**Additional file 3 —**

**An in-depth explanation of the choices made when applying the linear-mixed models**

Variance inflation factor (VIF) values were below 2 for all independent variables and cytokines, apart for IL-4, for which VIF values were below 4.5. An interaction term was hypothesized between WCC and temperature, but since the Akaike information criterion (AIC) was lower without the interaction term and merely 2 out of 42 cytokines were significant (*p* < 0.05) in an analysis of variance (ANOVA), we decided to keep the model without interaction terms.

A first-order autoregressive model was employed, since it was best in terms of AIC when comparing several autoregressive moving average (ARMA) models; autoregressive integrated moving average (ARIMA) were not used as the Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test was insignificant at *p* < 0.05. Visual inspection of the first-order autocorrelation function and the partial autocorrelation function were nonsignificant and the residuals were small for this model. Furthermore, for the linear mixed-effect model, visual inspection of residual and Q-Q plots did not reveal any obvious deviations from homoscedasticity or normality **[Supplementary Materials: Figure 1 code]**. In order to compare the parameters of fixed effects to each other and across different cytokines, we normalized the regression coefficients by multiplication of the fraction of standard deviations of the independent variable and the dependent variable; these may be regarded as correlations.

In short, the model that has the best information criteria and may show how inflammation parameters are associated with brain cytokine levels, is the following:

where

and

*M* is the brain cytokine level for a particular cytokine, *t* is the time, *A* is the arterial cytokine level, *C* is CRP, *L* is white cell count, *T* is temperature, *I* is presence of infection, *X* is treatment randomization, *R* is a random error, with a first-order auto-regressive structure, *S* is the individual error term, and *i* is the measurement occasion for individual *j*. In summary, this is a mixed-effect model, with individual intercepts and time gradients for each patient.

In order to compare the inflammation parameters, all partial gradients *ßk* for each cytokine are weighted with the fraction of standard deviations of the parameter itself and the brain cytokine. That is,

where *Pk* is the inflammation parameter *k*. By rewriting the expression,

it is clear that the weighted gradient is a scaling of the data adjusted for its spread. This was then repeated and performed using different parameters in different analyses, changing between predicting arterial and brain-ECF cytokines.

The normalized fixed effect coefficients are plotted as a heatmap in, including a dendrogram using 1 minus Pearson correlation distance with average linkage.