**Title:** Developmental meta-analyses of the functional neural correlates of bipolar disorder

*Reviewed by Prof. J.C.Soares and Dr I.Bauer*

**Outcome:** major revisions, then resubmission

This review used the ALE technique to examine fMRI studies in pediatric BD. While this technique has been previously used to examine fMRI studies, fMRI studies in children do not appear to have been systematically reviewed. Further, this review compares fMRI results across emotional and non-emotional fMRI paradigms.

*Abstract:* The abstract summarizes the manuscript well however the conclusions refer to brain regions not listed in the results section of the abstract. Hence, it is unclear which brain regions are relevant for final conclusions.

*Introduction:* overall unstructured, wordy and not easily understandable. Compared to the introductory paragraphs regarding bipolar disorder in children, the paragraph/sentences explaining the rationale for reviewing fMRI studies in children is extremely brief, vague and unconvincing. For example, the reader is left guessing what the authors mean by “brain/behavior alterations”. It is also unclear how this review can answer any question related to the brain/behavior issue since the authors did not include or interpret cognitive or clinical data together with their fMRI findings. Also, in some instances the authors make vague statements/logic leaps while explaining their hypotheses e.g. line 151-152 where greater amygdala activation was expected because “BD youths often make more errors than controls… “. Hence I would recommend that the rationale for the hypotheses be further refined. I also wonder why the authors formulated initial hypotheses since a review is traditionally an exploratory piece of work. Furthermore, it is unclear why the authors think that fMRI results in pediatric BD differ from those in adulthood, and the reasons that they did not mention task-related functional connectivity studies in pediatric and adult bipolar populations.

*Hypotheses* are overall well-defined, however I wonder whether the research question of this paper is sufficiently novel since previous studies (see lines 112 to 124) have already answered the main question asked by this review. An alternative approach could have been to place additional emphasis on the strengths of the ALE technique and the kind of questions that the ALE technique can answer compared to “standard” systematic or meta-analyses.

*Methods:* in terms of search criteria, I wonder if the authors attempted to include unpublished and possibly negative findings. Also given the ongoing progress and development of MRI-related techniques, software, scanner parameters, how did the authors compare results from studies published in 2013 to those published in 2001?

*Results:* given the abundance of the results, the authors should summarize the most relevant findings in a table/graphic. Also highly recommended is a publication bias plot or a sensitivity analysis to determine the number of negative studies required to correct a statistically difference into a non-significant one.

*Discussion:* The authors compared their findings with the previous literature but did not appraise critically the meaning of their results and did not discuss the clinical implications of these results. For example more emphasis could have been placed on the meaning of the increased cortico-limbic-cingulate activation in pediatric BD (instead of repeatedly highlight the importance of further studies in understanding possible neurodevelopmental abnormalities). Much more should have been said in terms of structural/functional connectivity and inhibitory/excitatory pathways in childhood and reasons for finding treatments to address these abnormalities. Also, since the primary question of this study was related to the brain/behavior alterations in BD the authors could have discussed how functional changes in relevant areas affect the cognitive development or emotion processing in adulthood.

Line 342: the authors refer to the concepts of “efficiency” and “underdevelopment of the brain in BD”. Surprisingly the authors do not discuss what they mean by “efficiency” and whether “underdevelopment” refers to developmental lag. If the authors are here referring to the concept of *neural efficiency* I wonder why they did not include additional information on behavioral data related to the fMRI task paradigms.

*References:* The authors should double-check their references. For example Line 151 refers to “a previous ALE study” (ref 32) but this study is not an ALE review. Same was observed for ref 38 and 39.

*Technical comments:*

Proofreading/editing is recommended prior to future re-submissions

Line 43: “age-related changes” changes of what?

Line 46: analysis not analyses

Line 52: what do the authors mean by “original task-dependent”

Line 59-60: in the abstract the authors mention that an improved Ginger ALE method was used, however these improvements are not described in the manuscript.

Overall: replace “vs” with appropriate preposition/English word

Line 62: what do the authors refer to when they say “both groups”

Line 65: logic leap, unclear why alterations in functional activation would lead the reader to think that brain regions are underdeveloped/less efficient

Line 67: please reformulate this sentence as it is unclear

Line 151: what does the author mean by “dichotomy” in this sentence?

Line 314: The author should refer to “across all paradigms” instead of “overall”