Author's response to reviews

Title: Developmental heterochrony and the evolution of autistic perception, cognition and behavior

Authors:

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Version: 3 Date: 24 March 2013

Author's response to reviews: see over
Dear Dr Crespi,

Many thanks for your submission to BMC Medicine. Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files.

Referee 3: http://www.biomedcentral.com/imedia/5996796739424577_comment.pdf
Referee 1: http://www.biomedcentral.com/imedia/2060326304930324_comment.pdf
Referee 2: http://www.biomedcentral.com/imedia/2018479192937133_comment.pdf

Editors comments:
As you will see, all three referees are positive about your manuscript, but have noted that important revisions are required before the manuscript can be considered for publication. However, I would like to highlight two points to guide you with your revisions:

1. Referee 1 has recommended that the manuscript should include a Methods and Results section. However, as this is an Opinion article (and hypothetical), this will not be appropriate. Therefore please ignore that recommendation. In revising your manuscript, please ensure it is presented appropriately, so that readers will not be confused if this is an actual systematic review.

I have done so.

In particular, under the section "Autism and age-related childhood phenotypes", your search strategy and criteria is quite informative, but it would be helpful if you could start the paragraph with a sentence to clarify this is not a systematic review, but the that you took a systematic approach to reviewing the literature in order to examine your hypothesis.

I have made this change. I added the relevant sentence to the end of the paragraph, though, as I think it reads rather better this way. (see the bottom of page 7).

2. Regarding Figure 1, could you clarify if this is an original figure? If not, then permission must be sought from the copyright holder and a statement to this
effect should be included in the figure legend.

This is an original figure.

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We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

I have done so.

Reviewer’s report
Title: Developmental heterochrony and the evolution of autistic perception, cognition and behavior
Version: 2 Date: 27 February 2013
Reviewer: Ze’ev Hochberg

Reviewer’s report:
Crespi offers an original view of the complex autism spectrum, using heterochrony and evolutionary considerations. This is novel, interesting, and worth its publication.

Major Compulsory Revisions
1. Since this ‘study’, as the author calls it, includes a systematic review of the literature, it requires chapters of Methods and Results.

The format rules of this journal require the structure and headings that are used.

2. P.20 From an evolutionary perspective… - I suggest to start here a new chapter. Otherwise, the evolutionary connotation gets lost. This should also come clearer in the Abstract and Introduction.

To address this point and highlight the evolutionary aspects of this article, I have (on page 18) changed the heading of this major section to:

Developmental heterochrony, human evolution, and the autism spectrum

I am afraid that a new, separate header on evolutionary considerations does not fit with the structure of the material, as there is only one paragraph here that focuses specifically and entirely on evolution.

Pages 4 and 5 of the Introduction discuss the evolutionary aspects of the article extensively, and it is not clear what could usefully be added here. In the Abstract, I do not see how to add more material on evolutionary considerations, in the short length allowed. I do believe that the evolutionary components of the article are sufficiently prominent as presented, and as further highlighted with this
3. It may be helpful to add ‘Future Directions’. This may include most of the text of the last two Discussion paragraph and that of the Summary. The latter is not much different than the Abstract.

I agree that discussion of future directions is very important. The Summary, however, is required by the journal in this form (and it does mention the most important implication and future direction, in the last sentence). In addition, I do specifically discuss future directions, and tests, in the paragraph just prior to the ‘Summary’, which starts ‘Further tests…’. I would be happy to add any additional specific material along these lines that the reviewers or Editor might suggest.

Discretionary Revisions

Abstract: there is nothing ‘simple’ about autism

I quite agree! But the model that I propose is the simplest I have seen, for helping to explain at least a subset of cases of autism (which is highly heterogeneous in its causes).

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interest with respect to this author and article

Reviewer’s report
Title: Developmental heterochrony and the evolution of autistic perception, cognition and behavior
Version: 2 Date: 6 March 2013
Reviewer: Frietson Galis
Reviewer’s report:
The article proposes an original and relevant hypothesis for the evolution and development of autism that is worthy of publication. It needs to be strengthened in several places:

1- it needs to be discussed how this hypothesis fits with well-known aspects of autism, importantly with the highly genetical component of autism.

Interesting point! I have now added the following sentence on page 21:

Genetic variation in age-structured gene expression patterns may indeed help to explain the high heritability of autism, as age-related expression adds an
additional, temporal dimension to genetic effects on phenotypic variation.

2-it needs to be discussed to what extent the 4 sets of phenotypes are independent. This is an especially important issue since it seems that some of these sets may be quite related. However, it can be argued that these are still different ways to approach the problem, but this needs to be clarified.

Yes, this is an interesting point. The only strong evidence i am aware of that connects the phenotypes is presented on pages 10, 14 and 19 (and copied just below). I am aware of no evidence available as yet that causally links other pairs of the four phenotypes.

This developmental shift from local to global bias has, moreover, been linked, among typically-developing 6-year olds, with grey matter reductions in right occipital and parietal visuospatial brain regions, such that anatomical maturation through differentially-local pruning appears to 'fine tune' the visual cortex for processing global visual information as development proceeds [78].

I have added a new sentence, just after this one, to address this reviewer's point:

These findings provide evidence for links of local and global visual processing with short and long range brain connectivity, indicating that such sets of phenotypes subject to developmental-heterochronic effects may be causally connected or otherwise interact.

I also note on page 19 that:

The latter three domains are also expected to be causally associated, in that shorter-range connectivity may subserve more-local perception and processing (e. g., [63, 120]) as well as finer-grained sensory discrimination, although such associations have yet to be studied in a targetted way.

and on page 10 I note, with regard to restricted interests and repetitive behavior, that:

higher levels of their expression are correlated with better performance on the embedded figures test, a relative visual-spatial strength found in autism [24, 25].

3-Throughout the article-support(s) the hypothesis/model- should be replaced with the more accurate -is in agreement with.

This change has been made throughout the article.

4-page 9, restricted interests are also characteristic of autistic people with high intelligence
I agree, and have edited the relevant sentence as shown (pages 9-10):

The causes of the delays per se in developmental attenuation of such behaviors have yet to be investigated; restricted interests and repetitive behavior are found most prominently in autistic individuals with relatively-low intellectual and language capacity (although restricted interests are also common among autistic individuals with higher intellectual capacity) [22],

5-page 11 the determination of brain size is not necessarily associated with changes in the degree of local connectivity

The relevant sentence states that

The causes of relatively-reduced long-range connectivity in autism (Figure 1) remain the subject of intense study, but appear to include, among other causes, larger overall brain size, especially in early childhood [28, 36],

The sentence focuses on larger brain size leading to reduced long-range connectivity, compared to short range connectivity. This pattern is expected based on simple geometric considerations; this issue is discussed, for example, in:


The authors in references 28, 36 discuss the expectation that larger brain size is expected to involve lower long-range connectivity. Citation 52 on page 12 also addresses this point.

6-page 18 (and abstract), the current hypothesis is not necessarily in contrast to the hypothesis that development is fundamentally atypical, due to deviations from early development. It may be causally involved in the abnormal development. Probably it is even in agreement with the hypothesis that the earliest neural changes occur during early embryogenesis.

I agree with this statement, and I have made some wording changes as a result. Thus, I have changed the relevant sentence in the Abstract to read:

Autism is usually conceptualized as a disorder or disease that involves fundamentally abnormal neurodevelopment. I evaluate the hypothesis that a suite of core autism-related traits may commonly represent simple delays or non-completion of typical childhood developmental trajectories.

Please also note that on page 19 (sentence copied just below) I did point out that the hypotheses need not be exclusive. One could argue that major slowdowns in development are 'fundamentally atypical' trajectories, but I would consider such slowdowns to be less atypical than major pathologies. I think the most important
points here are that this heterochronc hypothesis has not been proposed before, there is convergent evidence consistent with it, and it has treatment implications.

In this article, I have evaluated an alternative, though not necessarily exclusive, model for the etiology of autism, which is based simply on shifts in the timing and rates of infant and child development

8- Please discuss to what extent this hypothesis is compatible or not with the extreme male bias hypothesis (or the male predominance of it).

Interesting point! I do not see any necessary connection between the extreme male brain idea and the developmental heterochrony idea, except that males tend to be relatively socially and verbally 'immature' compared to females, during childhood (and this immaturity could be mediated by fetal teststerone levels, as suggested by some of Baron-Cohen’s work). This male-biased immaturity could contribute to the male bias in autism under the developmental heterochrony model (if males are more vulnerable to heterochronic effects). Generally, I would prefer to avoid getting onto this topic much in this MS, and it is tangential, and rather speculative, and I want to focus strongly on description of the main hypothesis, and its evaluation. However, I think adding this sentence to page 20 is a nice addition to the MS:

Finally, the developmental heterochronic model may help to explain the strong male bias found in autism, given that typically-developing males tend to undergo slower verbal and social development than typically-developing females, and thus may be more vulnerable to alterations that notably delay or impede normative development.

7- page 20 The suggestion that without the proposed hypothesis the evolutionary origin of autism is otherwise inexplicable is not true, see for instance the hypothesis in: Evolutionary approaches to autism. Ploeger & Galis 2011, Mcgill J Med. 2011 Jun;13(2):38. This hypothesis is of course compatible with the current one.

Please note that I was here referring to 'the otherwise-inexplicable constellation of morphological, psychological and behavioral traits first described by Kanner and Asperger.' (full section copied below), not to the the evolutionary basis or origin of autism. Thus, this developmental heterochrony model can help to explain why a very specific and apparently unusual suite of traits (the ones discussed in this MS) is altered in particular ways in autism. This has been a difficult problem to solve and the developmental heterochrony model should be useful in addressing it.

The purpose of a developmental heterochronic conceptualization for the autism spectrum is not to equate it with other diagnostic tools or categories, such as
developmental delay, but to demonstrate the nature and ultimate, evolutionary causes of the continuity of autism spectrum phenotypes with typical childhood phenotypes, and to help explain the sources of the otherwise-inexplicable constellation of morphological, psychological and behavioral traits first described by Kanner and Asperger.

In all a very nice paper, but it needs still substantially more discussion of certain aspects, as indicated.

**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare that I have no competing interests

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**Reviewer's report**  
**Title:** Developmental heterochrony and the evolution of autistic perception, cognition and behavior  
**Version:** 2  
**Date:** 12 March 2013  
**Reviewer:** Martin Bruine  
**Reviewer’s report:**  
The paper is nicely written and comprehensive. Much of what is said is, however, hypothetical. Some of the hypotheses could be addressed experimentally, others are more difficult. With regard to the neoteny hypothesis, some features associated with autism actually seem to fit quite well. On the other hand, perfect pitch, though much more prevalent in autism than the population mean, is still found in only 5-10% of autistic children. I would expect a much higher number if this were indicative of neoteny.

**Autism is, of course, a highly heterogeneous condition as regards its causes, so the developmental heterochrony model would be expected to apply in only a subset of cases.**

**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare that I have no competing interests