

Bilateral amygdala damage linked to impaired ability to predict others' fear but preserved moral judgements about causing others fear

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Final acceptance: 21 December 2020

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2020-2651.R0 (Original submission)

Review form: Reviewer 1

Recommendation

Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?

Excellent

General interest: Is the paper of sufficient general interest?

Good

Quality of the paper: Is the overall quality of the paper suitable?

Excellent

Is the length of the paper justified?

Yes

Should the paper be seen by a specialist statistical reviewer?

No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.

No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?

N/A

Is it clear?

N/A

Is it adequate?

N/A

Do you have any ethical concerns with this paper?

No

Comments to the Author

This excellent manuscript describes a study, in which a patient with bilateral amygdala damage due to Urbach-Wiethe disease was tested both for social fear recognition and the moral permissibility of causing others fear by means of written statements.

The results demonstrate that the patients has a specific fear recognition deficit, but shows preserved moral judgements, which suggests that the two rely on dissociable processes.

My only comment is that the authors do not make reference to a relevant series of neuroimaging and lesion studies conducted by Gamer and colleagues that focus on emotion recognition by using a clever eyetracking-based task (e.g. Gamer & Büchel 2009; Boll et al. 2013; Gamer et al. 2013).

Review form: Reviewer 2

Recommendation

Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?

Good

General interest: Is the paper of sufficient general interest?

Good

Quality of the paper: Is the overall quality of the paper suitable?

Good

Is the length of the paper justified?

Yes

Should the paper be seen by a specialist statistical reviewer?

No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.

No

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Yes

Is it clear?

N/A

Is it adequate?

N/A

Do you have any ethical concerns with this paper?

No

Comments to the Author

This is a most interesting study of a single case of bilateral amygdala damage. The authors suggest that this patient has lost a conceptual understanding of fear since she fails to recognise verbal descriptions of situations that most people think should induce fear. However, at the same time, the patient still considers it wrong to make people fearful. I am less convinced by the interpretation of this aspect of the results.

Of great interest is the association of fear and anger. The patient had a bias to choose anger rather than fear. Is it possible to do an SDT type analysis to see whether her problem concerned bias rather than sensitivity?

I would like to see a more nuanced analysis of the nature of expressions of fear. The authors make the point that fearful expressions can be signals of appeasement, but this only applies when the source of the fear is another person being angry. This is the case with all the examples used in the present study. What happens if the fear-eliciting situations are encroaching fire, falling rock, &c.?

Confrontation with an angry person elicits an approach/avoidance conflict. Should I be angry too (emotional mirroring) or should I try to appease them? The patient seems to adopt the approach option in real life as well as in the task used here, responding to fear inducing situations with anger.

But, if this is the case, could her response to moral question be based on the belief that it is wrong to make people angry? In which case there is no dissociation.

Decision letter (RSPB-2020-2651.R0)

25-Nov-2020

Dear Dr Cardinale:

Your manuscript has now been peer reviewed and the reviews have been assessed by an Associate Editor. The reviewers' comments (not including confidential comments to the Editor)

and the comments from the Associate Editor are included at the end of this email for your reference. As you will see, the reviewers and the Editors have raised some concerns with your manuscript and we would like to invite you to revise your manuscript to address them.

We do not allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Associate Editor, your manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available we may invite new reviewers. Please note that we cannot guarantee eventual acceptance of your manuscript at this stage.

To submit your revision please log into <http://mc.manuscriptcentral.com/prsb> and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions", click on "Create a Revision". Your manuscript number has been appended to denote a revision.

When submitting your revision please upload a file under "Response to Referees" - in the "File Upload" section. This should document, point by point, how you have responded to the reviewers' and Editors' comments, and the adjustments you have made to the manuscript. We require a copy of the manuscript with revisions made since the previous version marked as 'tracked changes' to be included in the 'response to referees' document.

Your main manuscript should be submitted as a text file (doc, txt, rtf or tex), not a PDF. Your figures should be submitted as separate files and not included within the main manuscript file.

When revising your manuscript you should also ensure that it adheres to our editorial policies (<https://royalsociety.org/journals/ethics-policies/>). You should pay particular attention to the following:

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In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should also be fully cited and listed in the references.

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If you have already submitted your data to dryad you can make any necessary revisions to your dataset by following the above link.

For more information please see our open data policy <http://royalsocietypublishing.org/data-sharing>.

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All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI. Please try to submit all supplementary material as a single file.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

Please submit a copy of your revised paper within three weeks. If we do not hear from you within this time your manuscript will be rejected. If you are unable to meet this deadline please let us know as soon as possible, as we may be able to grant a short extension.

Thank you for submitting your manuscript to Proceedings B; we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Best wishes,
Dr Robert Barton
<mailto:proceedingsb@royalsociety.org>

Associate Editor
Board Member: 1
Comments to Author:

We have now heard from two reviewers, both of whom found your manuscript interesting. One reviewer has raised some concerns about your interpretation of the individual's behaviour with respect to anger and other situations where fear might be expected to be invoked. I think you need to deal with the concerns of this reviewer in a revised and resubmitted manuscript.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)

This excellent manuscript describes a study, in which a patient with bilateral amygdala damage due to Urbach-Wiethe disease was tested both for social fear recognition and the moral permissibility of causing others fear by means of written statements.

The results demonstrate that the patients has a specific fear recognition deficit, but shows preserved moral judgements, which suggests that the two rely on dissociable processes.

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Referee: 2

Comments to the Author(s)

This is a most interesting study of a single case of bilateral amygdala damage. The authors suggest that this patient has lost a conceptual understanding of fear since she fails to recognise verbal descriptions of situations that most people think should induce fear. However, at the same time, the patient still considers it wrong to make people fearful. I am less convinced by the interpretation of this aspect of the results.

Of great interest is the association of fear and anger. The patient had a bias to choose anger rather than fear. Is it possible to do an SDT type analysis to see whether her problem concerned bias rather than sensitivity?

I would like to see a more nuanced analysis of the nature of expressions of fear. The authors make the point that fearful expressions can be signals of appeasement, but this only applies when the source of the fear is another person being angry. This is the case with all the examples used in the present study. What happens if the fear-eliciting situations are encroaching fire, falling rock, &c.?

Confrontation with an angry person elicits an approach/avoidance conflict. Should I be angry too (emotional mirroring) or should I try to appease them? The patient seems to adopt the approach option in real life as well as in the task used here, responding to fear inducing situations with anger.

But, if this is the case, could her response to moral question be based on the belief that it is wrong to make people angry? In which case there is no dissociation.

Author's Response to Decision Letter for (RSPB-2020-2651.R0)

See Appendix A.

Decision letter (RSPB-2020-2651.R1)

21-Dec-2020

Dear Dr Cardinale

I am pleased to inform you that your manuscript entitled "Bilateral amygdala damage linked to impaired ability to predict others' fear but preserved moral judgments about causing others fear" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

If you have any queries regarding the production of your final article or the publication date please contact procb_proofs@royalsociety.org

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All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Thank you for your fine contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Sincerely,

Dr Robert Barton
Editor, Proceedings B
mailto:proceedingsb@royalsociety.org

Associate Editor:

Board Member

Comments to Author:

Thank you for submitting your revised manuscript. I have read over your response to the reviewers carefully, and I am pleased to recommend acceptance. Congratulations on a fine paper.

Appendix A

Referee 1:

This excellent manuscript describes a study, in which a patient with bilateral amygdala damage due to Urbach-Wiethe disease was tested both for social fear recognition and the moral permissibility of causing others fear by means of written statements.

The results demonstrate that the patients has a specific fear recognition deficit, but shows preserved moral judgements, which suggests that the two rely on dissociable processes.

We thank the reviewer for their kind words regarding our work.

1. *My only comment is that the authors do not make reference to a relevant series of neuroimaging and lesion studies conducted by Gamer and colleagues that focus on emotion recognition by using a clever eyetracking-based task (e.g. Gamer & Büchel 2009; Boll et al. 2013; Gamer et al. 2013).*

We apologize for the oversight in not including reference to these papers by Gamer and colleagues and thank the reviewer for the suggestion. We now include these citations in the introduction:

On (p. 3):

“The amygdala is a subcortical structure implicated in a wide array of social and affective processes but essential for relatively few.^{1–5}”

And on (p. 4):

“An alternate theory holds that the amygdala supports social fear recognition by directing spontaneous attention to salient, diagnostic perceptual features of faces, like the eyes of fearful expressions, thus facilitating their recognition.^{28–31}”

Referee 2:

This is a most interesting study of a single case of bilateral amygdala damage. The authors suggest that this patient has lost a conceptual understanding of fear since she fails to recognise verbal descriptions of situations that most people think should induce fear. However, at the same time, the patient still considers it wrong to make people fearful. I am less convinced by the interpretation of this aspect of the results.

We thank the reviewer for their positive assessment of the manuscript and believe the revisions outlined below improve the clarity and interpretation of the results.

1. *Of great interest is the association of fear and anger. The patient had a bias to choose anger rather than fear. Is it possible to do an SDT type analysis to see whether her problem concerned bias rather than sensitivity?*

We appreciate this important comment and have now assessed SM's patterns of errors and potential anger bias as well as potential interpretations of any potential bias. First, we analyzed whether SM does in fact exhibit a greater bias towards making anger false-hits for fear-eliciting statements relative to healthy comparisons (p. 9). As we now describe:

“Given the apparent bias towards anger responses, we conducted a chi-squared test to examine whether distributions of error responses for fearful expressions differed between SM and healthy comparisons. No significant difference emerged, $\chi^2(3)=3.94$, $p=0.27$, confirming that while SM demonstrated a proportional increase in anger error-responses (90.48% of error responses to fear-eliciting statements) it was not significantly different than that observed in healthy comparisons (70.92% of error responses).”

We used this approach rather than a standard signal detection theory (SDT) approach because our paradigm includes 5 response options. SDT approaches would either require us to categorize all non-fear responses as false-hits or ignore all non-anger responses and treat only anger responses as false-hits. As these two approaches would respectively result in an inability to assess bias and discriminability between anger and fear specifically or would result in inaccurate representation of the decision sampling distribution, we chose not to employ an SDT approach.

2. *I would like to see a more nuanced analysis of the nature of expressions of fear. The authors make the point that fearful expressions can be signals of appeasement, but this only applies when the source of the fear is another person being angry. This is the case with all the examples used in the present study. What happens if the fear-eliciting situations are encroaching fire, falling rock, &c.?*

We appreciate these points. We agree that not all fear-eliciting situations are social or have the function of appeasement (for example, work by Andersen and colleagues suggests fearful expressions also serve to widen the field of view), and now have modified our Discussion to state on p. 12:

“fearful expressions are primarily interpreted by observers as appeasing and appetitive (fearful expressions may also serve other functions that are relevant in non-social situations, such as widening the field of view).”

This clarifies that fearful expressions primarily serve an appeasing function in social situations where there is an observer to interpret them, whereas other features of the expression may be more relevant in non-social settings.

3. *Confrontation with an angry person elicits an approach/avoidance conflict. Should I be angry too (emotional mirroring) or should I try to appease them? The*

patient seems to adopt the approach option in real life as well as in the task used here, responding to fear inducing situations with anger.

This is a very interesting point. A subset of fear-eliciting statements in our set can be used to address the question of whether SM's selection of 'anger' in response to fear-eliciting statements reflects her mirroring an angry speaker. This subset of statements are fear-eliciting but not direct interpersonal threats and thus presumably do not reflect anger. If SM were mirroring the state of the speaker, she presumably would NOT choose anger for these statements, which are warnings about external threats (e.g., "I think you are being followed"). However, as we now describe, SM also primarily picked anger in response to these statements, (ps. 8-9):

"Considering responses to only the 20 fear-eliciting statements, SM preferentially rated these statements as anger-eliciting (Figure 2), an option she chose in 47.50% of these trials. These trials include fear-eliciting statements that did not involve direct interpersonal threat but rather helpful warnings of potential threat in one's environment (e.g. "I think something moved behind you", "I think you are being followed", and "I don't think you are safe here") for which SM also predominantly picked anger (5 out of 6 responses across the two testing sessions) as the elicited emotional response."

In the Discussion, we describe these results in detail (p. 14):

"It also does not appear to reflect her potentially simulating the state of the speaker. We specifically considered SM's responses to the small subset of fear-eliciting statements that do not involve direct threats but rather warnings of external threats (e.g., "I don't think you are safe here"). Here, SM also predominantly selected anger for 5 out of 6 responses."

In addition to the examination of the data described above, we have also included additional discussion of existing literature examining SM's generally calm or interested response to threatening situations (p. 13),

"A less likely possibility is that her selecting anger reflects SM simulating how she would feel in response to the statements; when her life was actually threatened in the past by a knife-wielding stranger who made a statement similar to those used in this study ("I'm going to cut you, bitch!") she reported she, "remained calm, did not panic, and did not feel afraid," and told the man, "If you're going to kill me, you're gonna have to go through my God's angels first" (for the full description see supplemental materials of Feinstein et al, 2011)."

This suggest she is also not selecting "anger" because this is how she typically responds to real-life threats, as we further describe on p. 14:

“This provides some support that SM’s impaired fear-recognition in the current task more likely results from difficulty simulating the fearful state that would result from such a statement. This is also consistent with data from experience sampling studies of SM’s real-time emotional experiences in everyday life, which revealed that she endorsed feeling “fearless” most across the three month period, but no tendency towards increased anger, suggesting a deficit of fear rather than excess of anger.”

However, we also describe on p. 13 that SM may select “anger” because it an approach-based response:

“Both SM and comparisons misjudged fear-eliciting statements as anger a large majority of the time. Proportionally, but not significantly, more of SM’s errors in response to fear were ‘anger’ responses. This outcome has several potential interpretations. One relates to the fact that SM’s reactions to real-life fear eliciting stimuli are dominated by approach-based responses. For example, SM responds to various real-life non-human threats--such as snakes, spiders and humans in monster costumes--with interest and curiosity.⁶ Thus, SM may have selected anger because it is an approach-based (if negative) emotion.”

We also now include a discussion that future work with free or alternate response options might further elucidate SM’s response tendencies (p. 14):

“Although our task did not provide “calm,” or “interested” answer option in order to simulate the format of facial emotion recognition paradigms, future work allowing these response options or a free choice option would allow for direct examination of whether she would select these choices over “anger.””

4. *But, if this is the case, could her response to moral question be based on the belief that it is wrong to make people angry? In which case there is no dissociation.*

This is also a very interesting possibility. Presumably, if this were the case SM would judge the morality of statements she judged as anger-eliciting more harshly than those she judged as fear-eliciting (or sadness or disgust-eliciting). We thus re-examined participants’ judgments of moral permissibility based on their own identification of the likely emotional response (p. 10). We found that the pattern of findings was unchanged regardless of whether we used the emotion labels as determined by the task or SM’s own emotion labels:

“Pairwise comparisons across SM’s item-level responses indicated that judgments of moral permissibility of anger-, fear-, and disgust-eliciting

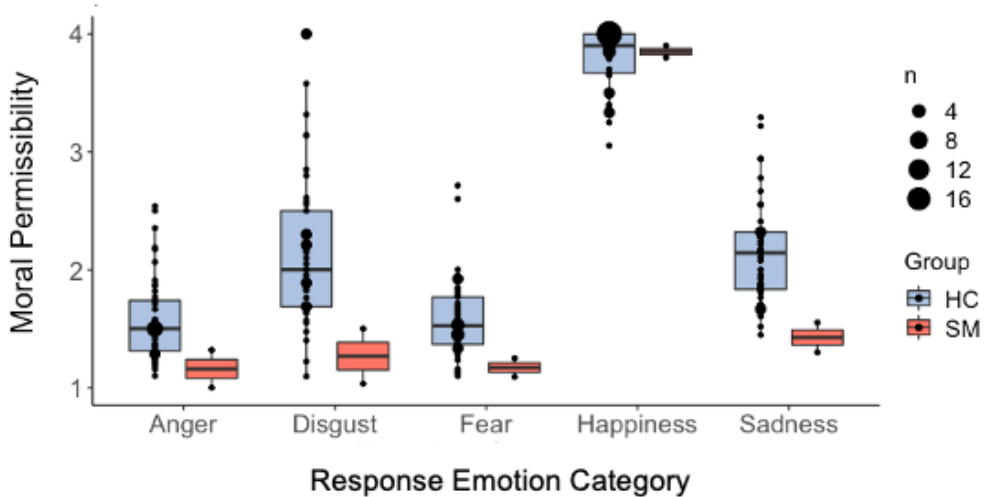
statements did not differ from one another (all $ps > .10$). Her judgments of sadness-eliciting statements did not differ from disgust-eliciting statements, $t(38) = -1.57$, $p = .13$, but they were judged as more morally permissible than anger-, $t(38) = -2.62$, $p = .01$, and fear-eliciting statements, $t(38) = -2.39$, $p = .02$. Neither of these pairwise comparisons remain significant after correcting for multiple comparisons ($p < .005$). Finally, SM rated happiness-eliciting statements as more morally permissible than all other emotions (all $ps < .001$). This pattern of findings emerged when examining judgments of moral permissibility regardless of whether the emotional labels were predetermined by the emotionally evocative statements task or were the labels she herself chose when responding to the emotion recognition portion of the task (Supplementary Table 1; Supplementary Figure 2).”

Supplementary Table 1. Average rating of moral permissibility broken down by the emotionally evocative statements task predetermined emotion label or participants’ chosen emotion labels.

	Anger	Disgust	Fear	Happiness	Sadness
SM					
Predetermined Emotion Label	1.15 (0.14) ^a	1.25 (0.35) ^a	1.15 (0.14) ^a	3.85 (0.07) ^b	1.45 (0.14) ^a
Chosen Emotion Label	1.14 (0.25) ^a	1.22 (0.33) ^a	1.16 (0.11) ^a	3.85 (0.07) ^b	1.49 (0.14) ^a
HC					
Predetermined Emotion Label	1.48 (0.30) ^a	2.17 (0.68) ^b	1.54 (0.30) ^a	3.81 (0.26) ^c	2.36 (0.30) ^b
Chosen Emotion Label	1.57 (0.36) ^a	2.17 (0.67) ^b	1.55 (0.33) ^a	3.79 (0.26) ^c	2.10 (0.30) ^b

Note. Values are Mean (SD), Different superscript letters indicate significant pairwise comparisons Bonferroni corrected for multiple comparisons. HC = Healthy Comparison

Supplementary Figure 2. Comparison of SM and matched healthy comparisons (HC) on ratings of moral permissibility based on chosen emotion category by participants in response to the emotion recognition portion of the task.



We also added the following to the discussion (ps. 15-16):

“This pattern of findings persisted regardless of whether the emotional labels in question were predetermined or the labels she herself chose. Thus, it does not appear that SM views causing any one particular emotion (including anger or fear) as particularly unacceptable. Instead, this suggests that acquired amygdala damage may lead to more heuristic or less nuanced evaluations of various moral violations such that causing unpleasant states of any kind is immoral.”