Reviewer's report

Title: Multimodal neuroimaging of frontal white matter microstructure in early phase schizophrenia: The impact of early adolescent cannabis use (study protocol)

Version: 2 Date: 29 August 2013

Reviewer: Katherine Karlsgodt

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This goal of the study proposed in this protocol is to use a variety of neuroimaging techniques focused on white matter microstructure and integrity in order to understand the effects of early and late cannabis use on individuals with schizophrenia. This is an important topic, and the design of the study seems well suited for the investigation. The use of multiple modalities will be useful to get a broader measure of white matter abnormality in patients, but the findings in the control group will also be useful for quantification of the relationship between these different measures.

Major compulsory revisions

1. In the Statistical Analysis section, age and gender are listed as variables to be tested in a post-hoc exploratory analysis, but they really should be corrected for in all of the primary analyses.

2. Duration of cannabis exposure is a concern, as there is the potential for a confound in which those individuals who start cannabis use at a younger age by definition have a higher cumulative lifetime dose. Will this be corrected for in any way? It also might be possible to address this in a post-hoc analysis by taking a subgroup of individuals from both early and late groups who have a similar duration of use (so, in this subgroup likely the individuals from the early group would have a history of cannabis use but not current use), and determine whether the larger effects remain even between these matched groups.

3. Why is the focus on the left SLF only? It is not clear what hypothesis would differentiate left from right enough to exclude the right side, and the rationale for this is not included in the protocol. Either bilateral regions should be included, or this should be specifically addressed.

Minor Essential Revisions

1. In the hypothesis section, it is indicated that reduced FA values may or may not be found in the schizophrenia group. However, earlier in the introduction it is stated that the SLF is one of the three tracts most commonly found to have reduced FA, with seven references cited. Thus, it seems quite probable that SLF FA levels will be lower in the patient group overall.

Discretionary Revisions
1. The introduction is overly long, even relative to other protocols published by this journal. It would be better to pare it down so that there is a focus on those aspects of each technique specifically relevant to this study (for instance, it is likely not necessary to define here the details of what DTI is, as it is now a fairly commonly used technique).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests.