The authors critically reviewed selected literature regarding the nature and underlying neurobiology of relapse. Important findings include high relapse rates with treatment discontinuation; the absence of a relationship between length of treatment and relapse risk; abrupt transitions from remission to relapse with little-to-no "warning", often very soon after treatment reduction or discontinuation; and a rapid improvement in symptoms following treatment for acute psychosis in most patients, although treatment resistance emerges in 1 in 6 patients.

The research topic is important and timely. This research group has expertise and is well-known in this field. The manuscript is very well written and easy to follow. Many important considerations for future research are discussed.

Addressing several Minor Essential Revisions would further enhance the quality of the manuscript:

1. In section 1, two additional references regarding the prevalence of antipsychotic discontinuation in first-episode psychosis could be included:


2. Page 5, line 6: the word "at" appears to be missing between 80% and 12.

3. Regarding the section on the neurobiology of relapse in schizophrenia, the following material could be considered in the discussion:

   Growing evidence supports a role for immune system dysfunction in schizophrenia, including evidence from meta-analyses that blood levels of some cytokine (a) and lymphocyte (b) parameters may be state-related markers for relapse in schizophrenia (levels in cross-sectional studies are significantly altered in relapsed patients versus controls; longitudinal studies show that these parameters begin to "normalize" following antipsychotic treatment for relapse). A study of patients who underwent weekly assessments for 1 year found that in vitro interleukin-2 production plus antihippocampal immunoglobulin G levels from the previous week significantly predicted relapse in some patients (c). Another study found increased cerebrospinal fluid interleukin-2 levels following
haloperidol withdrawal were a significant predictor of acute psychotic relapse. The potential relationship between inflammation and relapse in schizophrenia is further supported by four trials that found adjunctive treatment with non-steroidal anti-inflammatory agents (versus placebo) in acutely relapsed patients showed significant improvement in total symptoms (e-h). Pro-inflammatory cytokine abnormalities may directly modulate dopaminergic neurotransmission, indirectly modulate glutamatergic neurotransmission through tryptophan catabolism, and/or contribute increased free radical production/oxidative stress, with resultant destabilization of neuronal cell membranes. Taken together, these findings suggest that immune/inflammatory dysfunction may play a role in the neurobiology of relapse in schizophrenia.


4. Table 1: Consider spelling out the word (Months) in the header rows for both "Treatment duration" and "Symptom recurrence rates", instead of using the abbreviation “m” throughout. Consider also adding a separate column for the 9
month recurrence rate for the study by Boonstra et al.

**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:**

The reviewers do not have any financial or non-financial competing interests to disclose.