

Journal of Visualized Experiments

Meta-analysis of voxel-based neuroimaging studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) --Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE59841R1
Full Title:	Meta-analysis of voxel-based neuroimaging studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI)
Keywords:	familywise error rate, functional magnetic resonance imaging (fMRI), meta-analysis, neuroimaging, permutation of subject images (PSI), seed-based d mapping (SDM), threshold-free cluster enhancement (TFCE), voxel-based morphometry (VBM)
Corresponding Author:	Q Dr. Radua
Corresponding Author's Institution:	
Corresponding Author E-Mail:	quimradua@gmail.com
Order of Authors:	Anton Albajes-Eizagire Aleix Solanes Miquel Angel Fullana John P. A. Ioannidis Paolo Fusar-Poli Carla Torrent Brisa Solé Caterina Mar Bonnín Eduard Vieta David Mataix-Cols Joaquim Radua
Additional Information:	
Question	Response
Please indicate whether this article will be Standard Access or Open Access.	Open Access (US\$4,200)
Please indicate the city, state/province, and country where this article will be filmed . Please do not use abbreviations.	Barcelona, Barcelona, Spain



Doctor Phillip Steindel
Journal of Visualized Experiments
(JoVE)

Barcelona, 15 May 2019

Dear Dr Steindel,

Re Manuscript " Meta-analysis of voxel-based neuroimaging studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI)"

Thank you for inviting us to resubmit the manuscript. We have carefully addressed the editorial and reviewer comments and the manuscript has improved. Three additional researchers collaborated in the revision and I have thus included them as co-authors.

On another note, we were wondering if it is not too late to pay the fees to have the manuscript and video open access.

We look forward to hearing whether you can publish the manuscript.

With the best regards,

Anton Albajes-Eizagirre and Joaquim Radua
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Barcelona
Spain

TITLE:

Meta-analysis of Voxel-Based Neuroimaging Studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI)

AUTHORS & AFFILIATIONS:

Anton Albajes-Eizagire^{1,2}, Aleix Solanes^{1,2}, Miquel Angel Fullana^{2,3}, John P. A. Ioannidis⁴, Paolo Fusar-Poli^{5,6,7}, Carla Torrent^{1,2,3,8}, Brisa Solé^{1,2,3,8}, Caterina Mar Bonnín^{1,2,3,8}, Eduard Vieta^{1,2,3,8}, David Mataix-Cols⁹, Joaquim Radua^{1,2,5,9}

¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

²Mental Health Research Networking Center (CIBERSAM), Madrid, Spain

³Hospital Clinic de Barcelona, Clinical Institute of Neuroscience, Barcelona, Spain

⁴Departments of Medicine, of Health Research and Policy, and of Biomedical Data Science, Stanford University School of Medicine, and Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, California, USA

⁵Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

⁶OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK

⁷Department of Nervous System and Behavioral Sciences, University of Pavia, Italy

⁸University of Barcelona, Barcelona, Spain

⁹Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Corresponding author:

Anton Albajes-Eizagire (antonae@gmail.com)

Email addresses of Co-Authors:

Aleix Solanes (al.solanes@gmail.com)

Miquel Angel Fullana (miguelangelfullana@gmail.com)

John P. A. Ioannidis (jioannid@stanford.edu)

Paolo Fusar-Poli (paolo.fusar-poli@kcl.ac.uk)

Carla Torrent (ctorrent@clinic.cat)

Brisa Solé (bsole@clinic.cat)

Caterina Mar Bonnín (cbonnin@clinic.cat)

Eduard Vieta (evieta@clinic.cat)

David Mataix-Cols (david.mataix.cols@ki.se)

Joaquim Radua (radua@clinic.cat)

KEYWORDS:

familywise error rate, functional magnetic resonance imaging (fMRI), meta-analysis, neuroimaging, permutation of subject images (PSI), seed-based d mapping (SDM), threshold-free cluster enhancement (TFCE), voxel-based morphometry (VBM)

SUMMARY:

We detail how to conduct a meta-analysis of voxel-based neuroimaging studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI).

ABSTRACT:

Most methods for conducting meta-analysis of voxel-based neuroimaging studies do not assess whether effects are not null, but whether there is a convergence of peaks of statistical significance, and reduce the assessment of the evidence to a binary classification exclusively based on p-values (i.e., voxels can only be “statistically significant” or “non-statistically significant”). Here, we detail how to conduct a meta-analysis using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI), a novel method that uses a standard permutation test to assess whether effects are not null. We also show how to grade the strength of the evidence according to a set of criteria that considers a range of statistical significance levels (from more liberal to more conservative), the amount of data or the detection of potential biases (e.g., small-study effect and excess of significance). To exemplify the procedure, we detail the conduction of a meta-analysis of voxel-based morphometry studies in obsessive-compulsive disorder, and we provide all the data already extracted from the manuscripts to allow the reader to replicate the meta-analysis easily. SDM-PSI can also be used for meta-analyses of functional magnetic resonance imaging, diffusion tensor imaging, position emission tomography and surface-based morphometry studies.

INTRODUCTION:

Since the introduction of magnetic resonance imaging, the neuroimaging community has published thousands of studies of the neural substrates of psychological functions and neuropsychiatric disorders. To summarize these findings, several methods have been developed¹⁻⁶. Original voxel-based neuroimaging studies report the coordinates of the peaks of maximum statistical significance (e.g., in a comparison of gray matter volume between patients and controls), and meta-analytic methods commonly assess whether there is convergence of peaks in certain brain regions.

However, we have shown that these tests for convergence of peaks rely on delicate assumptions that might influence the patterns of meta-analysis results and their statistical significance⁷. Specifically, these tests assume that voxels are independent and that they have the same probability of a “false” peak, while in real gray matter, voxels correlate with their neighbors and the probability that a voxel has a “false” peak depends on its tissue composition. In addition, they also encompass paradoxes such as that the statistical power increases in the presence of few true effects, and decreases when there are multiple true effects.

To overcome these problems, we developed a method that imputes the brain maps of statistical effects for each study and then conducts a standard random-effects meta-analysis to formally test whether the effects are different from zero. This method is called “Seed-based d Mapping with Permutation of Subject Images” (SDM-PSI)⁸ and its main features include:

- Accounting for both increases and decreases of the outcome of interest (e.g., activation

and deactivation) so that contradictory findings cancel each other⁴;

- Use of effect size estimates with random-effects modeling, which increases reliability and performance⁹;
- Potential simultaneous inclusion of available 3D statistical images (i.e., maps of t-test values)¹⁰;
- Subject-based permutation tests identical to those of FSL “randomize” tool¹¹;
- Use of threshold-free cluster enhancement (TFCE) statistics¹².

We have detailed and fully validated the SDM methods elsewhere^{4,8,10,13,14}.

In addition, we suggest not relying on a binary classification of the voxels based on the level of statistical significance (significant vs. not significant) but, conversely, assessing the strength of the evidence using a set of criteria. The binary statistical significance reductionism leads to poor control of the false positive and false negative rates¹⁵, whereas the criteria use ranges of statistical significance levels and take into account the amount of data or potential biases. The SDM-PSI software returns the necessary elements to conduct such a classification¹⁰ and thus they can be employed to afford a more granular classification of the strength of the evidence.

Here we show how to conduct a meta-analysis of voxel-based neuroimaging studies using SDM-PSI. To exemplify the protocol, we use data from a published meta-analysis of voxel-based morphometry studies that investigated gray matter abnormalities in patients with obsessive-compulsive disorder (OCD)¹. However, we will not use the methods employed in that early meta-analysis, but the aforementioned state-of-the-art procedures. The reader can download the software and these data from our website (<http://www.sdmproject.com/>) to replicate the analysis.

All researchers who aim to conduct a meta-analysis of voxel-based neuroimaging studies to can follow this protocol. The method can be used with functional magnetic resonance imaging (fMRI, e.g., BOLD response to a stimulus)¹⁶, voxel-based morphometry (VBM, e.g., gray matter volume)¹⁷, diffusion tensor imaging (DTI, e.g., fractional anisotropy)¹⁸, position emission tomography (PET, e.g., receptor occupancy)¹⁹ and surface-based morphometry (SBM, e.g. cortical thickness) studies/datasets.

PROTOCOL:

1. Installation of SDM-PSI

1.1. Go to <https://www.sdmproject.com/software/> to download the version of SDM-PSI for the operating system of the computer as a ZIP file.

1.2. Decompress the ZIP file. To avoid problems, decompress it within a local folder without blank spaces in its path.

1.3. Click the file **SdmPsiGui** to execute the graphical interface of SDM-PSI, and close the **About** splash window that will automatically open.

1.4. If **SdmPsiGui** does not find all required paths, it will automatically offer to display the preferences window. Press **Yes**.

1.4.1. If MRICron is not installed in the computer go to https://www.nitrc.org/frs/?group_id=152 to download the version for the operating system of the computer as a ZIP file, and decompress the ZIP file.

1.4.2. In the **Brain viewer** tab of the preferences window, ensure that **Brain viewer** is set to **MRICron**, and click the folder icon next to **Brain viewer executable** to find the MRICron executable.

1.4.3. Ensure that all remaining paths in the different tabs have blue marks, which indicate that the paths are correct.

1.5. In case that SdmPsiGui has not automatically displayed the preferences window, go to the **Tools** menu and click **Preferences**.

1.6. In the **Multithreading** tab, specify the number of concurrent threads to use in the calculations. Some SDM-PSI calculations take a very long time (from hours to days) and consume a large amount of RAM memory (from hundreds of megabytes to gigabytes). The use of multiple threads (parallel processing) substantially decreases the time but increases the memory used.

1.7. Close the preferences window and SdmPsiGui.

2. Meta-analysis plan

2.1. Specify a precise question. For instance, “do patients with OCD have gray matter volume regional abnormalities?”

2.2. Write clear inclusion criteria that allow a systematic inclusion of the studies. For instance, “all studies that performed whole-brain voxel-based comparison of gray matter volume between individuals with OCD and healthy controls”.

2.3. Write clear exclusion criteria that allow a systematic exclusion of those studies that cannot or should not be included for specific reasons. For instance, “studies with less than 10 patients, duplicated datasets, or studies from which the required information cannot be retrieved”.

2.4. Write down the data to extract from each study. The following list includes the

recommended data (some of them are not strictly required, but their absence would impoverish the meta-analysis):

- An identification of the study.
- The sample sizes.
- The statistical significance level, which is the t-value, z-value or p-value used in the study to determine which voxels were statistically significant.
- The software and stereotactic space. See **Table 1** for the list of software packages and stereotactic spaces understood by SDM-PSI.
- The coordinates and height of the peaks. The height of a peak is its t-value or z-value, but a p-value is also useful.
- Variables that will be used to describe the samples or to conduct subgroup analyses or meta-regressions.

2.5. To increase the quality of the review, consider following the “Ten simple rules for neuroimaging meta-analysis”²⁰ and the PRISMA checklist³.

2.6. To increase the transparency of the review, consider registering the protocol beforehand on a publicly available database such as PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>).

3. Exhaustive search

3.1. Select a set of keywords that allow finding any study that might meet the inclusion criteria. For instance, the keywords might be "obsessive-compulsive disorder" plus "morphometry", "voxel-based" or "voxelwise".

3.2. Conduct the search on databases such as PubMed and Web of Science:

3.2.1. Go to database website, e.g. <https://www.ncbi.nlm.nih.gov/pubmed/> for PubMed.

3.2.2. Type the search query. In the example meta-analysis, the query might be "obsessive-compulsive disorder" AND ("morphometry" OR "voxel-based" OR "voxelwise"). In this query, the operator “AND” means that the studies must have all keywords, the operator “OR” means that the studies must have at least one of the keywords, and the parentheses indicate the order of these logical operations. Therefore, the retrieved studies must have the keyword "obsessive-compulsive disorder" and at least one of the keywords "morphometry", "voxel-based" or "voxelwise". Note that other strategies are possible.

3.3. Apply the inclusion/exclusion criteria. For instance, from the results provided by the

databases, select only the articles that analyze differences in gray matter volume between patients with obsessive-compulsive disorder and controls performing whole-brain voxel-based morphometry studies, and discard studies including less than 10 patients and studies that re-analyzed previously published data.

3.4. To increase the exhaustiveness of the search, consider conducting a manual search over the referenced works in the selected studies.

3.5. To maximize the inclusion of studies and avoid uncertainty in the collection of data, consider contacting the corresponding authors to ask for any missing or unclear data.

3.6. Record the number of studies retrieved and the number of studies excluded for each reason. Consider creating a PRISMA flow diagram²¹ with these numbers.

4. Collection of the data

4.1. For each included study, read the manuscript to find the specific data to extract.

4.2. Save the data from the studies systematically, e.g., typing the data in pre-formatted spreadsheet files. To minimize typing errors, consider copying and pasting the numbers of interest and double-checking the saved data.

4.3. When the statistical significance level is unclear, consider following these recommendations:

4.3.1. If the manuscript reports peaks obtained using two whole-brain statistical significance levels, e.g. $p\text{-value} < 0.001$ without correction for multiple comparisons (from now on, “uncorrected threshold”) and familywise error rate (FWER) < 0.05 (from now on “corrected threshold”), select the uncorrected threshold, and include all peaks obtained using this uncorrected threshold. The reason to prefer the uncorrected threshold is that studies usually obtain more peaks applying an uncorrected threshold, and SDM estimates the maps more accurately if it has information from more peaks.

4.3.2. If the manuscript reports peaks obtained using an uncorrected threshold for increases and a corrected threshold for decreases (or vice versa), select the uncorrected threshold but include only the peaks obtained using the corrected threshold. This is a conservative approximation because it might discard some peaks obtained using the uncorrected threshold. An example of this situation might be when a manuscript states something such as “we detected FWER-corrected larger gray matter volumes in some regions, while we did not detect smaller gray matter volume in any region even using uncorrected $p\text{-value} < 0.001$ ”.

4.3.3. If the authors applied cluster-based statistics, use the cluster-forming height threshold. This is a conservative approximation because some voxels might have had t-values higher than the threshold, but the authors discarded them because their clusters were not large enough.

4.3.4. If the manuscript does not specify a threshold, use the t-value of the smallest peak. The reason to use this t-value is that if the authors had applied this statistical significance threshold without requiring a minimum size for the clusters, they would have found the same peaks.

4.4. When recording the peak information do the following:

4.4.1. Exclude peaks obtained using a statistical significance threshold that is more liberal than the threshold selected for the rest of the brain. An example of this situation is when the authors applied more liberal thresholds or small volume corrections to some a priori brain regions.

4.4.2. Convert z-values and p-values into t-values. Click the button **Convert peaks** in the SDM-PSI software to convert them easily. Alternatively, convert them in the same spreadsheet file (e.g., “=T.INV(1-0.001,34)” for p-value = 0.001 and 34 degrees of freedom; the degrees of freedom are the sum of the sample sizes minus the number of parameters, which are two plus the number of covariates used in the original comparison).

4.4.3. Use positive t-values for peaks of increase (e.g., activation) and negative t-values for peaks of decrease (e.g., deactivation). See **Table 2** for guidance on how to decide the sign of the t-values.

NOTE: We obtained information from studies “Heuvel” and “Soriano-Mas” after personal communication.

5. Introduction of data into SDM-PSI

5.1. Open **SdmPsiGui** and close the **About** splash window (avoid having any key pressed while closing it).

5.2. Click the **Change meta-analysis** button at the upper-left part of the graphical interface to select a directory for the meta-analysis (any new empty directory of choice will do).

5.3. Click the button **SDM table editor** to input general information from the studies, including their identification (column “study”), their sample sizes (columns “n1” and “n2”), the t-value that they used as statistical thresholds (column “t_thr”), and other potential variables to conduct subgroup analyses or meta-regressions.

5.4. Within the selected directory, create a text file for each study with the coordinates and t-value of each peak:

5.4.1. Open a text editor to create a text file named as [the identification of study] + “.” + [the software] + “_” + [the stereotactic space] + “.txt”. For instance, for the study “Carmona” that was conducted with SPM and reports the coordinates in MNI space, the name of the text file must be “Carmona.spm_mni.txt”. If the study has no peaks, the software and stereotactic space can be replaced by “no_peaks”.

5.4.2. Write the coordinates and t-value of each peak in a different row. For instance, the first rows of the text file “Carmona.spm_mni.txt” should be:

40,39,21,-5.14

53,27,21,-3.77

56,23,20,-3.63

6. Pre-processing

6.1. Click in the **Preprocessing** button at the left menu bar, select the modality of the studies at the list box labeled “Modality” and press **OK**. In the example meta-analysis, the modality is “VBM – gray matter”.

6.2. Wait (some minutes) while SDM-PSI calculates the maps of the lower and upper bounds of potential effect sizes. SdmPsiGui will show four progress bars that display the status of the execution and the expected remaining time for the current process. During the calculations, the color of the circle next to “Processing status” will be yellow, and will change to green if the execution ends successfully, or to red if it fails (**Figure 1**).

7. Main analysis

7.1. Click the **Mean** button at the left menu bar and press **OK**.

7.2. Wait (some minutes) while SDM-PSI conducts the multiple imputation and meta-analysis.

7.3. Click the **Threshold** button in the left menu toolbox, select the uncorrected p-values of the main analysis (“MyMean_uncorrp” by default) and press **OK**. SDM-PSI will automatically open both MRICron to visualize the results and a webpage with a detailed report of them.

7.4. Press the **FWE correction** button at the left menu toolbox, select the main analysis in the list box (“MyMean” by default) and press **OK**.

7.5. Wait (some hours or even days) while SDM-PSI conducts the permutation test.

7.6. Click the **Threshold** button in the left menu toolbox, select the TFCE-correction of the main analysis (“MyMean_corrpf_tfce” by default) and press **OK**. SDM-PSI will automatically open both MRICron to visualize the results and a webpage with a detailed report of them.

8. Heterogeneity, publication bias and grading

8.1. Click the **Extract** button on the left menu toolbox, select a peak from the main analysis (“MyTest_z_p_0.05000_10_neg_peak1” by default) and press **OK**. SDM-PSI will automatically open a webpage with statistics of this peak. Write down the heterogeneity I^2 statistic.

8.2. Click the **Bias Test** button on the left menu toolbox, select a peak from the main analysis ("MyTest_z_p_0.05000_10_neg_peak1" by default) and press **OK**. SDM-PSI will automatically open a webpage with a funnel plot and the results of a test for small-study effect and a test for excess significance. The former tests whether there is asymmetry in the funnel plot (i.e., larger effect size in small studies), which could indicate that small studies are only published if they find large effect sizes or other sources of bias. The latter tests whether the number of studies with statistically significant results is larger than expected, which could indicate that studies are only published if they find statistically significant results or other sources of bias.

8.3. Press the **Evidence grading** button from the top toolbox, select the main analysis ("MyMean" by default) from the list box and press **OK**. After some seconds, SDM-PSI will automatically open MRICron to show the classes of evidence as well as sub-categories for negative results (1: cannot exclude even large effects, 2: can exclude large effects, 3: can exclude modest effects; 4: can exclude even small effects).

REPRESENTATIVE RESULTS:

As shown in the map open in MRICron when thresholding of the main analysis (**Figure 2**, step 7.6), patients with OCD had statistically significantly smaller gray matter volume in dorsal anterior cingulate/medial frontal cortex. The accompanying webpage details that the cluster is moderately small (143 voxels) and mainly located at Brodmann area 32, and that the peak of the cluster is at MNI [2, 32, 32] and has a z-value of -4.97 and a FWER-corrected p-value of 0.01.

In the webpage obtained in step 8.2, the low I^2 statistic (1.5%) indicates very small heterogeneity, the funnel plot does not show asymmetries (**Figure 3**), and both the test for small-study effect and the test for excess of significance are negative. However, the evidence of smaller gray matter volume in dorsal anterior cingulate cortex is weak, as shown in the map open in MRICron when grading evidence, especially due to limited amount of data.

When the main analysis was thresholded using a less stringent statistical significance level (step 7.3), patients also had statistically significantly larger gray matter volume in the striatum and superior parietal gyrus (uncorrected p-values = 0.00006 and 0.0002 respectively), but the evidence of these abnormalities should be considered weaker.

Finally, the map of negative subcategories open in MRICron when grading the evidence showed that the effect sizes in non-statistically significant voxels were mostly null to small, and no large effects were observed in any non-statistically significant voxel.

FIGURE & TABLE LEGENDS:

Figure 1: Main window of the SDP-PSI graphical user interface during a pre-processing execution.

Figure 2: Regions of statistically significantly smaller gray matter volume in patients with

obsessive-compulsive disorder as compared to matched healthy controls. The cluster of statistical significance covers 143 voxels, has its peak at MNI [2,32,32], and includes mostly dorsal anterior cingulate/medial frontal cortex, Brodmann area 32.

Figure 3: Funnel plot for the peak of the cluster of statistically significantly smaller gray matter volume in dorsal anterior cingulate cortex.

Table 1: List of software packages and stereotactic spaces understood by SDM-PSI.

Table 2: Sign of the t-values of the peaks.

DISCUSSION:

As introduced earlier, most voxel-based meta-analytic methods use a test for convergence of peaks that has some limitations, and then conduct a binary classification of the evidence exclusively based on p-values.

In this protocol, we detailed how to conduct a voxel-based meta-analysis using SDM-PSI, which has a number of positive features including a standard permutation test to assess the statistical significance of the effects. In addition, we show how the strength of the evidence can be graded using a set of criteria that go beyond a binary classification that solely relies on one statistical significance level.

To facilitate the replication of the example meta-analysis, we provide the data already extracted from the manuscripts from a previous meta-analysis. Interestingly, in the manuscript of that meta-analysis, the evidence “seemed” stronger than the evidence that we found with the updated methods. We therefore suggest that unsystematic evaluations of the evidence in previous voxel-based meta-analyses are taken with caution.

We hope that following this protocol, neuroimaging meta-analyses provide a richer and more granulate description of the evidence of neuroimaging findings.

ACKNOWLEDGMENTS:

This work was supported by Miguel Servet Research Contract MS14/00041 and Research Project PI14/00292 from the Plan Nacional de I+D+i 2013–2016, the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación and the European Regional Development Fund (FEDER). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DISCLOSURES:

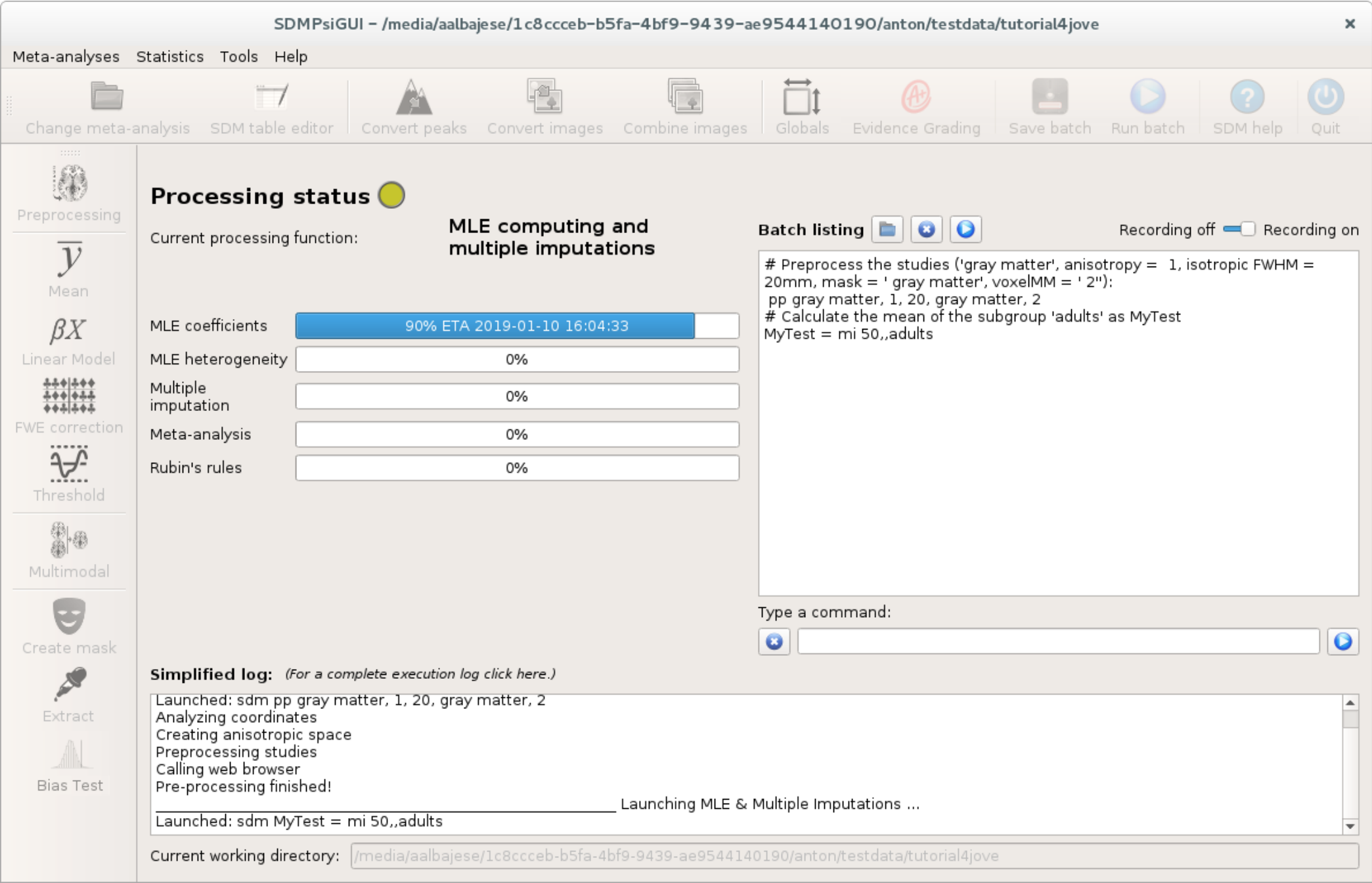
The authors have nothing to disclosure.

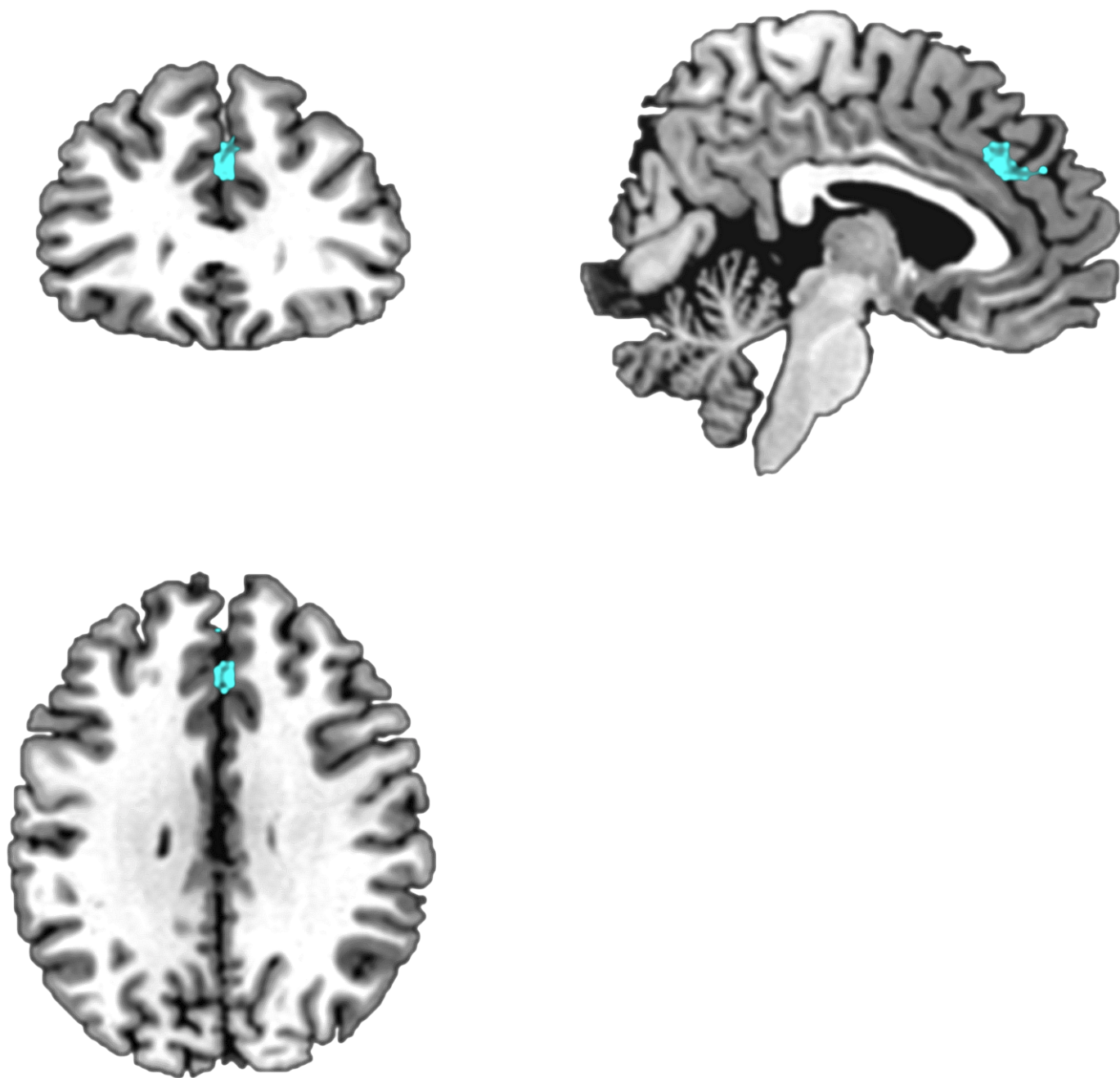
REFERENCES:

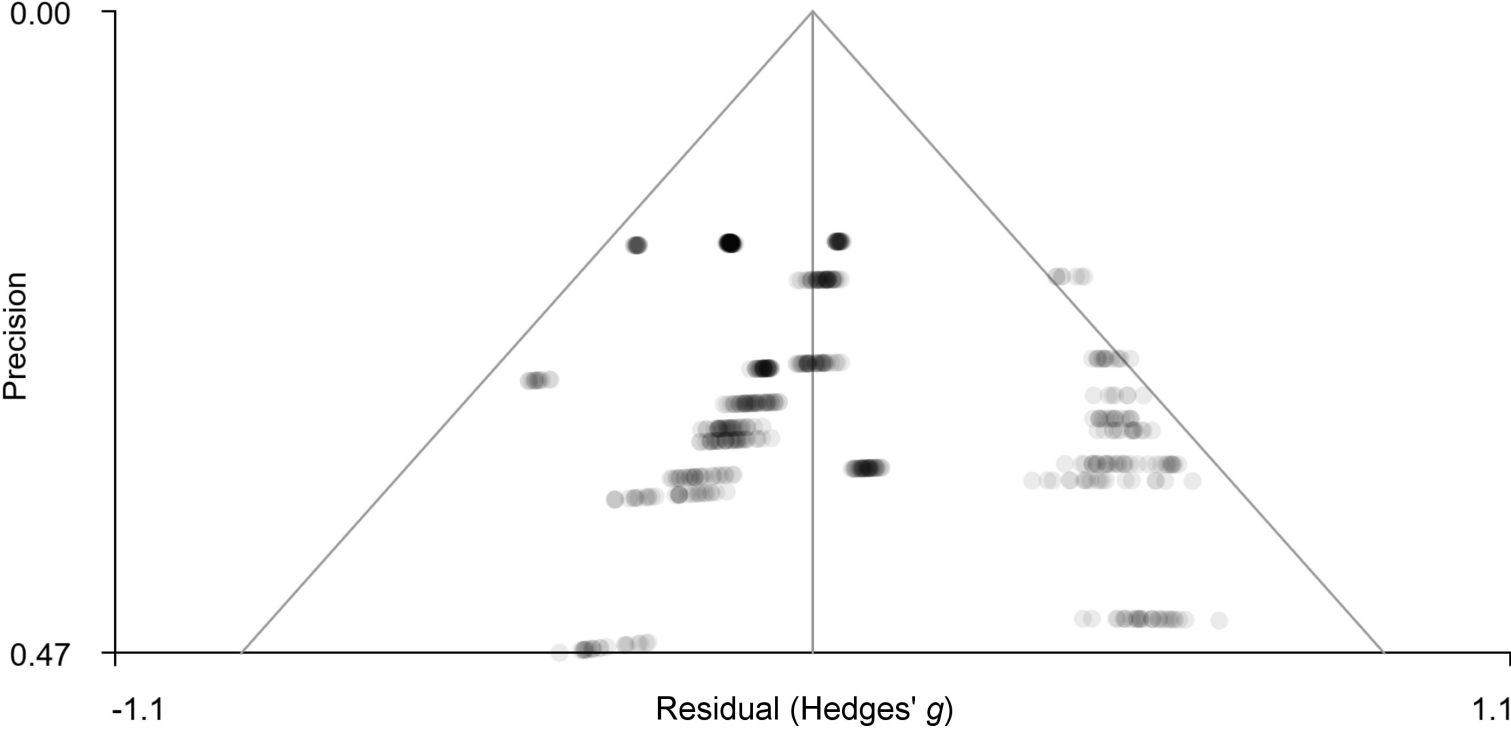
1 Turkeltaub, P. E., Eden, G. F., Jones, K. M. & Zeffiro, T. A. Meta-analysis of the functional

- neuroanatomy of single-word reading: method and validation. *Neuroimage*. **16** (3 Pt 1), 765-780 (2002).
- 2 Laird, A. R. et al. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*. **25** (1), 155-164, doi:10.1002/hbm.20136 (2005).
- 3 Wager, T. D., Lindquist, M. & Kaplan, L. Meta-analysis of functional neuroimaging data: current and future directions. *Social Cognitive and Affective Neuroscience*. **2** (2), 150-158, doi:10.1093/scan/nsm015 (2007).
- 4 Radua, J., Mataix-Cols, D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry*. **195** (5), 393-402, doi:10.1192/bjp.bp.108.055046 (2009).
- 5 Eickhoff, S. B. et al. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*. **30** (9), 2907-2926, doi:10.1002/hbm.20718 (2009).
- 6 Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., Fox, P. T. Activation likelihood estimation meta-analysis revisited. *Neuroimage*. **59** (3), 2349-2361, doi:10.1016/j.neuroimage.2011.09.017 (2012).
- 7 Albajes-Eizagirre, A., Radua, J. What do results from coordinate-based meta-analyses tell us? *Neuroimage*. **176**, 550-553, doi:10.1016/j.neuroimage.2018.04.065 (2018).
- 8 Albajes-Eizagirre, A., Solanes, A., Vieta, E., Radua, J. Voxel-based meta-analysis via permutation of subject images (PSI): Theory and implementation for SDM. *Neuroimage*. **186**, 174-184, doi:10.1016/j.neuroimage.2018.10.077 (2018).
- 9 Bossier, H. et al. The Influence of Study-Level Inference Models and Study Set Size on Coordinate-Based fMRI Meta-Analyses. *Frontiers in Neuroscience*. **11**, 745, doi:10.3389/fnins.2017.00745 (2017).
- 10 Radua, J. et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry*. **27** (8), 605-611, doi:10.1016/j.eurpsy.2011.04.001 (2012).
- 11 Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., Nichols, T. E. Permutation inference for the general linear model. *Neuroimage*. **92**, 381-397, doi:10.1016/j.neuroimage.2014.01.060 (2014).
- 12 Smith, S. M., Nichols, T. E. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*. **44** (1), 83-98, doi:10.1016/j.neuroimage.2008.03.061 (2009).
- 13 Radua, J. et al. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Frontiers in Psychiatry*. **5**, 13, doi:10.3389/fpsy.2014.00013 (2014).
- 14 Albajes-Eizagirre, A., Solanes, A., Radua, J. Meta-analysis of non-statistically significant unreported effects. *Statistical Methods in Medical Research*. 962280218811349, doi:10.1177/0962280218811349 (2018).
- 15 Durnez, J., Moerkerke, B., Nichols, T. E. Post-hoc power estimation for topological inference in fMRI. *Neuroimage*. **84**, 45-64, doi:10.1016/j.neuroimage.2013.07.072 (2014).
- 16 Fullana, M. A. et al. Fear extinction in the human brain: A meta-analysis of fMRI studies in healthy participants. *Neuroscience & Biobehavioral Reviews*. **88**, 16-25, doi:10.1016/j.neubiorev.2018.03.002 (2018).

- 485 17 Wise, T. et al. Common and distinct patterns of grey-matter volume alteration in major
486 depression and bipolar disorder: evidence from voxel-based meta-analysis. *Molecular*
487 *Psychiatry*. **22** (10), 1455-1463, doi:10.1038/mp.2016.72 (2017).
- 488 18 Radua, J. et al. Multimodal voxel-based meta-analysis of white matter abnormalities in
489 obsessive-compulsive disorder. *Neuropsychopharmacology*. **39** (7), 1547-1557,
490 doi:10.1038/npp.2014.5 (2014).
- 491 19 He, W. et al. Meta-analytic comparison between PIB-PET and FDG-PET results in
492 Alzheimer's disease and MCI. *Cell Biochemistry and Biophysics*. **71** (1), 17-26,
493 doi:10.1007/s12013-014-0138-7 (2015).
- 494 20 Muller, V. I. et al. Ten simple rules for neuroimaging meta-analysis. *Neuroscience &*
495 *Biobehavioral Reviews*. **84**, 151-161, doi:10.1016/j.neubiorev.2017.11.012 (2018).
- 496 21 Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Group, P. Preferred reporting items for
497 systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal*.
498 **339**, b2535, doi:10.1136/bmj.b2535 (2009).
- 499







Sheet1	
<u>Software packages</u>	<u>Coding in SDM</u>
Statistical Parametric Mapping (SPM)	spm
FMRIB Software Library (FSL)	fsl
Other packages	other
<u>Stereotactic space</u>	<u>Coding in SDM</u>
Montreal Neurological Institute (MNI)	mni
Raw Talairach	tal
MNI converted to Talairach using Brett transform	brett

Sheet1

t-values must be positive when:

One-sample fMRI studies
Two-sample fMRI studies
Two-sample VBM / FA studies

task > baseline (activation)
patients > controls in task > baseline (hyper-activation)
patients < controls in task < baseline (failure of deactivation)
patients > controls (larger volume / FA)

Sheet1

t-values must be negative when:

task < baseline (deactivation)

patients < controls in task > baseline (hypo-activation)

patients > controls in task < baseline (hyper-deactivation)

patients < controls (smaller volume / FA)



Name of Material/ Equipment

Company

Computer

Catalog Number

Comments/Description

32- or 64-bit Windows, 64-bit Mac OSX, c

or 64-bit Linux

ARTICLE AND VIDEO LICENSE AGREEMENT

Title of Article:

Meta-analysis of voxel-based neuroimaging studies and grading of the evidence of their results with Seed-based d Mapping (SDM)

Author(s):

Anton Albajes-Eizagire, Aleix Solanes, Miquel Angel Fullana, John P. A. Ioannidis, Paolo Fusar-Poli, Eduard Vieta, David Mataix-Cols, Joaquim Radua

Item 1: The Author elects to have the Materials be made available (as described at <http://www.jove.com/publish>) via:

☒ Standard Access

☐ Open Access

Item 2: Please select one of the following items:

☒ The Author is **NOT** a United States government employee.

☐ The Author is a United States government employee and the Materials were prepared in the course of his or her duties as a United States government employee.

☐ The Author is a United States government employee but the Materials were NOT prepared in the course of his or her duties as a United States government employee.

ARTICLE AND VIDEO LICENSE AGREEMENT

1. **Defined Terms.** As used in this Article and Video License Agreement, the following terms shall have the following meanings: "**Agreement**" means this Article and Video License Agreement; "**Article**" means the article specified on the last page of this Agreement, including any associated materials such as texts, figures, tables, artwork, abstracts, or summaries contained therein; "**Author**" means the author who is a signatory to this Agreement; "**Collective Work**" means a work, such as a periodical issue, anthology or encyclopedia, in which the Materials in their entirety in unmodified form, along with a number of other contributions, constituting separate and independent works in themselves, are assembled into a collective whole; "**CRC License**" means the Creative Commons Attribution-Non Commercial-No Derivs 3.0 Unported Agreement, the terms and conditions of which can be found at: <http://creativecommons.org/licenses/by-nc-nd/3.0/legalcode>; "**Derivative Work**" means a work based upon the Materials or upon the Materials and other pre-existing works, such as a translation, musical arrangement, dramatization, fictionalization, motion picture version, sound recording, art reproduction, abridgment, condensation, or any other form in which the Materials may be recast, transformed, or adapted; "**Institution**" means the institution, listed on the last page of this Agreement, by which the Author was employed at the time of the creation of the Materials; "**JoVE**" means MyJove Corporation, a Massachusetts corporation and the publisher of The Journal of Visualized Experiments; "**Materials**" means the Article and / or the Video; "**Parties**" means the Author and JoVE; "**Video**" means any video(s) made by the Author, alone or in conjunction with any other parties, or by JoVE or its affiliates or agents, individually or in collaboration with the Author or any other parties, incorporating all or any portion

of the Article, and in which the Author may or may not appear.

2. **Background.** The Author, who is the author of the Article, in order to ensure the dissemination and protection of the Article, desires to have the JoVE publish the Article and create and transmit videos based on the Article. In furtherance of such goals, the Parties desire to memorialize in this Agreement the respective rights of each Party in and to the Article and the Video.

3. **Grant of Rights in Article.** In consideration of JoVE agreeing to publish the Article, the Author hereby grants to JoVE, subject to **Sections 4 and 7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Article in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Article into other languages, create adaptations, summaries or extracts of the Article or other Derivative Works (including, without limitation, the Video) or Collective Works based on all or any portion of the Article and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and (c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. If the "Open Access" box has been checked in **Item 1** above, JoVE and the Author hereby grant to the public all such rights in the Article as provided in, but subject to all limitations and requirements set forth in, the CRC License.

4. **Retention of Rights in Article.** Notwithstanding the exclusive license granted to JoVE in **Section 3** above, the Author shall, with respect to the Article, retain the non-exclusive right to use all or part of the Article for the non-commercial purpose of giving lectures, presentations or teaching classes, and to post a copy of the Article on the Institution's website or the Author's personal website, in each case provided that a link to the Article on the JoVE website is provided and notice of JoVE's copyright in the Article is included. All non-copyright intellectual property rights in and to the Article, such as patent rights, shall remain with the Author.

5. **Grant of Rights in Video – Standard Access.** This **Section 5** applies if the "Standard Access" box has been checked in **Item 1** above or if no box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby acknowledges and agrees that, Subject to **Section 7** below, JoVE is and shall be the sole and exclusive owner of all rights of any nature, including, without limitation, all copyrights, in and to the Video. To the extent that, by law, the Author is deemed, now or at any time in the future, to have any rights of any nature in or to the Video, the Author hereby disclaims all such rights and transfers all such rights to JoVE.

6. **Grant of Rights in Video – Open Access.** This **Section 6** applies only if the "Open Access" box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby grants to JoVE, subject to **Section 7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Video in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Video into other languages, create adaptations, summaries or extracts of the Video or other Derivative Works or Collective Works based on all or any portion of the Video and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and (c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. For any Video to which this **Section 6** is applicable, JoVE and the Author hereby grant to the public all such rights in the Video as provided in, but subject to all limitations and requirements set forth in, the CRC License.

7. **Government Employees.** If the Author is a United States government employee and the Article was prepared in the course of his or her duties as a United States government employee, as indicated in **Item 2** above, and any of the licenses or grants granted by the Author hereunder exceed the scope of the 17 U.S.C. 403, then the rights granted hereunder shall be limited to the maximum

rights permitted under such statute. In such case, all provisions contained herein that are not in conflict with such statute shall remain in full force and effect, and all provisions contained herein that do so conflict shall be deemed to be amended so as to provide to JoVE the maximum rights permissible within such statute.

8. **Protection of the Work.** The Author(s) authorize JoVE to take steps in the Author(s) name and on their behalf if JoVE believes some third party could be infringing or might infringe the copyright of either the Author's Article and/or Video.

9. **Likeness, Privacy, Personality.** The Author hereby grants JoVE the right to use the Author's name, voice, likeness, picture, photograph, image, biography and performance in any way, commercial or otherwise, in connection with the Materials and the sale, promotion and distribution thereof. The Author hereby waives any and all rights he or she may have, relating to his or her appearance in the Video or otherwise relating to the Materials, under all applicable privacy, likeness, personality or similar laws.

10. **Author Warranties.** The Author represents and warrants that the Article is original, that it has not been published, that the copyright interest is owned by the Author (or, if more than one author is listed at the beginning of this Agreement, by such authors collectively) and has not been assigned, licensed, or otherwise transferred to any other party. The Author represents and warrants that the author(s) listed at the top of this Agreement are the only authors of the Materials. If more than one author is listed at the top of this Agreement and if any such author has not entered into a separate Article and Video License Agreement with JoVE relating to the Materials, the Author represents and warrants that the Author has been authorized by each of the other such authors to execute this Agreement on his or her behalf and to bind him or her with respect to the terms of this Agreement as if each of them had been a party hereto as an Author. The Author warrants that the use, reproduction, distribution, public or private performance or display, and/or modification of all or any portion of the Materials does not and will not violate, infringe and/or misappropriate the patent, trademark, intellectual property or other rights of any third party. The Author represents and warrants that it has and will continue to comply with all government, institutional and other regulations, including, without limitation all institutional, laboratory, hospital, ethical, human and animal treatment, privacy, and all other rules, regulations, laws, procedures or guidelines, applicable to the Materials, and that all research involving human and animal subjects has been approved by the Author's relevant institutional review board.

11. **JoVE Discretion.** If the Author requests the assistance of JoVE in producing the Video in the Author's facility, the Author shall ensure that the presence of JoVE employees, agents or independent contractors is in accordance with the relevant regulations of the Author's institution. If more than one author is listed at the beginning of this Agreement, JoVE may, in its sole

ARTICLE AND VIDEO LICENSE AGREEMENT

discretion, elect not take any action with respect to the Article until such time as it has received complete, executed Article and Video License Agreements from each such author. JoVE reserves the right, in its absolute and sole discretion and without giving any reason therefore, to accept or decline any work submitted to JoVE. JoVE and its employees, agents and independent contractors shall have full, unfettered access to the facilities of the Author or of the Author's institution as necessary to make the Video, whether actually published or not. JoVE has sole discretion as to the method of making and publishing the Materials, including, without limitation, to all decisions regarding editing, lighting, filming, timing of publication, if any, length, quality, content and the like.

12. Indemnification. The Author agrees to indemnify JoVE and/or its successors and assigns from and against any and all claims, costs, and expenses, including attorney's fees, arising out of any breach of any warranty or other representations contained herein. The Author further agrees to indemnify and hold harmless JoVE from and against any and all claims, costs, and expenses, including attorney's fees, resulting from the breach by the Author of any representation or warranty contained herein or from allegations or instances of violation of intellectual property rights, damage to the Author's or the Author's institution's facilities, fraud, libel, defamation, research, equipment, experiments, property damage, personal injury, violations of institutional, laboratory, hospital, ethical, human and animal treatment, privacy or other rules, regulations, laws, procedures or guidelines, liabilities and other losses or damages related in any way to the submission of work to JoVE, making of videos by JoVE, or publication in JoVE or elsewhere by JoVE. The Author shall be responsible for, and shall hold JoVE harmless from, damages caused by lack of sterilization, lack of cleanliness or by contamination due to

the making of a video by JoVE its employees, agents or independent contractors. All sterilization, cleanliness or decontamination procedures shall be solely the responsibility of the Author and shall be undertaken at the Author's expense. All indemnifications provided herein shall include JoVE's attorney's fees and costs related to said losses or damages. Such indemnification and holding harmless shall include such losses or damages incurred by, or in connection with, acts or omissions of JoVE, its employees, agents or independent contractors.

13. Fees. To cover the cost incurred for publication, JoVE must receive payment before production and publication the Materials. Payment is due in 21 days of invoice. Should the Materials not be published due to an editorial or production decision, these funds will be returned to the Author. Withdrawal by the Author of any submitted Materials after final peer review approval will result in a US\$1,200 fee to cover pre-production expenses incurred by JoVE. If payment is not received by the completion of filming, production and publication of the Materials will be suspended until payment is received.

14. Transfer, Governing Law. This Agreement may be assigned by JoVE and shall inure to the benefits of any of JoVE's successors and assignees. This Agreement shall be governed and construed by the internal laws of the Commonwealth of Massachusetts without giving effect to any conflict of law provision thereunder. This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together shall be deemed to be one and the same agreement. A signed copy of this Agreement delivered by facsimile, e-mail or other means of electronic transmission shall be deemed to have the same legal effect as delivery of an original signed copy of this Agreement.

A signed copy of this document must be sent with all new submissions. Only one Agreement is required per submission.

CORRESPONDING AUTHOR

Name:

Anton Albajes-Eizagirre

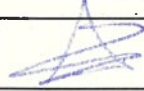
Department:

Institution:

IDIBAPS, Barcelona, Spain

Title:

Signature:



Date:

Feb 14th 2019

Please submit a **signed** and **dated** copy of this license by one of the following three methods:

1. Upload an electronic version on the JoVE submission site
2. Fax the document to +1.866.381.2236
3. Mail the document to JoVE / Attn: JoVE Editorial / 1 Alewife Center #200 / Cambridge, MA 02140

We thank the editor and the reviewers for the positive comments and suggestions, which have improved the manuscript.

Editorial comments:

General:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

RESPONSE: We have thoroughly proofread the manuscript to correct spelling and grammar issues.

2. Please include email addresses for all authors in the manuscript itself.

RESPONSE: We have included email addresses for all authors.

3. JoVE cannot publish manuscripts containing commercial language.

RESPONSE: We have removed commercial software (Excel, Windows and Mac)

Protocol:

1. For each protocol step, please ensure you answer the “how” question... on conducting a database search and applying the inclusion/exclusion criteria, ... and on how exactly the data is collected-is this all manual?

RESPONSE: We have provided more details of the steps required to conduct the database search, the application of inclusion/exclusion criteria, and on how the data are manually collected (page 5).

Figures:

1. Figure 2: Please explain this further in the legend.

RESPONSE: We now provide details in the legend (page 9).

References:

1. Please do not abbreviate journal titles.

RESPONSE: We now provide full journal titles.

Reviewers' comments:

1. Some key terms are not defined in the protocol, but only referenced. I think the protocol would be made more accessible by defining important terms such as "excess significance" and "small-study effect".

RESPONSE: We now define the small-study effect and the excess significance (page 9).

2. There are a few typos in the protocol (such as "make ensure" on line 253), which should be corrected.

RESPONSE: We have thoroughly proofread the manuscript to correct typos.