

# Does Traumatic Brain Injury Cause Risky Substance Use or Substance Use Disorder?

## *Supplement*

Box S1

*Lifetime exposure in TBI cohorts*—retrospective elicitation of histories preceding an index TBI allows discernment of whether the index TBI was the first; however, temporal onset of first TBI versus problem substance use typically is not elicited. It might be safely concluded that those with an early childhood TBI incurred their TBI first, but adolescent onset of both conditions is frequent and defies temporal ordering. These studies typically do not allow confounders to be ruled out.

*Population studies of association*—these studies allow estimation of the strength of association but typically do not discern temporal onset. Like lifetime exposure, very early childhood TBIs might be presumed to precede onset of problematic substance use. Studies that link multiple sources of data for large populations are able to rule out confounders by accounting for developmental exposures via comparisons to siblings without TBI and risk-taking via comparison to persons with orthopedic injury but not TBI.

*Birth cohorts*—though expensive in terms of time and resources, this method holds the most promise for establishing the relative temporal onset and ruling out confounders. However, if not initially designed to examine these factors, definitive conclusions about the relationships still may not be possible.

## Box S2

*Conditioned Place Preference (CPP)* — A test that measures the conditioned rewarding effect of a drug of abuse. CPP uses a two- or three-chamber apparatus with different contextual cues in each chamber. After a pre-conditioning test assessment of time spent in each chamber of the apparatus, a series of conditioning sessions begins. In each of these sessions, the drug is paired with isolation to one chamber or the absence of the drug (e.g., injection of the drug's vehicle) is paired with isolation in another chamber. During the post-conditioning test, subjects have access to all chambers. The primary outcome measure is preference for the drug-paired chamber.

*Two Bottle Choice* — A test that measures voluntary consumption of ethanol (alcohol). Subjects have access to two bottles: one containing an alcohol solution and one containing water. The primary outcome measures are preference for the alcohol compared to water and total alcohol consumption.

*Intravenous Drug Self-Administration* — A test that measures reinforcement of a drug of abuse. Subjects receive an intravenous catheter and operant conditioning, where performance of an operant response (e.g., a lever press) results in brief presentation of cues (e.g., a light) and intravenous infusion of drug. The primary outcome measure is number of drug infusions earned.

*Extinction* — A test that measures the reduction of a learned behavior over time. In studies of substance abuse, a reduced rate of extinction is interpreted as persistent drug seeking behavior. Extinction tests can be performed following CPP (repeated measurement of preference for the drug-paired chamber in the absence of drug) and intravenous drug self-administration (repeated measurement of operant responding in the absence of drug infusions).

*Reinstatement* — A test that measures resumption of a previously extinguished drug-associated response (e.g., re-expression of a preference for the drug-paired chamber in CPP, resumption of operant responding in self-administration) following a stimulus, typically the drug-conditioned stimulus (e.g., cue light), stress, or a priming injection of the drug itself. Tests are done under extinction conditions.