Supporting Information

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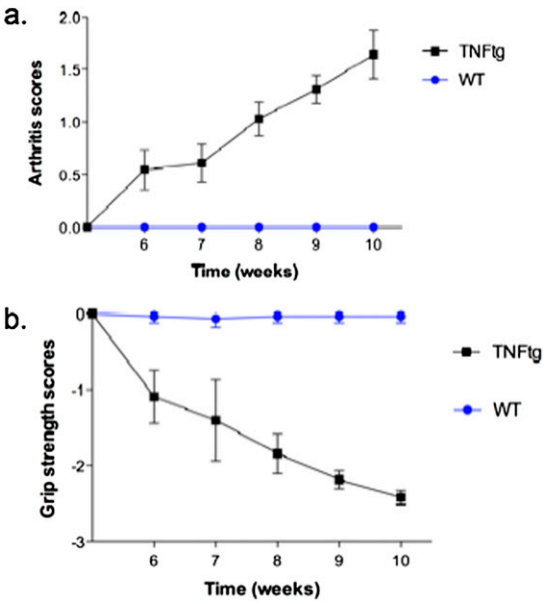

Fig. S1. Clinical course of arthritis. Joint swelling (*A*) and grip strength (*B*) of WT (blue) and human TNF transgenic (TNFtg) mice between week 5 (before disease onset) and week 10.

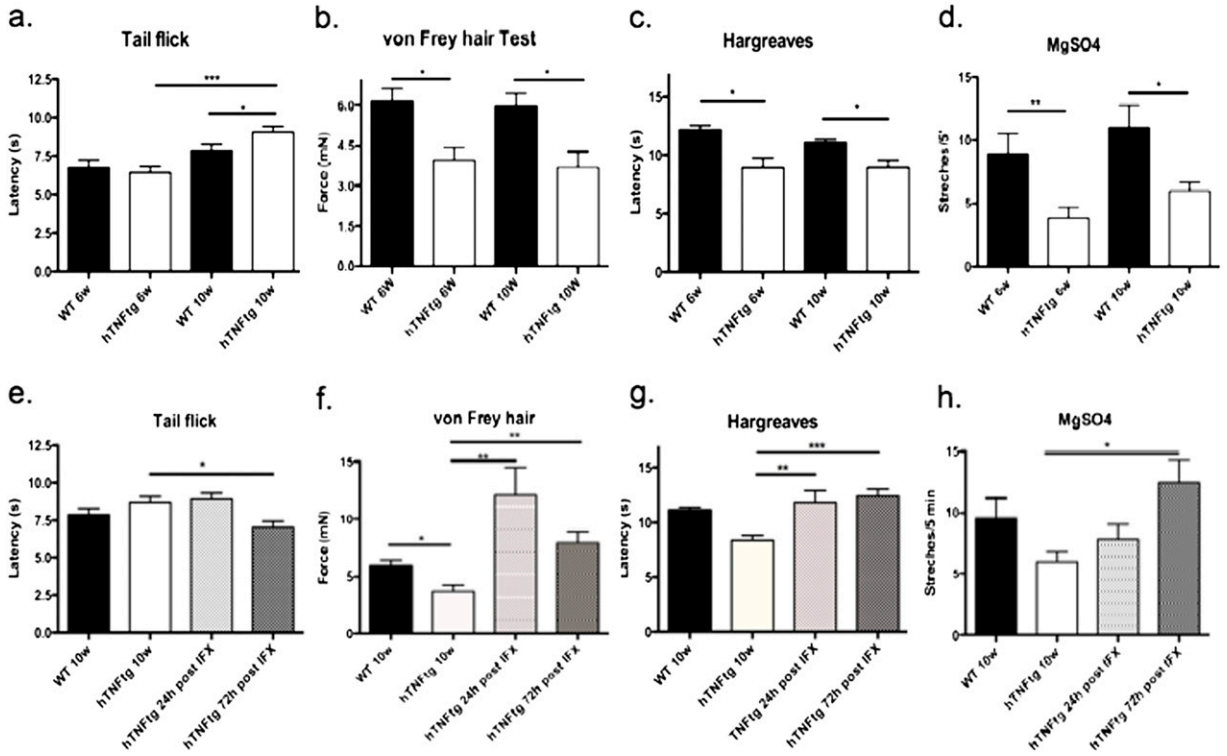

Fig. S2. Nociception tests and rapid reversal of sensitization to nociception by TNF-α blockade. Testing for spinal reflex arches by the tail-flick test (*A* and *E*), peripheral nociception by von Frey hair (*B* and *F*) and Hargreaves test (*C* and *G*), and of visceral nociception by $MgSO_4$ injection (*D* and *H*). (*A*–*D*) Experiments were performed in 6- and 10-wk-old WT and human TNFtg mice. (*E*–*H*) Experiments were performed in 10-wk-old WT and TNFtg mice treated either with vehicle or with the human anti-TNF antibody infliximab (IFX). Analyses were performed 24 and 72 h after antibody treatment. Asterisks indicate significant differences (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

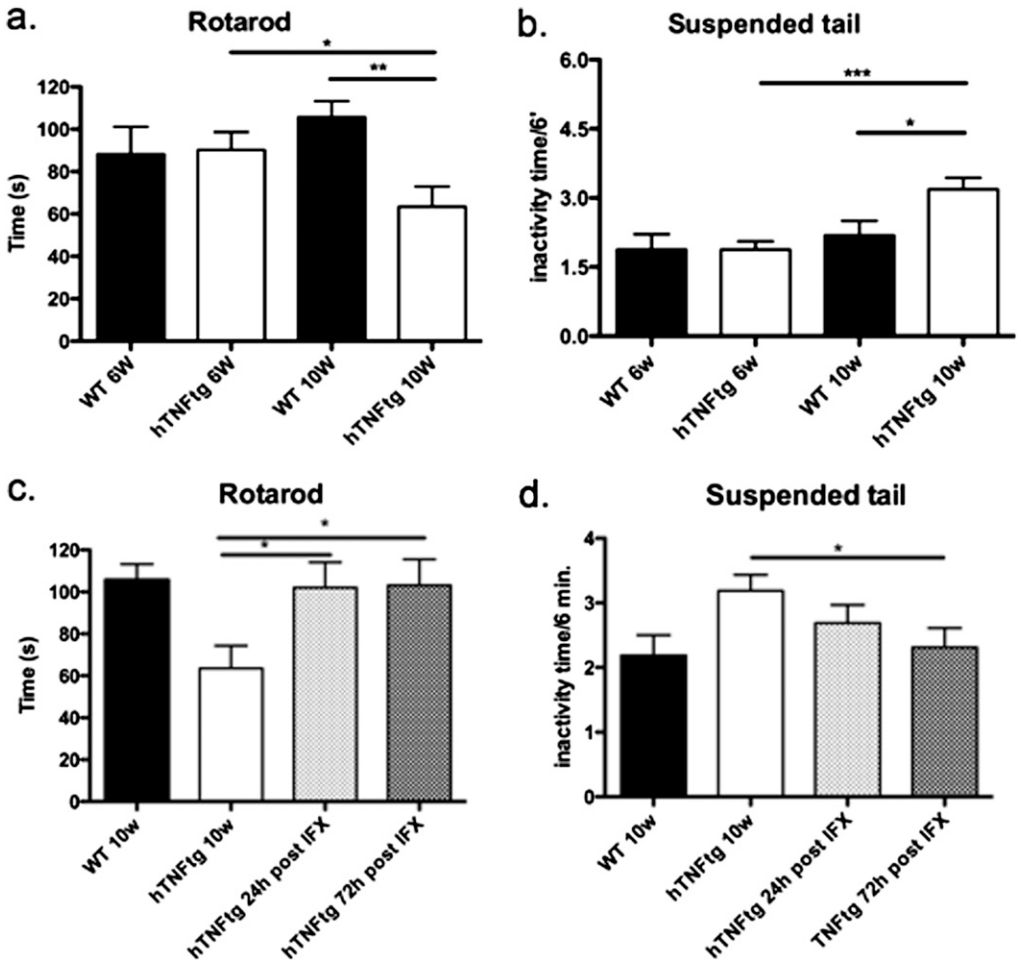

Fig. S3. Behavioral tests and their modulation by arthritis and TNF blockade. Testing for sensory-motor control by Rotarod test (*A* and *C*) and motivation/depression by the suspended-tail flick test (*B* and *D*). (*A* and *B*) Experiments were performed in 6- and 10-wk-old WT and human TNFtg mice. (*C* and *D*) Experiments were performed in 10-wk-old WT and human TNFtg mice treated either with vehicle or with the human anti-TNF antibody IFX. Analyses were performed 24 and 72 h after antibody treatment. Asterisks indicate significant differences (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

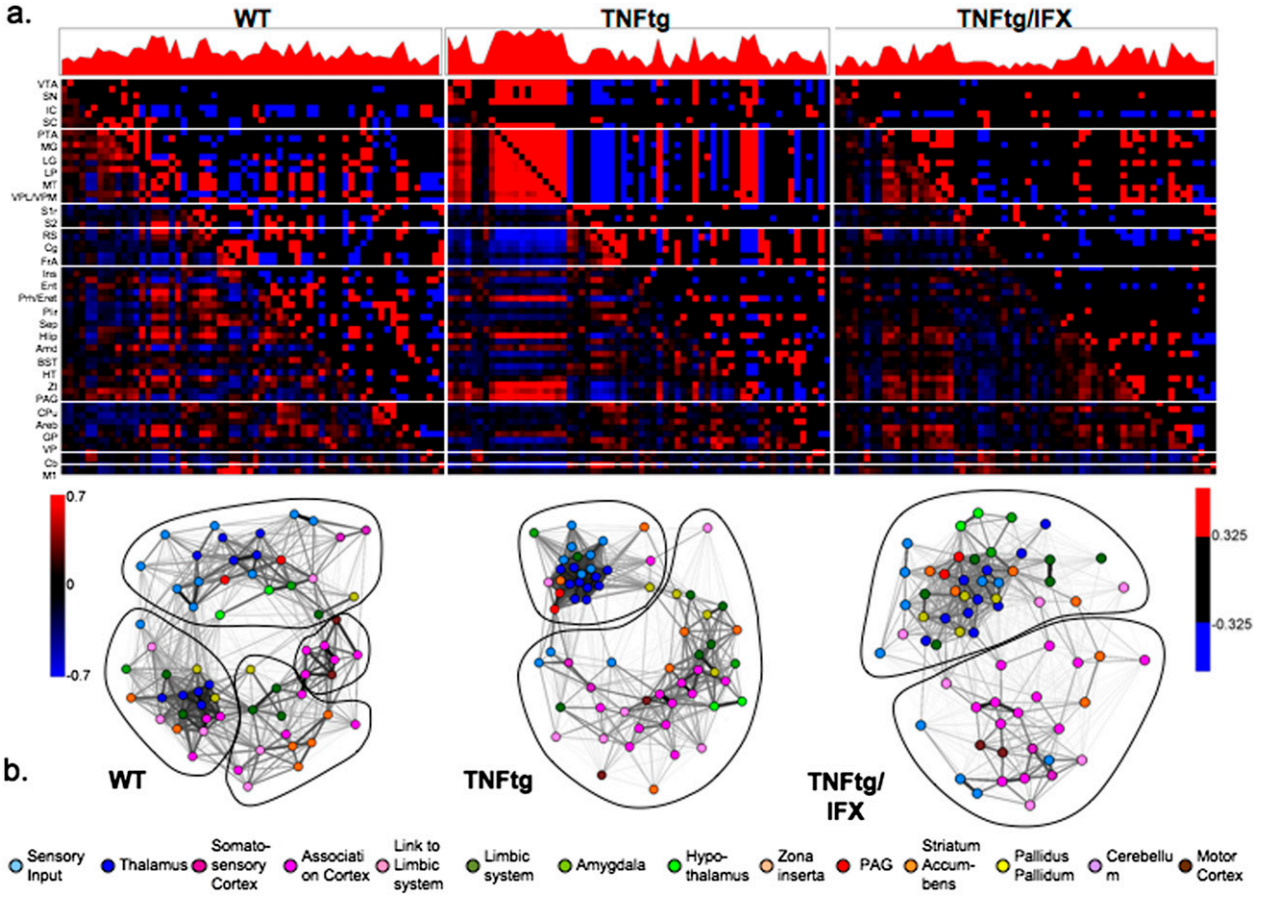

Fig. S4. Correlation maps and network graphs of pain-induced brain activity. (*A*) The lower triangular half of each column shows the cross-correlation matrices (−0.7 to 0.7) of the time course after regressing out the global trend between all structures of the pain matrix for the WT mice (*Left*), human TNFtg mice (*Center*), and TNFtg mice 24 h after IFX treatment (*Right*). The upper triangular half shows the connectivity matrix after thresholding the correlation matrix (red: values above 0.325, blue: values below −0.325). At this threshold level, the matrix of TNFtg mice became fully connected, whereas the ones of WT mice and TNFtg mice treated with IFX were connected at 91% and 41%, respectively (Table S1). The graphs at the top show the connection strength for each node (brain region). Note the strong coupling (red peaks) within the thalamus and the periaqueductal gray (PAG) in TNFtg mice. Brain structures are labeled at the left side. Note that for each brain structure its left and right side are not labeled but shown next to each other. (*B*) Kamada-Kawai plots showing the network connections in a force-based layout. WT mice show four modules, untreated and IFX-treated TNFtg mice show two modules. Note the tight coupling of the brainstem, thalamus, PAG, and the contralateral amygdala in the smaller module for TNFtg mice (see Table S1 for corresponding clustering and modularity indices). This cluster and its tight coupling does not exist in the WT mice and is dissolved partially in TNFtg mice after IFX, indexed by overall decreased clustering and modularity. The color code at the bottom refers to the different functional groups of brain structures (light blue: brainstem; dark blue: thalamus; pink: somatosensory, insular, retrosplenial, cingulated, and frontal cortices; light pink: entorhinal, perirhinal/ectorhinal, and pirifom cortices; green: septal area, hippocampus, and stria terminals; light green: amygdala; dark green: hypothalamus; beige: zona incerta; red: periaqueductal gray; orange: striatum and nucleus accumbens; yellow: globus pallidus, ventral pallidum; dark pink: cerebellum; brown: motor cortex).

Table S1. Serum levels of C-reactive protein and IL- 6 at baseline and after TNF blockade

		Baseline	Day 1	Day 14	Day 42
C- reactive protein					
Patient 1	(mg/mL)	3.2	3.3	1.2	0.3
Patient 2	(mg/mL)	2.1	2.3	0.7	0.1
Patient 3	(mg/mL)	2.7	2.7	0.6	0.2
Patient 4	(mg/mL)	1.9	1.8	1.2	0.9
Patient 5	(mg/mL)	4.7	4.9	0.9	0.4
Mean ± SD	(mg/mL)	2.9 ± 1.1	3.0 ± 1.2	0.9 ± 0.3*	0.3 ± 0.3**
IL- 6					
Patient 1	(pg/mL)	27.5	29.2	9.7	7.2
Patient 2	(pg/mL)	13.4	12.3	5.1	3.2
Patient 3	(pg/mL)	25.8	26.0	16.3	10.6
Patient 4	(pg/mL)	10.7	12.5	8.3	4.6
Patient 5	(pg/mL)	32.3	36.6	17.5	7.9
Mean ± SD	(mg/mL)	21.9 ± 9.3	23.3 ± 10.6	11.3 ± 5.3*	6.7 ± 2.9**

*$P < 0.05$.
**$P < 0.01$.

Table S2. Characteristics of CNS network structure

	Percent connected network	Cluster coefficient	Modularity index
WT	91%	1.633 ± 0.013	0.393
TNFtg	100%	2.006 ± 0.021	0.412
hTNFtg/IFX	41%	1.502 ± 0.012	0.299

To determine the fraction (%) of the connected network, the value was set to 100% in TNFtg mice and, compared with WT mice and TNFtg mice, treated with the TNF-α blocker infliximab (IFX). The cluster coefficient indicates the mean (± SD) number of connections per brain region.