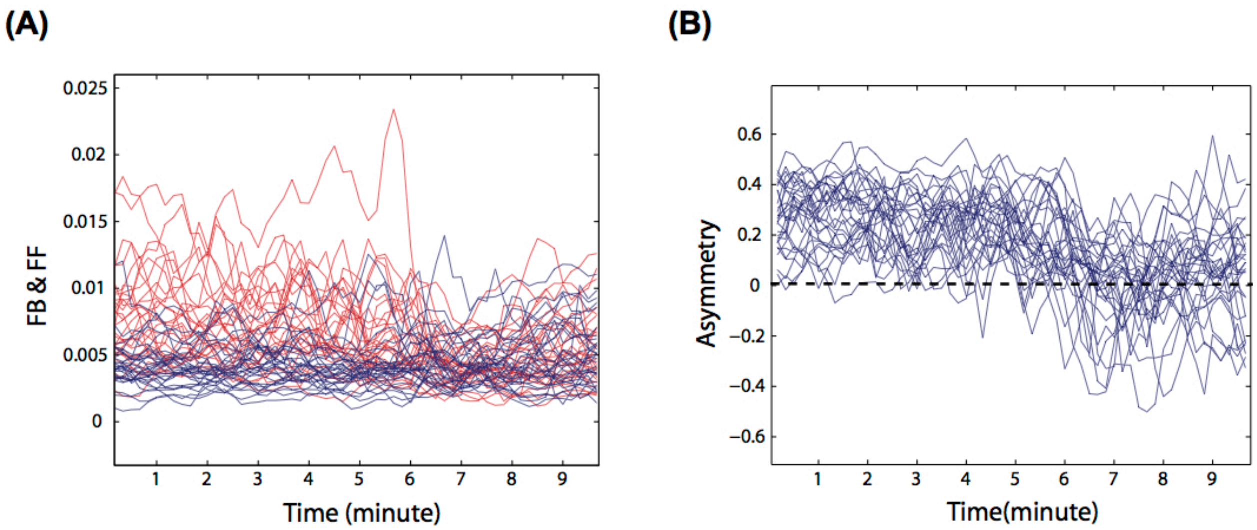

Fig. 3. The variance of connectivity over 30 patients during ketamine anesthesia. (A) All individual feedback (FB: red solid line) and feedforward (FF: blue solid line) connections measured by normalized symbolic transfer entropy (NSTE) between frontal and parietal channels, $\overline{NSTE}_{f\rightarrow p}$ $and\ \overline{NSTE}_{p\rightarrow f}$, respectively, and (B) All asymmetries of feedback and feedforward connections between frontal and parietal regions are presented. Despite large individual variances of connectivity, the feedback dominance in baseline state and the significant inhibition of feedback connection after ketamine anesthesia are salient.