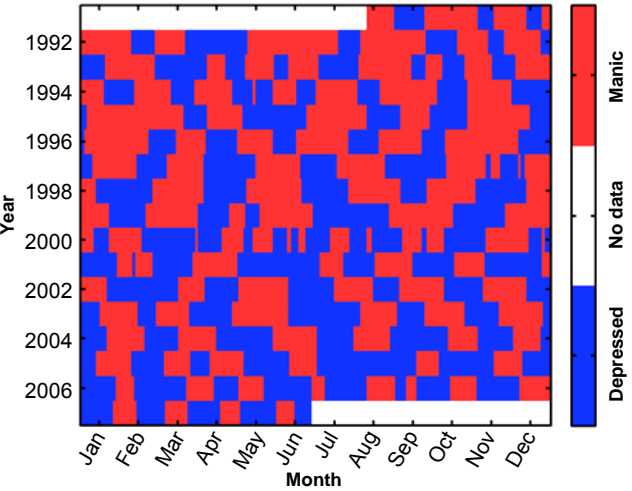
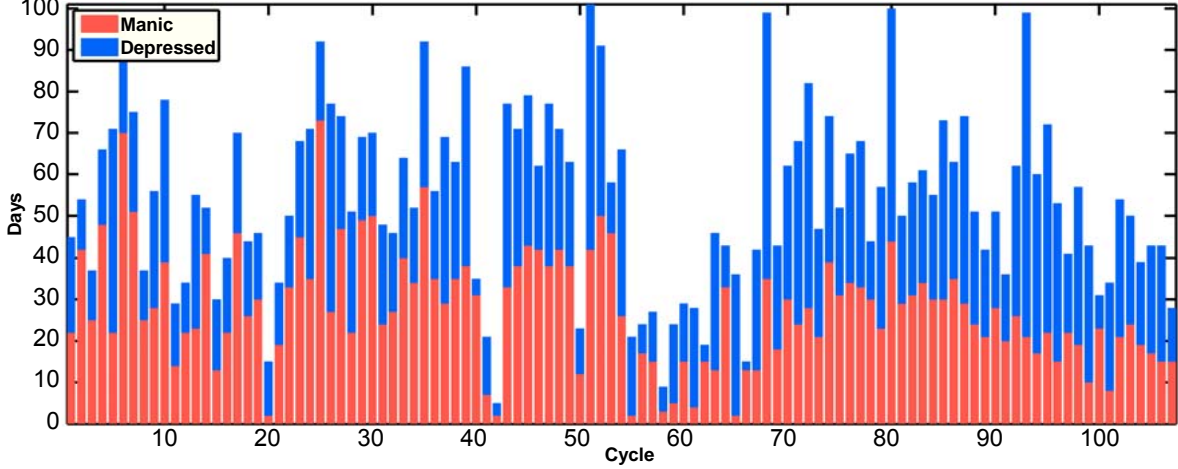


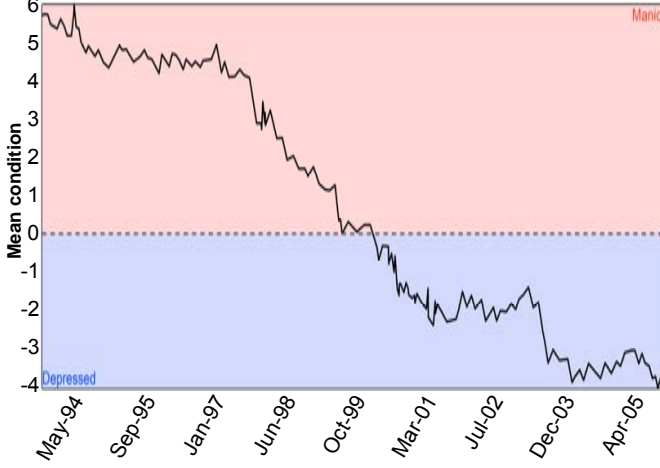
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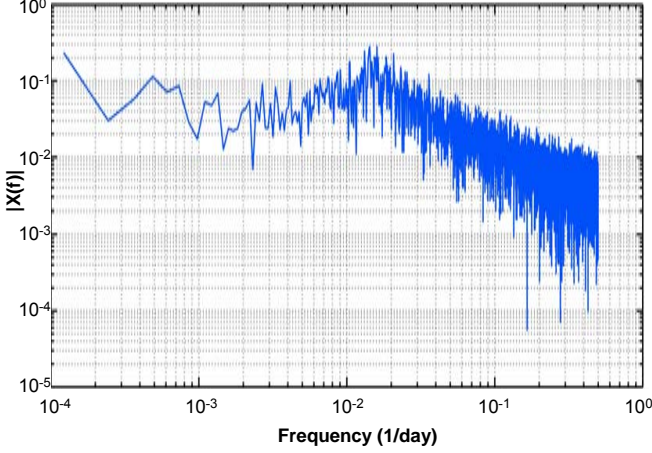
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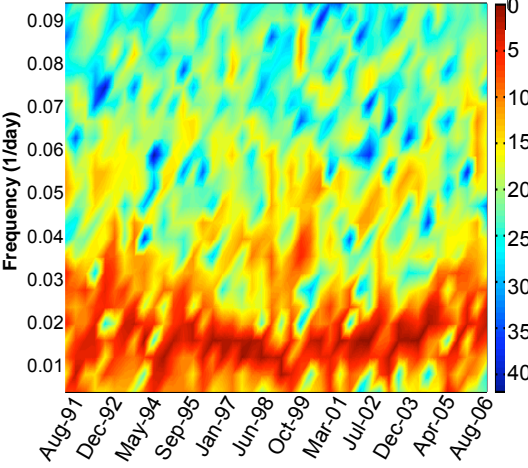
C



D

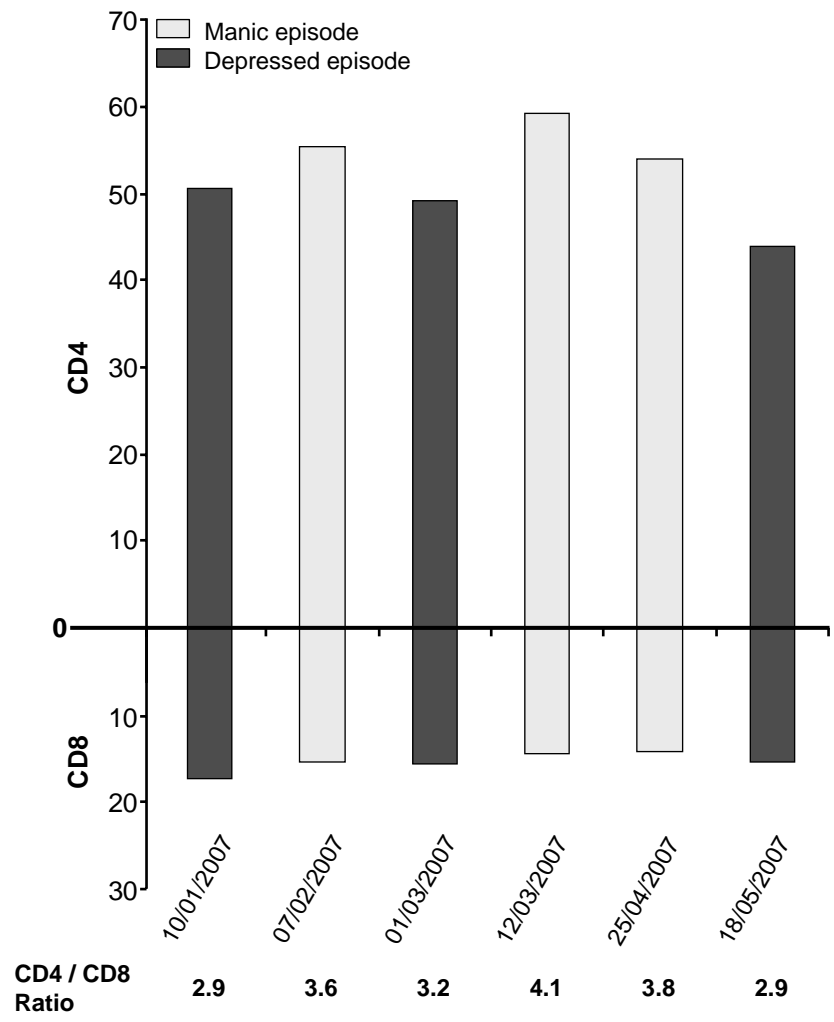


E



Supplementary Figure 1.
Time series of manic and depressed episodes over 16 years

Time series of rapidly alternating manic and depressed episodes range from August 1991 to June 2007 plotted according to the calendar (a) and to the specific cycle number (b). A time series $x(t)$ was reconstructed from the intervals by concatenating corresponding step functions, where manic episodes were encoded by 1 and depressed episodes by -1. The time intervals have been analyzed by taking differences of the length of manic and depressed half-cycles respectively. These differences were smoothed by taking mean over windows, where the optimal window size of $w=60$ cycles has been determined by maximizing smoothness when at the same time minimizing deviation from the original time course. There was an obvious trend from the strong presence of manic episodes initially to the pronounced presence of depressed episodes later in the course of the illness (c). The fast Fourier transformation (FFT) $X(f)$ of the time series $x(t)$ revealed that the spectrum contained a characteristic frequency of $f_0=0.0141$ (71 days) (d). The log-log periodogram indicated that the data followed a power-law. This was to be expected due to the fact that the data consisted of overlaid Heaviside functions with varying episodes). The short-time Fourier transformation (SFT) was computed with a window length of 256 days. The resulting lowest frequencies in the windows are shown in the spectrogram (e). The frequency distribution varied over the course of the illness. For example, high-frequency components were more pronounced in 2000 in contrast to the other years where the low frequencies were more dominant.



Supplementary Figure 2.
Episode-specific shifts of T cell subsets

Percentage of CD3+/CD4+ (top) and CD3+/CD8+ (bottom) T cells were measured by fluorescence activated cell sorting (FACS) in three independent manic (open bars) and three independent depressed episodes (filled bars). The bottom line denotes the respective ratio of CD4/CD8 cells. Mean results showed that in depressed episodes, there were 47.9±3.6% T helper cells and 16.1±1.1% suppressor cells with a ratio CD4/CD8 of 2.98±0.2, whereas in the manic episodes, there were 56.2±2.7% helper cells and 14.6±0.6% suppressor cells with a CD4/CD8 ratio of 3.8±0.2 (nonparametric independent Mann-Whitney-U-test (two-tailed); p=0.05 in all tests). Dates are denoted in the order day/month/year. The percentage of natural killer cells and B cells showed no alteration in this series (data not shown).

Supplementary Material

Supplementary Table 1:

Oligonucleotides used for qRT-PCR amplification of differentially expressed genes

Gene	orientation	primer sequence 5' => 3'
PTGDS	Fwd Rev	CGGCTCCTACAGCTACCG CAGCGCGTACTGGTCGTA
AKR1C3	Fwd Rev	CATTGGGGTGTCAAACCTTCA CCGGTTGAAATACGGATGAC
NRG1	Fwd Rev	CACAGCCCATCACTCCACTA AAGGATGCTTTCAGTGTGTCC
SPON2	Fwd Rev	AGGACACGGTGACCGAGATA GCGGGTAGTAGAAGGAGTTGG
HBA1	Fwd Rev	GACCCGGTCAACTTCAAGC AGAAGCCAGGAAGTGTCCA
HBB	Fwd Rev	GCACGTGGATCCTGAGAACT ATGGGCCAGCACACAGAC
GZMA	Fwd Rev	CCTGTGATTGGAATGAATATGGT AGGGCTTCCAGAATCTCCAT
GZMB	Fwd Rev	TAAGGGGGAAACAACAGCAG CATGTCCCCCGATGATCT
KLRD1	Fwd Rev	GTGGGAGAATGGCTCTGC TTTGTATTAAGTTTCAAATGATGGA
GAPDH	Fwd Rev	CTGACTTCAACAGCGACACC TGCTGTAGCCAAATTCGTTGT

Primer sequences of other genes mentioned in the text, including those listed below, can be made available from the authors upon request.

As expected, a number of genes that were suggested to be episode-regulated in the initial screening could not be confirmed by qRT-PCR (including samples obtained more than one year after the microchip strategy was performed). These include ORF52, ECGF, TNFSF13b, STAT1, NFKB, KCNQ1, MAPB2K3, MAPB3K5, FKBP5, NFKBIZ, NCAM1, KIR3DL2, SRGAP2 (slit-robo), BCL6, S100A12 and CSPG2 (versican) (data not shown). On the other hand, we performed qRT-PCR on genes that, perhaps due to low abundance, were not found by the microchip screening to be episode-specifically regulated, e.g. GZMB which tended to be regulated like GZMA (Figure 1d), or PER2, a circadian regulator, which was not found to be episode-dependently expressed (not shown). Also, globin-regulating genes (FOG1, GATA, BRG1, EPOR and HIF1alpha) were unaltered during episodes(not shown).