Topological analysis of differential effects of ketamine and propofol anaesthesia on brain dynamics

Thomas F. Varley, Vanessa Denny, Olaf Sporns and Alice Patania

Review History

RSOS-201971.R0 (Original submission)

Review form: Reviewer 1 (Nao Tsuchiya)

Is the manuscript scientifically sound in its present form?
Yes

Are the interpretations and conclusions justified by the results?
Yes

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

Recommendation?
Accept with minor revision (please list in comments)

Comments to the Author(s)
This paper presents two analyses on the previously collected open data (NeuroTycho). Their first analysis uses EPC with TDA and the second uses OPNs. I have some comments to improve the paper, but I think this paper can be accepted with minor revision.

Signed review by Naotsugu Tsuchiya.

Major issues.

1. Consideration of "nonconscious neural activity" vs. high dimensional space of neural activity

While you mention the issue of conscious vs. nonconscious neural activity in some places, I would suggest that you discuss this issue in Discussion as this is a serious issue in consciousness research.

The paper reviews an adequate amount of the literature on the "level" of consciousness, however, it doesn't cover "contents" of consciousness. This is fine in itself. However, the latter literature has generated a huge amount of empirical evidence to suggest that not all neural activities are relevant for consciousness (See for example, Koch 2016 Nat Rev Neuro, Mashour et al 2020 Neuron). Given this, including all the available channels (>120) for the analysis can possibly reflect neural activities that are irrelevant for supporting consciousness but more directly related to nonconscious processing. This needs to be acknowledged and you may want to discuss how to resolve this issue in the future.

One possible approach is the identification of "complex" as suggested by the integrated information theory (IIT) by Tononi.

2. Structural measures/characterizations of consciousness

Page 3. L15 -
"these point-summary measures, while informative, collapse multi-scale dynamics into a single number and thus have difficulty capturing its specific shape or form."

I totally agree with this statement. And I would say that this is pretty much in line with the philosophy of the integrated information theory (IIT). This aspect has become more explicit since IIT3.0. Recently, we have published a paper directly addressing this structural and topological consideration on the level of consciousness based on the empirical neural data (Leung et al 2021 PLoS Comp), which you might want to look at.

Also, as you refer to epsilon machines several times in the manuscript as an alternative way to characterize the topology/shape of information structure, it may be worth looking at our recent paper where we applied the epsilon machine on the loss of consciousness (Munos et al 2020 Physical Review Research).

3. Limits of OPN

With respect to the limit of OPN, I think it is better to mention other approaches that have also taken multivariate approaches. IIT can be considered as one of them, where it explicitly deals with the integration among channels, which your OPN approach explicitly ignores. To the extent

that integration is critical to understand consciousness, this may be a potential oversight / limitation of your approach.

Along with this line, I also think you should acknowledge a couple of papers that have already analyzed the same NeuroTycho data with different ways (e.g., Tajima et al 2015 PLoS Comp).

4. Lack of principles and theories.

Your approach is data-driven and highly descriptive. It may make more sense to explicitly admit this in Discussion and discuss its limitations. Alternatively, you may want to try to link your findings with predictions from some theories. I would imagine some of the findings can be linked with the other theories of consciousness other than the Entropy hypothesis or IIT, but I will leave this to you.

Minor issues

Page 2, line 30-
Lots of double negatives make this paragraph difficult to read for those who are not familiar with these concepts.
Line 34: "light central nervous system stimulation". Probably, you meant that weak stimulation of the nervous system? Better if you can revise here.
Line 41: result it -> result in?

P3 L5: Ref 51&53 didn't really measure entropy. The sentence needs to be revised.
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There are several typos throughout. (e.g., "spacial" "repetoire" "asses")

Decision letter (RSOS-201971.R0)

We hope you are keeping well at this difficult and unusual time. We continue to value your support of the journal in these challenging circumstances. If Royal Society Open Science can assist you at all, please don't hesitate to let us know at the email address below.

Dear Mr Varley

On behalf of the Editors, we are pleased to inform you that your Manuscript RSOS-201971 "Topological Analysis of Differential Effects of Ketamine and Propofol Anesthesia on Brain Dynamics" has been accepted for publication in Royal Society Open Science subject to minor revision in accordance with the referees' reports. Please find the referees' comments along with any feedback from the Editors below my signature.

We invite you to respond to the comments and revise your manuscript. Below the referees' and Editors' comments (where applicable) we provide additional requirements. Final acceptance of your manuscript is dependent on these requirements being met. We provide guidance below to help you prepare your revision.

Please submit your revised manuscript and required files (see below) no later than 7 days from today's (ie 19-Apr-2021) date. Note: the ScholarOne system will 'lock' if submission of the revision is attempted 7 or more days after the deadline. If you do not think you will be able to meet this deadline please contact the editorial office immediately.

Please note article processing charges apply to papers accepted for publication in Royal Society Open Science (https://royalsocietypublishing.org/rsos/charges). Charges will also apply to papers transferred to the journal from other Royal Society Publishing journals, as well as papers submitted as part of our collaboration with the Royal Society of Chemistry (https://royalsocietypublishing.org/rsos/chemistry). Fee waivers are available but must be requested when you submit your revision (https://royalsocietypublishing.org/rsos/waivers).

Thank you for submitting your manuscript to Royal Society Open Science and we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Kind regards,
Royal Society Open Science Editorial Office
Royal Society Open Science
openscience@royalsociety.org

on behalf of Dr Mark Walton (Associate Editor) and Essi Viding (Subject Editor)
openscience@royalsociety.org

Associate Editor Comments to Author (Dr Mark Walton):

I'm sorry that it has taken so long to get the review back to you. It proved unprecedentedly difficult to secure reviewers for this article, in spite of the best efforts of all. Given the nature of the comments, I will be happy to make a final decision on a revised version without sending it out to review again.

Reviewer comments to Author:

Reviewer: 1
Comments to the Author(s)

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===PREPARING YOUR MANUSCRIPT===

Your revised paper should include the changes requested by the referees and Editors of your manuscript. You should provide two versions of this manuscript and both versions must be provided in an editable format:
one version identifying all the changes that have been made (for instance, in coloured highlight, in bold text, or tracked changes);
a 'clean' version of the new manuscript that incorporates the changes made, but does not highlight them. This version will be used for typesetting.
Please ensure that any equations included in the paper are editable text and not embedded images.

Please ensure that you include an acknowledgements' section before your reference list/bibliography. This should acknowledge anyone who assisted with your work, but does not qualify as an author per the guidelines at https://royalsociety.org/journals/ethics-policies/openness/.

While not essential, it will speed up the preparation of your manuscript proof if you format your references/bibliography in Vancouver style (please see https://royalsociety.org/journals/authors/author-guidelines/#formatting). You should include DOIs for as many of the references as possible.

If you have been asked to revise the written English in your submission as a condition of publication, you must do so, and you are expected to provide evidence that you have received language editing support. The journal would prefer that you use a professional language editing service and provide a certificate of editing, but a signed letter from a colleague who is a native speaker of English is acceptable. Note the journal has arranged a number of discounts for authors using professional language editing services (https://royalsociety.org/journals/authors/benefits/language-editing/).

===PREPARING YOUR REVISION IN SCHOLARONE===

To revise your manuscript, log into https://mc.manuscriptcentral.com/rsos and enter your Author Centre - this may be accessed by clicking on "Author" in the dark toolbar at the top of the page (just below the journal name). You will find your manuscript listed under "Manuscripts with Decisions". Under "Actions", click on "Create a Revision".

Attach your point-by-point response to referees and Editors at Step 1 'View and respond to decision letter'. This document should be uploaded in an editable file type (.doc or .docx are preferred). This is essential.

Please ensure that you include a summary of your paper at Step 2 'Type, Title, & Abstract'. This should be no more than 100 words to explain to a non-scientific audience the key findings of your research. This will be included in a weekly highlights email circulated by the Royal Society press office to national UK, international, and scientific news outlets to promote your work.

At Step 3 'File upload' you should include the following files:
-- Your revised manuscript in editable file format (.doc, .docx, or .tex preferred). You should upload two versions:
1) One version identifying all the changes that have been made (for instance, in coloured highlight, in bold text, or tracked changes);
2) A 'clean' version of the new manuscript that incorporates the changes made, but does not highlight them.
-- An individual file of each figure (EPS or print-quality PDF preferred [either format should be produced directly from original creation package], or original software format).
-- An editable file of each table (.doc, .docx, .xls, .xlsx, or .csv).
-- An editable file of all figure and table captions.
Note: you may upload the figure, table, and caption files in a single Zip folder.
-- Any electronic supplementary material (ESM).
-- If you are requesting a discretionary waiver for the article processing charge, the waiver form must be included at this step.
-- If you are providing image files for potential cover images, please upload these at this step, and inform the editorial office you have done so. You must hold the copyright to any image provided.
-- A copy of your point-by-point response to referees and Editors. This will expedite the preparation of your proof.

At Step 6 'Details & comments', you should review and respond to the queries on the electronic submission form. In particular, we would ask that you do the following:
-- Ensure that your data access statement meets the requirements at https://royalsociety.org/journals/authors/author-guidelines/#data. You should ensure that you cite the dataset in your reference list. If you have deposited data etc in the Dryad repository, please only include the 'For publication' link at this stage. You should remove the 'For review' link.

-- If you are requesting an article processing charge waiver, you must select the relevant waiver option (if requesting a discretionary waiver, the form should have been uploaded at Step 3 'File upload' above).

-- If you have uploaded ESM files, please ensure you follow the guidance at https://royalsociety.org/journals/authors/author-guidelines/#supplementary-material to include a suitable title and informative caption. An example of appropriate titling and captioning may be found at https://figshare.com/articles/Table_S2_from_Is_there_a_trade-off_between_peak_performance_and_performance_breadth_across_temperatures_for_aerobic_scope_in_teleost_fishes_/3843624.

At Step 7 'Review & submit', you must view the PDF proof of the manuscript before you will be able to submit the revision. Note: if any parts of the electronic submission form have not been completed, these will be noted by red message boxes.

Author's Response to Decision Letter for (RSOS-201971.R0)

See Appendix A.

Decision letter (RSOS-201971.R1)

We hope you are keeping well at this difficult and unusual time. We continue to value your support of the journal in these challenging circumstances. If Royal Society Open Science can assist you at all, please don't hesitate to let us know at the email address below.

Dear Mr Varley,

It is a pleasure to accept your manuscript entitled "Topological Analysis of Differential Effects of Ketamine and Propofol Anesthesia on Brain Dynamics" in its current form for publication in Royal Society Open Science.

Please ensure that you send to the editorial office an editable version of your accepted manuscript, and individual files for each figure and table included in your manuscript. You can send these in a zip folder if more convenient. Failure to provide these files may delay the processing of your proof. You may disregard this request if you have already provided these files to the editorial office.

You can expect to receive a proof of your article in the near future. Please contact the editorial office (openscience@royalsociety.org) and the production office (openscience_proofs@royalsociety.org) to let us know if you are likely to be away from e-mail contact -- if you are going to be away, please nominate a co-author (if available) to manage the proofing process, and ensure they are copied into your email to the journal.

Due to rapid publication and an extremely tight schedule, if comments are not received, your paper may experience a delay in publication.

Please see the Royal Society Publishing guidance on how you may share your accepted author manuscript at https://royalsociety.org/journals/ethics-policies/media-embargo/. After publication, some additional ways to effectively promote your article can also be found here

https://royalsociety.org/blog/2020/07/promoting-your-latest-paper-and-tracking-your-results/.

Thank you for your fine contribution. On behalf of the Editors of Royal Society Open Science, we look forward to your continued contributions to the Journal.

Kind regards,
Royal Society Open Science Editorial Office
Royal Society Open Science
openscience@royalsociety.org

on behalf of Dr Mark Walton (Associate Editor) and Essi Viding (Subject Editor)
openscience@royalsociety.org

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Appendix A

1   **Response to Reviewers**

2   Reviewer: 1

3   Comments to the Author(s)

4   This paper presents two analyses on the previously collected open data (NeuroTycho). Their
5   first analysis uses EPC with TDA and the second uses OPNs. I have some comments to improve
6   the paper, but I think this paper can be accepted with minor revision.

7   Signed review by Naotsugu Tsuchiya.

8   We would like do that Dr. Tsuchiya for his thoughtful and insightful comments on this paper.
9   We have responded to them below and hope that they are satisfactory. Our responses are noted in
10 blue font. Where we are quoting from the main manuscript, we use *italicized font*.

11   - Thomas Varley (on behalf of all authors)

Major issues.

13   1. Consideration of "nonconscious neural activity" vs. high dimensional space of neural activity
14   While you mention the issue of conscious vs. nonconscious neural activity in some places, I would
15   suggest that you discuss this issue in Discussion as this is a serious issue in consciousness research.

16   The paper reviews an adequate amount of the literature on the "level" of consciousness, however,
17   it doesn't cover "contents" of consciousness. This is fine in itself. However, the latter literature has
18   generated a huge amount of empirical evidence to suggest that not all neural activities are relevant
19   for consciousness (See for example, Koch 2016 Nat Rev Neuro, Mashour et al 2020 Neuron). Given
20   this, including all the available channels (¿120) for the analysis can possibly reflect neural activities
21   that are irrelevant for supporting consciousness but more directly related to nonconscious processing.
22   This needs to be acknowledged and you may want to discuss how to resolve this issue in the future.

23   One possible approach is the identification of "complex" as suggested by the integrated informa-
24   tion theory (IIT) by Tononi.

25   The distinction between conscious and non-conscious complex activity is a good one - we agree
26   that it is worth discussing. We were, however, limited in our ability to make any inferences about
27   the content of consciousness at all since 1. anaesthesia is typically light on content and 2. the animal
28   models cannot report their experience. We have added the following to the Introduction to make
29   the distinction between level and content of consciousness clear:

30   *We should note that in this project we have focused primarily on the issue of level of consciousness*
31   *rather than the content of consciousness. This is a subtle distinction that has been discussed in*
32   *detail (for review, see Koch, 2016) but briefly, the level of consciousness quantifies the "amount"*
33   *of consciousness, such as the vividness or intensity of subjective experience, while the content of*
34   *consciousness refers to the specific perceptions that are being consciously perceived. The question*
35   *of the content of consciousness is well explored by psychophysical studies (Wackerman, 2010) and*
36   *more recently discussed theoretically in the context of Integrated Information Theory (Tononi, 2008,*
37   *Oizumi et al., 2014) however it is beyond the focus of the results presented here, for several reasons.*
38   *Primarily, anaesthetic states are typically light on complex contents, and macaques are unable to*

1

report their subjective experience, we have no access to the contents of their consciousness, only their
status as awake or anesthetized based on externally observable variables, and the drug in question.

2. Structural measures/characterizations of consciousness

Page 3. L15 - "these point-summary measures, while informative, collapse multi-scale dynamics into a single number and thus have difficulty capturing its specific shape or form."

I totally agree with this statement. And I would say that this is pretty much in line with the philosophy of the integrated information theory (IIT). This aspect has become more explicit since IIT3.0. Recently, we have published a paper directly addressing this structural and topological consideration on the level of consciousness based on the empirical neural data (Leung et al 2021 PLoS Comp), which you might want to look at.

We have added a reference to the work by Leung et al., which is a fascinating piece of research. *This notion was recently given empirical support by the finding that, when attempting to discriminate between conscious and anesthetized states, high-dimensional information structures did a significantly better job than standard scalar measures (Leung et al., 2021). This strongly suggests that* when attempting to characterize a system as complex as a conscious (or even unconscious) brain, which can vary along many different axes, a more comprehensive picture is necessary

Also, as you refer to epsilon machines several times in the manuscript as an alternative way to characterize the topology/shape of information structure, it may be worth looking at our recent paper where we applied the epsilon machine on the loss of consciousness (Munos et al 2020 Physical Review Research).

I added the Munoz citation and discussed it briefly in the context of ϵ-machines. *Previous work using ϵ-machines to explore the effects of anaesthesia on neural dynamics in insects found that temporal complexity, and information asymmetry are strongly altered by loss of consciousness (Munoz et al., 2020), which suggests that these kinds of statistical state-transition analyses can be informative.*

3. Limits of OPN

With respect to the limit of OPN, I think it is better to mention other approaches that have also taken multivariate approaches. IIT can be considered as one of them, where it explicitly deals with the integration among channels, which your OPN approach explicitly ignores. To the extent that integration is critical to understand consciousness, this may be a potential oversight / limitation of your approach.

We have expanded the discussion to include references to several different frameworks that explicitly explore integration between many elements, including the recent work in integrated information decomposition, historical work on functional connectivity network approaches, IIT, and work on criticality and consciousness. We stress that the methods developed here may be useful additions to existing frameworks, rather than replacements.

The OPN and EPC framework may be complemented by other research frameworks that explicitly aim to understand "integration" in the form of statistical dependencies between many interacting elements of the brain, for example the recent work on consciousness an integrated information decomposition (ΦID) (Luppi et al., 2020a, Luppi et al., 2020b), consciousness and critical brain dynamic (Fekete et al., 2018, Varley et al., 2020) functional connectivity network analysis (Lewis et al.,

2012, Demertzi et al., 2019, Cavanna et al., 20128), and integrated information theory (Tononi,
2008, Toker et al., 2019). Given that previous research suggests that this kind of "integration" is
key for the maintenance of consciousness a key future refinement of the topological data analysis
framework would be incorporating measures of integration and higher-order statistical dependencies.

Along with this line, I also think you should acknowledge a couple of papers that have already
analyzed the same NeuroTycho data with different ways (e.g., Tajima et al 2015 PLoS Comp).

We have added the following to the discussion:

Within the time-delay and state-space reconstruction framework, work on cross-embeddings using
the same NeuroTycho data has found that multivariate state-space reconstruction can yield insights
into how anaesthesia changes the interactions between brain regions (Tajima et al., 2015). This
approach could be unified with approaches for constructing cross- and joint-OPNs (Guo et al., 2018)
to enable the applications of our methods to multivariate datasets.

4. Lack of principles and theories.

Your approach is data-driven and highly descriptive. It may make more sense to explicitly admit
this in Discussion and discuss its limitations. Alternatively, you may want to try to link your findings
with predictions from some theories. I would imagine some of the findings can be linked with the
other theories of consciousness other than the Entropy hypothesis or IIT, but I will leave this to
you.

Done - we make it explicit that we are doing a data-driven analysis and deliberate choose not to
adjudicate between various theories of consciousness.

he work presented here is explicitly data driven, rather than theory-driven. There are a large
number of competing theories of consciousness, such as IIT (Tononi, 2008), the information closure
theory of consciousness (Chang et al., 2020), and the global workspace theory (Mashour, 2020), to
name a few, and rather than attempting to adjudicate between them, we instead developed these an-
alytical pipelines to empower future researchers interested in empirically testing the various theories
of consciousness.

Minor issues

Page 2, line 30- Lots of double negatives make this paragraph difficult to read for those who are
not familiar with these concepts.

I can't seem to find what he's referring to. Perhaps I am too familiar with these concepts

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Fixed

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I'm not sure what this is referring to here - we don't cite 51 and 53 on page 3?

P4 L34: Description of Chibi doesn't make sense. Probably typo for George?

I am not entirely clear what this refers to.

P8: Figure 2 mentions "temporal principal component" but this is not explained anywhere else in the manuscript. (By the way, I was not able to access to the Supplementary Material for this paper)

This was a typo left in from an earlier iteration of the project - there were no temporal PCs involved in this analysis.

P8: No significant differences on the lag parameter is mentioned but the data is not shown. Please show it on Supplementary Material.

These data have been added to the S.I. in the form of a figure

P8: "a directed network X with N" -¿ "a directed network X with N nodes/states"? P9: the equations for determinism and degeneracy are identical. I think the one for degeneracy should use W_in?

They equations are not the same, although they look very similar. The determinism has the term $\langle H(W^{out}\rangle$ in it (the average entropy of all the rows of the TPM, while the degeneracy has the term $H(\langle W^{out}\rangle)$ which is the entropy of the average row.

P10: The right side of Table 1 is not visible (if something is there?)

The right side is a tad cut off due to the LaTeX formatting, but there are no missing columns. This will presumably be fixed when the paper is formatted for the journal.

P13: Determinism (Fig 5C) is lowest for awake, which is inconsistent with Table 3. I guess the figure is correct?

Yes, I goofed up the LaTeX table. Thank you for catching that - the table has been corrected.

There are several typos throughout. (e.g., "spacial" "repetoire" "asses") Thank you for the detailed proofreading