Basal Hippocampal Activity and Its Functional Connectivity Predicts Cocaine Relapse

Supplemental Information

Supplemental Methods

Measures of Cocaine Craving

Cocaine-use history was assessed with the Timeline Follow-back (TLFB) (1). The TLFB uses a calendar and other memory aids to gather retrospective estimates of an individual's cocaine use (days used and dollars spent) across the lifetime (from age of first use) as well as during the 90 days prior to abstinence. The Cocaine Craving Questionnaire (CCQ) is a 10-item self-report measure adapted from the original 45-item CCQ-Now that asks subjects to indicate how much they agree or disagree with statements related to cocaine craving. The Obsessive Compulsive Cocaine Scale is a 14-item self-report questionnaire adapted from the Obsessive-Compulsive Drinking Questionnaire (2). It is used to examine obsessive thoughts of cocaine use and compulsive cocaine use.

Quantification of Regional Cerebral Blood Flow

The following equation was then used to estimate regional cerebral blood flow (rCBF) (3):

$$f_{pCASL}(x,y,z) = \frac{\lambda \cdot \Delta M(x,y,z) \cdot e^{\frac{\delta}{T_{1a}}}}{-2\alpha \cdot M_b^0(x,y,z) \cdot T_1 \cdot [e^{\frac{\min(\delta - w, 0)}{T_1}} - (1 - \frac{T_{1RF}}{T_1}) e^{-\frac{w}{T_1}}]}$$

where $f_{pCASL}(x,y,z)$ is the blood flow value at voxel (x,y,z) in milliliters of blood per minute per 100 g brain tissue; the labeling efficiency α = 0.86 (3); the blood-brain partition coefficient λ = 0.98 mL/g (4); δ is the arterial transit time of blood from the labeling place to the imaging slice and assumed to be 2 s (5); the post labeling delay w = 1.525 s; the brain tissue T1 = 1.165 s (6); the arterial blood T1a = 1.624 s (7); the brain tissue T1 in the presence of off-resonance irradiation T1RF = 0.75 s (8); and, $M_b^0(x, y, z)$ is the value of equilibrium magnetization of brain tissue at voxel (x,y,z), which was approximated by the intensity of average control images.

Predictive Models of Relapse

As time to relapse was assessed for up to 24 weeks following discharge from residential treatment, we considered whether functional imaging measures differing between the three groups further predicted days to relapse up to 168 days. A hierarchical survival analysis was performed to predict the time to relapse post-treatment using the average $rCBF_n$ values and the average resting state functional connectivity (rsFC) strength extracted from the brain regions showing significant group effects as predictors in a Cox regression model (SPSS 20.0, IBM Corporation, Armonk, NY). At the first regression step (model 1), the time to relapse was predicted by $rCBF_n$. At the second step (model 2), functional connectivity strength was added to the model. All hypotheses were tested at a global type I error of a = 0.05.

Time-dependent receiver operator curves (ROC) were also used to estimate the positive predictive value of the relapse model. Time-dependent ROC analysis calculates sensitivity and specificity of cumulative relapse cases that accrue for any point of time (e.g., 30 day intervals) over a fixed time period (168 days in this study). Using this approach, relapse cases are observed for any point of time (t) and can characterize the sequence of predictions that occur continually for any time *t* (9). Time-dependent ROC first uses Cox regression models to estimate predicted relapse rate and then predicted rates plus rCBF and rsFC measures were supplied as inputs to a time-dependent ROC analysis to estimate the area under the curve (AUC) at time t, (t = 30, 60, 90, and 120 days). RisksetROC with the R software framework, was used to create time-dependent ROC curves and calculate time-dependent area under curve, AUC (t) (cran.r-project.org).

Supplemental References

1. Sobell LC, Sobell MB (1992): A technique for assessing self-reported ethanol consumption. In: Allen J, Litten RZ, editors. *Measuring Alcohol Consumption: Psychological and Biological Methods*. Totowa, N.J.: Humana Press, pp 41-72.

2. Anton RF, Moak DH, Latham P (1995): The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcohol Clin Exp Res*. 19:92-99.

3. Aslan S, Xu F, Wang PL, Uh J, Yezhuvath US, van Osch M, *et al.* (2010): Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. *Magn Reson Med*. 63:765-771.

4. Herscovitch P, Raichle ME (1985): What is the correct value for the brain--blood partition coefficient for water? *J Cereb Blood Flow Metab*. 5:65-69.

5. Alsop DC, Detre JA (1996): Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J Cereb Blood Flow Metab*. 16:1236-1249.

6. Lu H, Nagae-Poetscher LM, Golay X, Lin D, Pomper M, van Zijl PC (2005): Routine clinical brain MRI sequences for use at 3.0 Tesla. *J Magn Reson Imaging*. 22:13-22.

7. Lu H, Clingman C, Golay X, van Zijl PC (2004): Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med*. 52:679-682.

8. Oguz KK, Golay X, Pizzini FB, Freer CA, Winrow N, Ichord R, *et al.* (2003): Sickle cell disease: continuous arterial spin-labeling perfusion MR imaging in children. *Radiology*. 227:567-574.

9. Heagerty PJ, Zheng Y (2005): Survival model predictive accuracy and ROC curves. *Biometrics*. 61:92-105.