

AWARD NUMBER: W81XWH-14-1-0316

TITLE: Genetic And Diagnostic Biomarker Development in ASD Toddlers Using Resting-State Functional MRI

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REPORT DATE: November 2017

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE November 2017		2. REPORT TYPE FINAL		1. REPORT DATE 1Sept2014 - 31Aug2017	
4. TITLE AND SUBTITLE Genetic and Diagnostic Biomarker Development in ASD Toddlers Using Resting-State Functional MRI				5a. CONTRACT NUMBER W81XWH-14-1-0316	
				5b. GRANT NUMBER W81XWH-14-1-0316	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) PETER T. FOX, MD E-Mail: fox@uthscsa.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Health Science Center at San Antonio 7703 Floyd Curl Dr. San Antonio, Texas 78229-3901				8. PERFORMING ORGANIZATION REPORT NUMBER NUM	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The primary objective of this project is to develop fMRI-based characterizations of functional connectivity networks during natural sleep as a neurologic biomarker for ASD that is suitable for diagnostic use in young children (ages 1-4). Existing neuroimaging and neurobehavioral resources developed by the principal investigators are being mined for ASD-relevant biomarkers. Structural and (constrained) functional meta-analyses of previously published, peer-reviewed neuroimaging studies in ASD have been conducted to inform regions-of-interest for further hierarchical network modeling. We have thus identified (1) consistent regions of brain overgrowth /atrophy and (2) consistent functional activation differences with social behaviors between ASD and typically developing (TD) individuals. These regions-of-interest will be extended through additional functional meta-analyses, network models will be created, and these models will be applied to primary ASD data.					
15. SUBJECT TERMS Autism Spectrum Disorders (ASD); functional magnetic resonance imaging (fMRI); connectivity modeling					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18 NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	a. REPORT			19b. TELEPHONE NUMBER
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1. INTRODUCTION. Despite more than 25 years of neuroimaging research in Autism Spectrum Disorders (ASD), clinical diagnosis remains behavioral. Behavioral diagnosis is error prone and would derive substantial benefit from a reliable, imaging-based biomarker. Highly functioning ASD children are generally brought to medical attention only when they enter school (5-7 years). Children with more profound behavioral disturbances may seek medical attention earlier (~ 3 years of age), but this is still well after symptom onset. Earlier diagnosis could have substantial positive impact as treatment efficacy is well established and has proportionally greater benefit when initiated early (Dawson et al., 2010; Landa et al., 2010). To this end, this research proposal sought to develop neuroimaging biomarkers which could be used to confirm (or disconfirm) clinical impressions in young children with suspected ASD.

The overall goal of this multi-site (UTHSCSA; Yale; UCSD) grant was to develop meta-analytic network (node and edge) models of ASD using the coordinate-based neuroimaging literature (UTHSCSA site) and to use these models as "priors" for probing primary neuroimaging data at the sites of collaborators from Yale and UCSD. If successfully validated with primary data, these network models could eventually serve as tools for early diagnosis -- i.e., for neuroimaging confirmation/disconfirmation of clinical diagnoses -- of ASD. In this way, neuroimaging biomarker(s) could enable earlier and more reliable diagnoses of ASD, resulting in earlier treatment onsets and, thereby, better long-term outcomes.

The general approach applied to ASD in this proposal -- meta-analytic development of a disease-specific network model using coordinate-based meta-analysis (CBMA) followed by primary data validation -- is a strategy pioneered by the PI (Fox et al., 2014) and successfully applied in temporal lobe epilepsy by a graduate student in this laboratory (Barron et al., 2013; 2014; 2015). Extending the scope of this approach, the PI is concurrently applying this strategy in other several disorders, including Alzheimer's disease, Frontotemporal dementia, Parkinsonian syndromes (Yu et al., 2015; Yu et al., 2017) multiple sclerosis, major depressive disorder (Muller et al., 2017; Gray et al., in preparation), metabolic syndrome, and posttraumatic stress disorder, with funding from the NIH/NIMH (MH74457), DoD (W81XWH-13-2-0065) and the Radiological Society of North America (various) via his supervision of various trainees and even more broadly via his collaborative network. Considered more broadly, the meta-analytic resources (data and software) developed by the PI and his laboratory have been used for > 750 peer-reviewed coordinate-based meta-analyses (Fox et al., 2014; BrainMap.org/pubs/)

Limitations of the CBMA network-modeling approach, however, must be addressed. In a recent, highly publicized report, Eklund and others used massive simulations to expose inflated false-positive rates (up to 70% false positive findings) for functional MRI (fMRI) studies that applied corrections for multiple comparisons as implemented in the most widely used fMRI software packages (Eklund, Nichols and Knutsson *PNAS* 2016). Given that the algorithms used to correct for multiple comparisons are the same for voxel-based morphometry (VBM) and for fMRI, this limitation applies to both literatures. Eklund's report calls for increased statistical rigor in this research domain but also notes the "important role" of coordinate-based meta-analysis in "teasing apart false-positive findings from consistent results". Eickhoff, Fox and colleagues -- also performing massive empirical simulations -- developed formal recommendations for CBMA, including the most reliable method for multiple-comparison corrections (Cluster-level Family-wise Error), corrections for small samples, and guidelines for the minimal number of independent studies (17-20) needed for a valid meta-analysis (Eickhoff et al., 2009; Turkeltaub et al., 2012; Eickhoff et al., 2012; Eickhoff et al., 2016; Mueller et al., 2017a).

Another limitation of the CBMA approach arises from literature heterogeneity. Meta-analysis is most productive for studies that are methodologically similar, that is, which have used similar task-activation paradigms (for fMRI studies) and have defined participants (both patients and controls) using similar diagnostic criteria. A recent negative report of multiple large-scale meta-analyses of task-activation studies in major depressive disorder cautions that even a disorder that has been extensively studied with fMRI may yield no converging results by CBMA (Meuller et al., 2017). An in-progress follow-up study of VBM and resting-state fMRI studies, also in unipolar depression, has yielded similarly negative results (Gray et al., in preparation).

To discover potential causes of these somewhat startling negative results of disorder-focused meta-analyses, our laboratory and our collaborators has begun performing transdiagnostic studies, looking beyond single

diagnoses. In a paradigm-shifting study, Goodkind and colleagues performed a CBMA of the psychiatric VBM literature which showed that multiple psychiatric disorders shared a similar, network-based atrophy pattern, calling into question the neurobiological specificity of psychiatric nosology (Goodkind et al., 2015). In our laboratory, Kotkowski demonstrated that structural covariance patterns can be shared by multiple disorders and recapitulate functional covariance patterns (Kotkowski et al., 2018; Appendix 3). Also in our laboratory, Vanasse concurrently applied independent components analysis (ICA) transdiagnostically to 43 different neurological, psychiatric and developmental disorders (including ASD) (Vanasse, in review; Appendix 4). This study reports that all the observed structural covariance networks weighted on multiple disorders, rather than on individual disorders. Further, it observed that the reliability (spatial/anatomical replicability) across studies of the structural abnormalities is much higher for neurologic disorders than for psychiatric disorders, with a working definition of this distinction being an International Classification of Disorders (ICD) 10 code of G (Neurologic) or F (Psychiatric). Finally, in this ranking of diseases by the strength of their loading on consistent atrophy patterns, ASD was at the bottom. That is, of all 43 diseases considered, ASD showed the least reliable atrophy patterns. It is from this perspective that we now describe our efforts to extract reliable results from the structural and functional neuroimaging literature in ASD.

2. KEYWORDS: Autism Spectrum Disorders; ASD; coordinate-based meta-analysis; CBMA; magnetic resonance imaging; MRI; functional MRI; fMRI, network modeling; connectomics; meta-analytic connectivity modeling; MACM.

3. ACCOMPLISHMENTS. What were the major goals of the UTHSCSA site? The primary goal of the work performed at the UTHSCSA site was to develop network models (node-and-edge models) of brain systems implicated in ASD by meta-analysis of the coordinate-based neuroimaging literature, i.e. using coordinate-based meta-analysis (CBMA). Because this work was performed by doctoral students under the supervision of the PI, graduate-level training in computational biology, including neuroimaging meta-analysis, meta-analytic network model construction and validations using primary data.

- **UTHSCSA Primary Goal:** Meta-analytic network model of ASD construction and validation.
- **UTHSCSA Secondary Goal:** Doctoral-level training in computational biology.

3.A. Administrative Tasks. Two administrative tasks were required: 1) Human Subject Protection Approval; and, 2) Staffing.

Task 1: Human Subjects Protection Approval. Work performed at UTHSCA is of two types: 1) meta-analytic modeling; and 2) primary data model validation. Meta-analytic modeling uses only as-published, group-wise summary data, which have no links to personal identifiers (birth date, SSN, etc.) or personal health information. Primary data used for model validation are anonymized, stripping them of all personal identifiers and personal health information. The UTHSCA IRB determined that this project did not require IRB approval. This determination was provided to HRPO.

Task 2: Staffing. Staffing was an ongoing issue during the term of this project. Rather than engaging a single post-doctoral fellow for a two-year research training project, three trainees (one post-doctoral fellow and two graduate students) were involved in the project with some hiring lag between them, causing delays.

a. Janessa Manning. As originally budgeted, project was intended to be performed by a post-doctoral fellow under Dr. Fox's supervision. The post-doctoral fellow intended for this work was Janessa Manning, a UTHSCSA Radiological Sciences doctoral student at the time of grant submission. Dr. Manning worked on Task 1 (see below 3B. Research Tasks) for 6 months as a post-doctoral fellow, using funding from other sources. However, she was recruited away from us to Research Scientist position with the NIH/NICHD intramural program in Detroit Michigan, leaving the project without a post-doctoral fellow.

b. Mariam Ishaque. After Dr. Manning's departure, the vacated position was filled by Mariam Ishaque, an MD/PhD candidate (MS3/GS2). Ms. Ishaque (now Dr. Ishaque) worked on this project for 4 months. After a brief tenure on this project, Dr. Ishaque requested transfer to an ongoing project (also with Dr. Fox as PI) studying the effect of anoxic brain injury (ABI) due to pediatric drowning. This request was granted.

c. David Brown. After Dr. Ishaque's departure, the vacated position was filled by David Neal Brown. Mr. Brown has an MS in Clinical Psychology and has extensive clinical experience working with patients with ASD. Mr. Brown is a doctoral student in Clinical Neuropsychology at Fielding Graduate University, Dr. Fox is his supervising professor. Creating and validating a CBMA-based network model of ASD is his dissertation research project, necessary for him to receive his PhD degree.

3.B. Research Tasks. The UTHSCSA site had two research tasks. Task 1: develop a structural covariance model using CBMA of the VBM literature in ASD and validate in primary data. Task 2: develop a functional covariance model using CBMA of the task-activation literature in ASD and validate in primary data. In addition to these two hypothesis-based, disease-specific tasks, exploratory, transdiagnostic analyses were performed by trainees (doctoral students) which have bearing on this undertaking.

Task 1: Structural Covariance Model. Structural differences between ASD and healthy controls were identified using ALE, as reported by Nickl-Jockschat (et al., 2012). Structural covariance patterns were identified using meta-analytic connectivity modeling. Preliminary primary-data validation was performed by testing for between-group co-variance abnormalities in resting-state fMRI data obtained during natural nocturnal sleep in an in-house sample of 7 ASD children and 7 health controls. The findings are summarized in an as-yet-unpublished manuscript (Manning et al.; Appendix 1). The structural covariance model has not yet been applied to the larger samples of ASD patients available via our collaborators at UCSD (Dr. Courchesne) and Yale (Dr. Glahn).

Task 2: Functional Covariance Model. Functional differences (differences in task-activation patterns) between ASD and healthy controls were sought using ALE of the fMRI literature.

In preparation for the ALE meta-analyses performed for this task, a comprehensive review of the fMRI literature in ASD was performed. Comprehensive literature reviews were conducted with 54 suitable manuscripts being identified, coded and entered into the BrainMap database. This increased to total ASD fMRI literature in BrainMap from 70 to 124 manuscript, a 56% increase.

Using this literature, 19 ALE meta-analyses were performed, of which only one (Face Monitor/Discrimination) yielded significant results. In this ALE, 4 regions showed significant between-group differences. This work is summarized in an in-preparation manuscript (Brown et al.; Appendix 2). Meta-analytic connectivity modeling (node and edge modeling) for these regions has not yet been performed.

An important implication of this work is that – despite a reasonably large fMRI literature in ASD – the yield of replicable, disease specific functional abnormalities is extremely slim. Explanations for this negative finding include: primary studies being insufficiently statistically rigorous (per Eklund et al., 2015); variability in the choice of task-activation paradigms, resulting in an literature, with too few examples of each paradigm to yield a meaningful meta-analysis; variability in the implementation of each task-activation paradigm across laboratories; inhomogeneity in the patient selection criteria (per Muller et al., 2017 and Gray, in preparation). As described above, we are seeing lack-of-replicability in other disorders, particularly in the task-activation literature.

Exploratory Analysis 1: Transdiagnostic Structural-Functional Covariance Modeling. Because the volume of available manuscripts reporting neuroimaging findings in a manner compatible with BrainMap and ALE quality standards for any individual disorder is often limited -- particularly for VBM studies -- our laboratory has begun to explore transdiagnostic structural covariance modeling. Transdiagnostic network modeling employs VBM studies from multiple disorders to explore network properties that may be common across disorders, so long as they affect similar brain regions. An early example of this strategy is provided by Crossley et al. (2014). In our most recent work, we used region-seeded meta-analytic connectivity modeling (MACM) of the entire VBM database to extract disease-related (transdiagnostic) structural co-variance patterns, demonstrated their relationship to normal functional covariance patterns (by applying MACM to the functional sector of the BrainMap database), and then computing disease-specific loadings on this network (Kotkowski et al., 2018; Appendix 3). This transdiagnostic approach offers an alternative that we will continue to explore in ASD.

Exploratory Analysis 2: Transdiagnostic Structural Independent Components Analysis (ICA).

Independent components analysis (ICA) is a fully data-driven, voxel-wise, multivariate statistical technique for extracting higher-order, spatial latent variables from neuroimaging data. ICA has proven extremely well adapted for meta-analysis of the BrainMap functional database (Smith et al., 2009; Ray et al., 2013), but had not previously been applied to the BrainMap structural (VBM) database. In this exploratory analysis, we performed ICA on the VBM database, including all disorders with ≥ 10 peer-reviewed manuscripts, a total of 43 distinct disorders, including ASD. This transdiagnostic approach yielded robust structural-covariance networks each of which was common to (loaded upon) multiple disorders. It also provided a rank ordering of disorders by strength of loading on atrophy networks. In the rank-ordering of atrophy-causing disorders, ASD was near the bottom of the list. That is, the structural alterations observed in ASD were among the least consistent.

What opportunities for training and professional development has the project provided?

- a. This project provided 6 months of post-doctoral training in computational biology to Janessa Manning, Ph.D.
- b. This project provided 4 months of pre-doctoral training in computational biology to Mariam Ishaque, Ph.D.
- c. This project is serving as the doctoral dissertation research project for David Neal Brown

How were the results disseminated to communities of interest? Results were disseminated by coding data in the BrainMap database and by publishing manuscripts. See below, Products.

What do you plan to do during the next reporting period to accomplish the goals. This is the final report for this project.

4. IMPACT.

a. What was the impact on the development of the principal discipline(s) of the project? The largely negative results of these meta-analyses have not yet been reported. We anticipate that they will reinforce a growing impression that the neuroimaging literature in ASD is not sufficiently rigorous, sufficiently homogenous and sufficiently large to allow any strong conclusions about this disorder. This impression is in keeping with the weakness of the conclusions derived from mining primary data contained in the Autism Brain Imaging Data Exchange (ABIDE), which was recently replaced with ABIDE II, in an effort to increase the scope and rigor of available data.

The establishment of ABIDE I demonstrated the feasibility and utility of aggregating MRI data across sites. However, the complexity of the connectome, along with the substantial heterogeneity of Autism Spectrum Disorder (ASD) and initial results from ABIDE I data analyses underscore the need for even larger and better-characterized samples. Accordingly, with support of an award from the National Institute of Mental Health ([R21MH107045](#)), ABIDE II was established to further promote discovery science on the brain connectome in ASD.

For Clinical Neuropsychology, these findings should raise concerns diagnostic nosology.

b. What was the impact on other disciplines? The lack of convergence of neuroimaging findings in ASD mirrors that emerging in other psychiatric and developmental (but not neurological) disorders. Collectively, this will motive a move toward: 1) larger samples, 2) obtained using a smaller number of task-activation conditions and 3) in more homogeneously defined patient populations for neuroimaging studies.

c. What was the impact on technology transfer? The lack of findings by "conventional", within-disease CBMA approaches has stimulated the development of the transdiagnostic CBMA strategies as described in the exploratory analyses (above) and reported in Appendices 3 and 4. These strategies have been very favorably reviewed and we expect them to be widely adopted.

d. What was the impact on society beyond science and technology? ASD is a disorder very much in the public eye and the subject of much controversy, particularly as regards etiology. Neuroimaging has an extremely important role to play in clarifying the nature of this disorder and is a research modality the results of which are

widely reported in the lay press. While our studies have not contributed -- as yet -- to clarifying the nature of the disorder, they should increase public awareness of the difficulties inherent in research in ASD.

5. CHANGES/PROBLEMS. As discussed throughout this report, the meta-analyses were largely unproductive. We plan to report the negative findings. However, this observation agrees with our observations in other disorders (e.g. major depressive disorder) and with psychiatric and developmental disorders more generally. This has lead use to consider transdiagnostic approaches which do not assume that distinct clinical categories (clinical nosology) imply neurobiological differences, as discussed in the exploratory analyses, above.

6. PRODUCTS. Two types of product were created: data were coded into and shared via the BrainMap database; and, manuscripts were authors.

Data coded: Fifty-four (54) peer-reviewed, coordinate-based fMRI manuscripts comparing ASD patients to healthy controls were coded and entered into the BrainMap database. These (along with 70 other ASD fMRI papers and their data) are now publically available for use in meta-analyses.

Papers Authored.

- a. One manuscript (Manning et al.; Appendix 1) has been submitted for publication to two journals but was not accepted. It will be re-conceived, re-analyzed and re-written by Mr. Brown.
- b. One manuscript is in preparation (Brown et al., Appendix 2). This will be completed and submitted by Mr. Brown.
- c. One manuscript (Kotkowski et al; Appendix 3) has been accepted for publication. This manuscript reports an exploratory, transdiagnostic node-and-edge modeling approach that may prove useful for ASD as well as for other disorders.
- d. One manuscript (Vanasse et al.; Appendix 4) is in the 2nd round of review. This manuscript reports an exploratory, transdiagnostic ICA latent modeling approach that may prove useful for ASD as well as for other disorders.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS.

What individuals have worked on the project? The following individuals worked directly on this project. Other individuals worked indirectly on this project, particularly in exploratory analyses (described above in Section 3) testing alternative analytic pipelines. Although the work products of indirect participants are provided as appendices 3 and 4, these individuals were not funded by this project (being funded from other grants) and are not listed as participants.

Peter T Fox, MD (dedicated at 5% effort, 36 months) is the Principal Investigator (PI) (ORCID ID: 0000-0002-0465-2028) on this project. Dr. Fox is a neuroimaging researcher and neurologist at the University of Texas Health Science Center at San Antonio. He is a professor in the Department of Radiology with joint appointments in Radiology, Medicine, and Psychiatry and is the founding director of the Research Imaging Institute (RII), a department-level, research-dedicated component of the University of Texas Health Science Center at San Antonio.

Janessa Manning (dedicated at 50% effort, 6 months) was a post-doctoral trainee at UTHSCSA. She continued in this capacity until she left the RII and UTHSCSA on February 14, 2014, to pursue a position as an NIH Intramural Position as a Research Scientist, based at the Merrill Palmer Skillman Institute, Wayne State University. She produced a manuscript (Appendix 1) which has been submitted to two peer-reviewed journals, but has not been accepted for publication.

Mariam Ishaque (dedicated at 50% effort, 4 months) was a pre-doctoral student, enrolled in the dual degree M.D./Ph.D., with her graduate studies being in the Radiological Sciences Graduate Program at UTHSCSA. This was originally intended to be her dissertation project. However, she requested a transfer to another project, investigating anoxic brain injury in toddlers. She did not produce a manuscript.

David Brown (dedicated at 49% effort, 20 months) is a doctoral student in the Clinical Neuro-Psychology program at Fielding Graduate University. This project is intended to be his dissertation research. He has produced an in-preparation manuscript (Appendix 2).

Janaye Dews (dedicated at 50% effort, 12 months) is a Research Assistant who works as a coder in the BrainMap team which is tasked with maintaining the BrainMap database and ensuring new submissions to the database are entered in a timely fashion. Ms. Dews was responsible for ensuring that the articles identified by Mr. Brown met criteria for inclusion into the BrainMap database, as well as coding these articles into the database.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? No.

What other organizations were involved as partners? As per the original application, the other organizations involved as partners are Yale University (Dr. Glahn, P.I. at that site) and the University of California San Diego site (Dr. Courchesne, P.I. at that site).

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARD: This project is part of a Collaborative Award and this Progress Report is from the University of Texas Health Science Center San Antonio site (Fox, the overall project P.I.). Comparable progress reports from Dr. Glahn at Yale University and Dr. Eric Courchesne at University of California San Diego will be submitted separately.

9. APPENDICES: Four appendices are provided.

Appendix 1: Manning et al. A study of aberrant intrinsic connectivity networks in 2-4 year olds with Autism Spectrum Disorders: A natural sleep study.

Appendix 2: Brown et al. Coordinate-based Meta-analyses of the Task-activation Literature in Autism Spectrum Disorders.

Appendix 3: Kotkowski et al. (2018) The hippocampal network model: A transdiagnostic, metaconnectomic Approach. *NeuroImage Clinical* DOI 10.1016/j.nicl.2018.01.002.

Appendix 4: Vanasse et al. (in 2nd round of review) BrainMap VBM: An Environment for Structural Meta-analysis. *Human Brain Mapping*: in 2nd round of review.

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A study of aberrant intrinsic connectivity networks in 2-4 year olds with Autism Spectrum Disorders: A natural sleep study

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Grants: CDMRP Award W81XWH-14-1-0316 (PTF). NIH Awards: R01-MH074457 (PTF), P50-MH081755 (EC), R01-MH036840 (EC).

Abstract

Autism Spectrum Disorder (ASD) emerges in the first three years of life but few functional neuroimaging studies have included such young children. We aimed to use resting state connectivity mapping to investigate the early stages of ASD brain development.

Here, we mapped resting-state networks obtained during EEG confirmed Non-REM stage 3 natural sleep in seven ASD and seven age- and gender-matched typically developing (TYP) 2-4 year olds to determine if differences in functional connectivity could be detected in toddler and pre-school aged children. In each child, a 15-minute resting-state functional MRI (BOLD) was acquired. Region-of-interest (ROI) connectivity analyses were performed on the resting state. ROI selection was based upon previously published areas of anatomical abnormality in ASD adults.

ASD children showed deviant connectivity patterns when seeded in the Left Central Sulcus, Left Putamen, Right Caudate, Right Parietal Operculum, and Right Medial Temporal Lobe. In each instance, ASD patients connected more diffusely than TYP children.

Clusters of increased ASD connectivity were consistent with a frontal, temporal, cerebellar gradient in early brain overgrowth. We believe that mapping resting-state functional connectivity through a region-seeded approach may be a powerful means of elucidating the neural bases of early functional deficits in ASD and, eventually, in the early detection of toddlers at risk for this disorder.

Key words: Autism Spectrum Disorder, Functional Connectivity Magnetic Resonance Imaging, Resting State Networks, region-seeded analysis

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45 Autism Spectrum Disorder (ASD) represents a family of heterogeneous, pediatric onset,
46 neurodevelopmental disorders. ASD presents a group of symptoms including impaired social
47 communication and unusually restricted or repetitive interests. Prevalence rates for ASD have been
48 increasing and are now estimated to be approximately 1 in 88 children with 1 in 54 boys being affected
49 (Centers for Disease Control and Prevention, 2008).

50

51 While state-of-the-field university-based studies show detectable onset to be at 1 to 2 years, the
52 average age at first diagnosis is 4 years of age or later in most US cities (Centers for Disease Control and
53 Prevention, 2008; Pierce et al., 2011). Variability in the age of diagnosis is contributed by severity of
54 language symptoms (positive correlation) and parental socio-economic/ education levels (negative
55 correlations) (Fountain et al., 2011). Efficacious interventions that are initiated following diagnosis may
56 begin later than they could. High-quality early intervention is well established to improve long-term
57 cognitive functioning and developmental outcomes (Johnson et al., 2007). Functional neuroimaging
58 (fMRI), we suggest, has the as-yet-unrealized potential to lower diagnostic age by demonstrating
59 presence or absence of functional brain abnormalities in toddlers suspected to be at risk for ASD. The
60 purpose of the present paper is to suggest a strategy for realizing this potential.

61

62 Converging evidence supports that the neurological anomalies in ASD may preferentially impact frontal,
63 temporal, and cerebellar regions with relative sparing of parietal and occipital cortices. Islands of
64 laminar disorganization have been observed in prefrontal and temporal but not visual cortex in post-
65 mortem tissue of ASD patients (Stoner et al., 2014). Older ASD children fail to develop long-distance
66 connections between nodes during adolescence (Washington et al., 2014). Studies of functional

connectivity in ASD have found hypoconnectivity when compared to controls' networks (Mueller et al., 2011) but these findings may be methodologically driven. Hypoconnectivity findings in ASD adults and adolescents include disruptions in cortico-cortical connections (Anderson et al., 2011), cortico-cerebellar diminution (Olivito et al., 2016), and default mode network weakening (Strack et al., 2013). Utilizing a region-of-interest (ROIs) connectivity analysis strategy instead of whole brain connectivity mapping, allows for increased statistical power in small sample studies but requires careful selection of *a priori* loci. Referencing the clinical neuroimaging literature, especially meta-analyses, is one strategy with the potential to improve ROI selection.

In the present study, we applied a natural sleep based fMRI acquisition strategy to compare 2-4 year old children with ASD and typically developing controls (TYP) to one another (Manning et al., 2013). To provide greater spatial specificity than is achieved with Independent Components Analysis (ICA), we used an alternate analysis technique to detect connectivity differences. Namely, we developed ROIs in areas deemed to have a high probability of abnormal connectivity in ASD patients. We selected *a priori* areas, using all ROIs identified in a previous meta-analysis as structurally abnormal by Voxel Based Morphometry (VBM) in ASD (Nickl-Jockschat et al., 2012). Further bolstering our decision to use region-seeding, our high-probability regions included anatomy that is represented in several ICA identified Intrinsic Connectivity Networks (Smith et al., 2009). We then selected control ROIs by identifying areas not reported in the meta-analytic literature on ASD adults and therefore deemed to have a low probability of having abnormal connectivity in ASD populations (bilateral primary visual, motor, and somatosensory cortices). By using two ROI types, anatomically anomalous and control, we aimed to determine if aberrant connectivity effects were systemic or localized.

METHODS

Participants.

Children were recruited by advertisements posted in the medical center area, physicians, therapists and community service organizations. Twenty-three children with probable ASD were referred for the study, with UTHSCSA IRB approved informed consent being provided by a parent or guardian prior to evaluation. Two study candidates were ineligible due to MRI incompatibility. Of the 21 remaining candidates, 8 failed to obtain a diagnostic threshold using the Autism Diagnostic Observation Schedule (ADOS). ADOS scores for the remaining ASD candidates exceeded diagnostic thresholds for Communication (Module 1: a code of 2+; Module 2: a code of 3+) and Reciprocal Social Interaction (Modules 1 and 2: a code of 4+) as well as a total ADOS (Module 1: a total of 7+; Module 2: a total of 8+) (See Table 1.) Of the 13 who met ADOS diagnostic inclusion criterion, acquisition of structural and functional MRI data during natural sleep was successful in seven (4 males, 24-58 mos; Table 1). The other six ASD children were unable to fall asleep or maintain sleep during MRI acquisition.

TYP children were invited to participate in a case-control manner, with each TYP child being entered into the study as an age- and gender-matched control for an ASD child who had successfully completed image-data acquisition. Candidate TYP children were also evaluated with the ADOS. TYP children scored under the diagnostic thresholds for both language and social sub-categories. All seven ADOS-compliant TYP children (Table 1) were successfully imaged during natural sleep.

Sleep Induction and patient preparation.

Participants and families arrived at or after the child's usual bedtime for imaging sessions. For any given evening, only one participant was scheduled for imaging. On the day of imaging, participants were sleep

deprived, restricting naps as possible, within the parent's judgment of level of tolerance. Participants were brought to the Research Imaging Institute by one or both parents. Prior to imaging, participants were put to bed by their parent(s) in an adjacent room decorated to resemble a child's bedroom. Parents employed whatever procedures they felt would be most conducive to sleep, including bringing stuffed animals, reading, nursing, etc. Once the parent(s) determined that deep sleep was established, the child was transferred to the MRI suite and positioned on the scanner bed. Foam earplugs were inserted and MRI-compatible, carbon-fiber electrodes were placed on frontal and peri-orbital locations to monitor sleep stage. The head was aligned symmetrically about the mid-sagittal plane and lightly restrained using foam pads.

Image Acquisition.

MRI data were acquired using a research-dedicated, 3-Tesla, Siemens (Siemens Medical Solutions, Erlangen, Germany) TIM-Trio. The integrated circularly polarized body coil served as transmitter; a 12-channel head coil served as receiver. Imaging sessions varied in length, depending upon each child's sleep duration. Scans were obtained in prioritized order: anatomical images (T1-weighted images), then 15-minutes of resting-state blood oxygen level dependent (BOLD; T2*-weighted) images, and lastly, arterial spin-labeled (ASL) perfusion images (not reported here). T1-weighted images were acquired using the MPRAGE pulse sequence with TR/TE = 2200/2.72 ms, flip angle = 13°, TI = 766 ms, with 1mm³ voxel size. T2*-weighted resting-state BOLD images were acquired with TR/TE= 3000/30, flip angle = 90°, volumes = 300, 2x2x4 mm³ spatial resolution. Because the children in this study had smaller total head volume than adults in most studies, all acquisitions included whole brain, including whole cerebellum.

ROI creation.

Two categories of ROI were created: High-Probability for anomaly areas shown to feature robust structural aberrations in our adult ASD meta-analysis (Nickl-Jockschat et al., 2012) and control areas with a low probability of ASD anomaly (placed bilaterally in primary visual, somatosensory, and motor cortices) (see Table 2 for central voxel coordinates of all ROIs). Using Multi-image Analysis graphic user interface version 2.6 (rui.uthscsa.edu/MANGO) a 10 mm³ cuboidal ROI was build around the identified central voxels. Cuboidal ROIs likely contain a mix of cortical tissues. However, all signal change should be driven by BOLD changes in grey matter.

Image Analysis: Preprocessing and First-level Analyses.

Anatomical MRI scans were preprocessed using FMRIB's Brain Extraction Tool (Jenkinson et al., 2005). Resting BOLD scans were motion corrected. Both anatomical and Resting BOLD scans were transformed from native into Talairach space using FSL's Linear Image Registration Tool (Jenkinson et al., 2002). Using FEATQuery for each ROI, time-series of the cube-wide BOLD fluctuations were built for each subject. First-level analyses of ASD and TYP data provided a map of each subject's correlated BOLD fluctuation patterns for each ROI. To achieve this, individual resting BOLD scans were entered into FMRIB's FMRI Expert Analysis Tool Version 6.0. In the first-level analyses, the mean time-series, as previously calculated in FEATQuery, were used to calculate each subject's connectivity from ROI to whole brain using a high-pass filter cutoff of 60s. MCFLIRT motion correction, an automatic volume alignment program was used to correct the minimal motion that was present (Jenkinson et al., 2002). Brain extraction utilizing FSL's Brain Extraction Tool was conducted. The remaining, brain extracted, automatically aligned volumes were and spatially smoothed with a 5mm FWHM filter. Functional data were co-registered to each subject's anatomically extracted brain using a full search to correct for any orientation changes between scans. Lastly, FLIRT was used to transform data into standard Talairach

space utilizing a 6 parameter affine registration (Jenkinson & Smith 2001; Redcay & Courchesne, 2008).
Visual inspection of registrations was conducted on all cases to ensure goodness of match.

Higher-level analyses: Groupwise analyses.

Higher-level analyses provided us with group-wise contrasts between the ASD and TYP children for each ROI. To accomplish this, for each ROI, the 14 per-subject connectivity maps developed in the first-level analysis were re-entered and data were statistically pooled by group (ASD or TYP) for FEAT higher-level analyses. Overall, group-wise contrasts were calculated for ASD mean, TYP mean, ASD > TYP and TYP > ASD. All group-wise contrasts were calculated at $p \leq 0.01$, adjusted for multiple comparisons using cluster thresholding to identify groupings of voxels with significant connectivity ($p \leq 0.01$). Where significant areas of divergent connectivity were identified, cluster analyses were run on all clusters with a minimum volume of 100 mm³.

RESULTS

ASD and TYP children mean activations.

Motion in TYP scans was minimal, with mean relative displacement ranging from 0.05 to 0.1 mm (mean = 0.072 (0.012)). Motion in completed scans of ASD subjects was slightly greater than motion in TYP children, with mean relative displacement ranging from 0.04 to 0.22 mm (mean = 0.097 (0.063)). Motion was not statistically different between TYP and ASD groups. MCFLIRT was able to correct for the minimal motion that was present. Motion parameters observed during the sleeping pediatric scans were less than what is typically reported in adult subjects and within accepted motion parameters. For most high-probability ROIs, the pattern of connectivity was strikingly different for the ASD children (Figure 1, first panels). Broader connectivity patterns were observed in ASD children from high-probability ROIs .

182

183 **High-probability for divergence ROIs: ASD > TYP.**

184 ASD children had connectivity to significantly more areas than TYP children. From four of the six
185 anatomically atypical ROIs, additional areas of functional connectivity were observed ($p \leq 0.01$) in
186 connectivity patterns in ASD relative to TYP children. Contrasts showed significantly broader
187 connectivity from Left Central Sulcus (LCS), Right Medial Temporal Lobe (RMTL), Right Parietal
188 Operculum (RPO), and Right Caudate (RCau) in ASD children (Figure 1, middle panels). Cluster analyses,
189 run on the 9 areas of significant ASD > TYP divergence of at least 100mm^3 , identified 2 frontal, 2
190 temporal/ limbic, and 5 sub-cortical areas, 4 of which were cerebellar (Table 3). ICNs from Left Putamen
191 (LPut) and Right V5 (RV5) were not statistically different at $p \leq 0.01$. However, when thresholds were
192 reduced to $p \leq 0.05$, LPut did demonstrate broader networks in ASD than TYP children.

193

194 **High-probability for divergence ROI: TYP > ASD.**

195 When thresholds were relaxed to $p \leq 0.05$, two areas of ASD hypo-connectivity were seen. From the
196 RMTL and RV5, TYP children had areas of unique connectivity. At the relaxed, $p \leq 0.05$, threshold, from
197 the RMTL, TYP children had only 1 connected more to left pre-central gyrus, namely, an area in frontal
198 lobe. From RV5, TYP children connected more to areas in post-central gyrus and inferior parietal lobule,
199 both in parietal lobe.

200

201 **Low-probability for divergence ROIs.**

202 When contrasts were run at $p \leq 0.01$ & $k > 100$ control seeds showed no differences in connectivity
203 patterns. However, when thresholds were reduced to $p \leq 0.05$, ASD > TYP regions were noted from each

of the control seeds. At the relaxed $p \leq 0.05$ threshold, 3 TYP > ASD connectivity clusters emerged: 2 from RV5 and 1 from RMTL.

DISCUSSION

Using resting-state imaging during natural sleep ASD 2-4 year olds showed diffuse hyper-connectivity from four of six high-probability ROIs (RCau, LCS, RPO, and RMTL) while ASD under-connectivity was not observed. Furthermore, when we relaxed the statistical threshold, all six high-probability ROIs and all six low-probability control ROIs demonstrated ASD hyper-connectivity, while only two regions demonstrated ASD under-connectivity (RMTL and RV5). This indicates that toddlers and very young children with ASD have diffuse hyper-connectivity, but with some regional specificity which is consistent with structural abnormalities in ASD adults.

It appears that the seed-based connectivity patterns of very young children with ASDs do not show focal connectivity between expected regions but instead have abnormally broad connectivity among a wide spectrum of regions. Compared to TYP children, ASD children demonstrated unique regions of connectivity bilaterally in both cortical and subcortical regions. Hyper-connectivity was widespread but most evident in frontal, temporal/limbic, and subcortical areas including cerebellum.

Our data support the “failure to prune” theory of ASD causation (Courchesne et al., 2001; Courchesne & Pierce, 2005; Courchesne et al., 2007). Evidence suggests that brain growth aberration in ASD is not linear across whole brain (Carper et al., 2005). Early anatomical overgrowth is often observed in frontal and temporal areas (Courchesne, Webb et al., 2011) Parietal and occipital areas are less enlarged (Courchesne, Webb et al., 2011; Courchesne, Campbell et al, 2011; Di Martino et al., 2009). Cerebellar

hypoplasia is also reliably observed in young ASD children (Courchesne, Campbell et al, 2011). That some of our high-probability for divergence ROIs come from regions outside frontal-temporal-cerebellar regions is likely due to the inclusion, in the source meta-analysis, of adult anatomical findings. Notably, from our high-probability ROIs, ASD children had increased connectivity with regions that are most highly implicated at younger ages in aberrant cortical growth trajectories (frontal, temporal, cerebellar) not with regions less associated with overgrowth (parietal, occipital). In fact, of the 9 clusters to which ASD children showed increased connectivity, 2 were frontal, 2 were temporal/ limbic, and 5 were subcortical including 4 cerebellar clusters. It appears that regions linked to anatomical differences in ASD toddlers also have hyper-connectivity patterns.

ASD > TYP and TYP > ASD differences.

ASD toddlers had diffuse activations when seeding was done at four of the six high probability of deviation areas. We observed areas that, when compared to TYP toddlers, ASD toddlers had greater connectivity from RCau, LCS, RMTL, and RPO areas. It appears that ASD 2-4 year olds demonstrate hyper-connectivity. It was striking that TYP children had no areas with greater connectivity than ASD. When statistical thresholding was relaxed, areas of TYP > ASD connectivity from RMTL and RV5 emerged as did ASD hyper-connectivity from the other two seeds, LPut and RV5.

Hyper-connectivity from 4 of 6 high-probability ROI's suggests that, while ASD children's networks included nodes that should be present, their networks also included nodes that should not be present, especially in frontal, temporal, and cerebellar regions. Seemingly, young children with ASDs associate both appropriate and inappropriate brain regions, resulting in disorganized connectivity networks. Hyper-connectivity in ASD may persist into late childhood (Nomi & Uddin, 2015).

Sleep Imaging.

Despite the clear importance of imaging ASD at young ages when the disorder first emerges and imaging ASD across the spectrum of impairment, most researchers continue to image a truncated range of age and functional ability, namely older high functioning ASD patients (Di Martino et al., 2009). This is because functional imaging typically requires immobile, compliant research subjects who can do an experimental task as directed; these papers often misleadingly call their preadolescents and adolescents “children”. To date there are only 3 published fMRI studies of ASD infants and toddlers (Dinstein et al., 2011; Eyler et al., 2012; Redcay et al., 2008).

By imaging ASD and TYP toddlers and infants during natural sleep, we were able to obtain interpretable resting-state connectivity MRI data. In the case of pediatric sleep imaging, the primary advantage of ICN mapping over more traditional fMRI is that research participants do not need to engage in any task for network connectivity to be investigated. The naturally high arousal threshold of toddlers allowed MRI data acquisition to be done without waking the children. We were able to get at least 300 volumes from each child with some providing 900 (45 minutes of resting-state EPI). Our small sample of sleeping toddlers was able to provide statistically-significant, high-quality data that were in agreement with the existing ASD neuropathology literature.

Traditional fMRI tasks in ASD toddlers have involved processing of language presented through headphones (Eyler et al., 2012; Redcay et al., 2008). Deficit areas other than receptive language are more challenging to investigate with auditory tasks during natural sleep. Consequently, while functional sleep imaging broadens the pool of potential research subjects from those able to stay still and comply

with a task, it is unable to investigate many areas of functional anomaly. Resting-state ICNs are task independent. We initially attempted independent components analysis mapping ($d=20$) but no between-group differences emerged. It is possible that with a larger sample or longer scans such differences might appear. ICN mapping, however, is sufficiently flexible and powerful that it can be used to investigate connectivity in many patient populations from *a priori* regions dependent upon the deficit of interest. By using region-seeding instead, we were able to maximize statistical power and demonstrate robust results despite the small sample size.

Limitations.

The primary limitation of this study is sample size. Data collection was attempted with many more children and they were unable to sleep in the scanner. Consequently this group of ASD subjects may represent a subset of ASD children for whom sleep is less problematic. Increasing the sample size may yield sufficient power to allow for analysis of particular symptoms and impairment ranges or for Independent Components Analysis with no need for *a priori* ROIs. Our cuboidal ROIs likely include both grey and white matter tissue. More sophisticated ROI development may increase specificity of the findings. Further, because of the smaller head size of the pediatric subjects, full cerebellar volume was included in all scans. Some cerebellar restriction is common in historic studies of adults, those that would be included in meta-analytic reviews. Consequently, when comparing network connectivity patterns in ASD toddlers to that of adults, or when developing ROIs from adult meta-analysis, care must be exercised because of potential field-of-view differences.

Future directions.

Given the small sample studied here, additional, confirmatory work with a larger ASD sample would be useful. As cerebellum emerged in the cluster analysis as frequently connected in ASD but not TYP, we believe that inclusion of cerebellum as an ROI might yield additional information about the nature and breadth of ASD hyper-connectivity. Additionally, it is likely that at least some resting state networks have a developmental trajectory (Manning et al., 2013). Future work should be able elucidate the expected trajectory in healthy children by acquiring data from more children and including age as a regressor. It may then be feasible to detect which networks follow an atypical trajectory in ASD and other developmental disorders. Furthermore, it will be important for future studies to examine whether therapeutic interventions that change clinical outcome shift ICN profiles.

ROIs developed from atypical VBM data demonstrated atypical connectivity from 4 of 6 locations at a rigorous statistical level. While all low probability ROIs demonstrated atypical connectivity patterns when threshold was relaxed, none survived the more demanding cutoff. Given the increase in sensitivity to functional connectivity differences that can be obtained by targeting ROIs based upon anatomical aberration, we believe this is a promising strategy both for ASD and other developmental disorders. There was strong agreement between the anatomical literature and our findings. Regional overgrowth likely occurs in areas that have hyper-connectivity and vice-versa. DTI, as a surrogate for white matter tract tracing, might be able to identify areas that are hyper- or hypo- connected. Investigating white matter abnormalities may lead to additional *a priori* ROIs.

Imaging Biomarker Development

Of particular importance is the development of sensitive and specific biomarkers of ASD that would increase diagnostic confidence in infants at risk for ASD. Unfortunately, because the majority of the

previous work in brain imaging has been in adults, the observed differences at those older ages are a mixed signal comprised of neurological differences that may have lead to ASD as well as differences that may have resulted from atypically engaging the environment for decades. Differences found in ASD adults will not necessarily be present in ASD children. Adult based VBM, however, can be helpful in narrowing the possible regions of investigation. By starting with high-probability ROIs we were able to test for anomalous connectivity and find differences from most regions. Pediatric ICN mapping provides the potential for the development of a reliable imaging biomarker that can assist clinicians in the early diagnosis of ASD. However due to the heterogeneity of ASD, subgrouping by behavioral phenotype may prove more useful for eventual biomarker development. Additionally, ICN mapping of sleeping infants, toddlers, and young children has the potential to be applied to a wide-range of neurodevelopmental disorders.

ACKNOWLEDGEMENTS.

This work was supported by pilot grants funds from: The Research Imaging Institute Utilization Review Committee (MRI126) and The Palmaz Endowment (Pilot award 48004). *JM* was supported by Translational Science Training (TST) Across Disciplines program at the University of Texas Health Science Center at San Antonio, with funding provided by the University of Texas System's Graduate Programs Initiative (128223), and the Kronkosky Foundation. PTF was supported by NIH grants MH074457, MH084812 and RR024387. EC was supported by NIMH Autism Center of Excellence grant P50-MH081755 and NIMH R01- MH036840.

We thank Elizabeth King, Robert Vargas, and Reagan Costello-White for assistance with participant preparation and data collection. We thank Crystal Franklin for training in data analysis. We thank Any Baby Can of San Antonio for assistance with recruitment of ASD participants.

CONFLICTS OF INTEREST.

The authors have no conflicts of interest to report.

Table 1. Ages, genders, and ADOS scores of ASD and TYP participants. ADOS scores reflect Communication and Social Interaction subtotal on the ADOS-R. Participants with asterisks were administered module 1. Determination regarding whether to administer Module 1 or 2 module was based upon verbal use.

Table 1.

<u>ASD (TYP)</u>	
Age (months): Gender	ADOS
26 (29): M	13 (1)
30 (24): F	21 (3)
31 (35): M	18 (3)
39 (37): M	13 (2)
52 (53): F	12 (0)
54 (56): F	11 (0)
58 (58): M	13 (0)

Table 2. Central voxel and anatomic label of seeded regions. A 10 mm³ ROI was built around the central voxel in high-probability for divergence areas(*) and control/ low probability for divergence areas. Connectivity, as measured by correlated BOLD changes, from the cubic ROI was calculated.

Table 2.

Seeded regions	Center voxel
R V5*	42, -60, -2
L Pericentral Sulcus*	-32, -39, 54
R Caudate*	6, 16, 3
R Parietal Operculum*	29, -11, 21
R Medial Temporal Lobe*	36, -22, -5
L Putamen*	-25, 4, 4
L Primary Motor Cortex	-49, -8, 44
R Primary Motor Cortex	49, -8, 44
L Primary Somatosensory Cortex	-31, -32, 54
R Primary Somatosensory Cortex	32, -32, 53
L Primary Visual Cortex	-15, -95, 1
R Primary Visual Cortex	19, -96, -1

Table 3. Central voxel and anatomic label of significantly different clusters. Clusters of ASD > TYP sorted by ROI and total volume ($p \leq 0.01$; cluster volume minimum = 100mm^3).

Significantly different			
ROI seed	cluster location	Volume (mm^3)	Center Voxel
RCau	Cerebellum	18801	5, -62, -33
	Caudate	4101	14, 13, -7
LCS	Inferior FG	5218	5, 59, 32
	Superior FG	104	-9, 67, 10
RMTL	Cerebellum	6278	14, -73, -36
RPO	Mid Temporal G	18206	62, -36, -12
	Cerebellum	5891	15, -57, -38
	Limbic	5735	-21, -15, -6
	Cerebellum	108	12, -38, -31

Figure Legend.

Figure 1. ASD, TYP, and ASD > TYP connectivity sorted by ROI. Mean connectivity ($p \leq 0.01$) by group showing ASD (blue, first panels) TYP (red, third panels) and ASD > TYP (green, middle panels) when seeded from L Central Sulcus, R Caudate, R Medial Temporal Lobe, and R Parietal Operculum respectively. Seeds in the L Putamen and R V5 did not demonstrate significant between group differences. Slices include the centroid for the largest cluster and are presented in neurological orientation. No areas had TYP > ASD connectivity ($p \leq 0.01$).

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Coordinate-based Meta-analyses of the Task-activation Literature in Autism Spectrum Disorders.

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Keywords: Autism, Autism Spectrum Disorder, ASD, meta-analysis, fMRI activation likelihood estimation, ALE.

Acknowledgements: CDMRP Award W81XWH-14-1-0316 (PTF). NIH Awards: R01-MH074457 (PTF).

ABSTRACT

The primary objective of this report was to perform coordinate-based meta-analyses (CBMA) using activation likelihood estimation (ALE) on the task-activation functional MRI (fMRI) literature in Autism Spectrum Disorders (ASD) to determine whether, where and under what task conditions reliable difference could be identified between persons with and without ASD. ALEs were performed in accordance with current recommendations for statistical methods and best practices. ALEs were computed for nineteen contrasts, all but one of which showed no reliable differences between ASD patients and healthy controls. Face Monitoring was the only condition in which reliable, between-condition abnormalities in task-induced activation were observed. Brain regions implicated were right Fusiform Gyrus (occipital and temporal lobes), right Superior Temporal Gyrus, and left Posterior Lobe of the cerebellum.

METHODS

A functional map of the brain associated with specific activation tasks will be created using meta-analysis. Existing studies will be mined for fMRI data to establish functionally connected seed regions of interest. Statistical parametric imaging (SPI) and Activation Likelihood Estimates (ALE) will be employed. This will be done using the BrainMap™ database at the UT Health Science Center under the direction of Dr. Peter Fox.

Data Extraction.

In order to conduct meta-analysis on fMRI studies relating to ASD, three hundred peer-reviewed papers were extracted from the PubMed database. These papers were the total available studies containing patients diagnosed with Autism Spectrum Disorder; these encompassed various activation tasks or experimental conditions (e.g. Oddball Discrimination, Go/No-go, Delayed Match to Sample, Face Monitor/Discrimination, etc.). This set of papers was screened to determine eligibility for inclusion in the BrainMap™ database, those criteria being the following: human neuroimaging papers, published in English-language peer-reviewed publications, that were based on whole-brain, voxel-wise imaging and analysis and reporting coordinate-based results in a standard space. Once screened, there were 24 remaining papers that met criteria. These were entered into the BrainMap™ database.

This process was repeated, and a set of 41,836 peer-reviewed publications, accessed from the PsychInfo database, was filtered down to 30 publications that met criteria. Further filtering was done to parse these studies by activation tasks. A significant amount of time was spent aligning experimental conditions to ensure that studies were appropriately comparable for meta-analysis. The final result of both searches increased the number of available ASD studies in the BrainMap™ database by 56%; from 70 to 124 articles.

The activation tasks that dominated the literature were face-processing tasks. We were able to divide studies using face-processing tasks into face tasks involving emotion and face tasks involving passive face identification. These groups were large enough to perform meta-analysis using ALE calculations.

RESULTS

Overview of ALE Meta-Analyses

As seen in Table 1, it was not feasible to do meta-analyses using a standard ALE method for the majority of activation tasks. The over-arching reason for so many null results is the small number of studies performed in each domain of interest. As well, many of the studies published use very small sample sizes, which creates confounds in generalizability. Further, the small sample sizes of studies hinder adequate statistical power and validity.

ALE Meta-analysis on fMRI studies using Face Processing Tasks Involving Emotion

As seen in Table 2, found four statistically significant regions of interest (ROI) in the ASD group using emotion-based face processing tasks. We found eight statistically significant ROIs in the healthy control group using emotion based face-processing tasks. Contrast analysis revealed that between healthy controls and ASD subjects, there were three significant ROIs that overlapped during emotion-based face-processing tasks and three distinct ROIs activated in healthy controls but not in ASD subjects.

Examining studies using passive viewing based face tasks, we found two statistically significant ROIs in the ASD group and we found eleven statistically significant ROIs in the healthy control group. Contrast analysis revealed two overlapping ROIs between healthy controls and ASD subjects. Contrast analysis further revealed that there are two statistically significant ROIs, which are activated in ASD subjects and not healthy controls, and there are two statistically significant ROIs, which are activated in healthy controls and not ASD subjects under passive face-viewing conditions. **The initial exploratory analysis is seen in Table 1 and the centroid clusters as well as descriptive statistics for each contrast can be seen in the subsequent tables and figures at the end of this document.**

The specific conditions under which each ALE analysis was conducted can be found in appendix A. The studies, which contributed to specific foci of significance, can be found in appendix B.

DISCUSSION

It became evident early in the process that whole brain fMRI studies on individuals with ASD were disproportionately concentrated on face tasks. This is likely due to researchers pursuing topics, which are centered on known effects, giving their study the strong likelihood of finding results. There are two problems with this approach. First, clinical observations suggest that there are many more deficits in functional connectivity than just deficits in facial recognition. Second, structural and functional deficits in the fusiform gyrus, involved in face processing tasks, are sensitive but not specific to classification of pervasive developmental disorders. Models based solely on face processing tasks can only yield binary results of neurotypical or not neurotypical as non-normal fusiform gyrus function and morphology cuts across diagnostic

categories. The studies performed thus far have not lead to a body of knowledge, which is comprehensive enough to perform fMRI meta-analyses.

The data available through peer-reviewed published studies presents many challenges. However, the failure of ALE meta-analytic techniques on this particular domain is not the end of the project. The BrainMap™™ database contains 3294 published papers utilizing 73235 subjects. These represent 112 activation tasks across 75 diagnostic categories. This produces 126,641 data points (coordinates). Across the body of literature many studies have small sample sizes and spurious effect sizes. However, the combination of peer review and careful curation of the BrainMap™ database, gives us confidence that the data is relevant and based on sound methodology. By taking the entire data set of coordinates, we can achieve statistical power for analysis.

When reduced, the activation tasks filtered by low control conditions, gives us the activations of task condition versus baseline. When further filtered so the diagnoses include only one diagnosis per data point, we obtain a data set of 68,814 data points. The characteristics of this data set present great challenges for analyses. The data is not normally distributed, there are mismatched sample sizes per condition, and there are underrepresented diagnoses and/or conditions. These characteristics make many of the common statistical analytic techniques inappropriate for use. However, machine-learning algorithms show great promise for handling data with these characteristics. I am currently coding a deep learning artificial intelligence algorithm that will serve as the predictive model that we initially had hoped to build through ALE and MACM techniques. Proof of concept models have been promising the progress on coding the algorithm in python/TensorFlow continues at a steady pace.

Overview of ALE Meta-Analyses

Table 1

ALE Meta-analyses Were Attempted on Studies Involving Subjects Identified as having ASD, Asperger's Syndrome, or High-functioning Autism on Following Activation Tasks

Activation Task	Findings	Reason for Findings
Face Monitor/Discrimination	Feasible	Significant Findings
Film Viewing	Null	Not Stat SIG
Finger Tapping/Button Press	Null	Not Stat SIG
Flanker	Null	Not Stat SIG
n-back	Null	Not Stat SIG
Passive Listening	Null	Not Stat SIG
Passive Viewing	Null	Not Stat SIG
Pitch Monitor/Discrimination	Null	Not Stat SIG
Reasoning/Problem Solving	Null	Not Stat SIG
Rest	Null	Not Stat SIG
Semantic Monitor/Discrimination	Null	Not Stat SIG
Sleep	Null	Not Stat SIG
Stroop-Counting	Null	Not Stat SIG
Stroop-Emotional	Null	Not Stat SIG
Theory of Mind	Null	Not Stat SIG
Video Games	Null	Not Stat SIG
Visual Motion	Null	Not Stat SIG
Visuospatial Attention	Null	Not Stat SIG
Word Generation (Overt)	Null	Not Stat SIG

Table 2

Regions of Interest Found by Meta-Analysis of Studies involving Face-processing with ASD and Healthy Control Subjects

Activation Task	Analysis Grouping	Number of ROIs
Emotion-based Face Task	ASD	4
	Healthy Control	8
	Contrast HC>ASD	3
	Contrast ASD>HC	0
	Conjunction	3
Passive Viewing Based Face Task	ASD	2
	Healthy Control	11
	Contrast HC>ASD	2
	Contrast ASD>HC	2
	Conjunction	2

ASD Subjects using Face Processing Tasks Involving Emotion

Table 3

Centroid Clusters Found in Studies using ASD Subjects for fMRI Face-processing Tasks Involving Emotion

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 4	0.021925123	36	-73	-9	Right Cerebrum	Occipital Lobe	Fusiform Gyrus
Cluster 2 of 4	0.012915934	40	-55	16	Right Cerebrum	Temporal Lobe	Sup Temporal Gyr
Cluster 3 of 4	0.014799966	-39	-56	-15	Left Cerebellum	Posterior Lobe	Declive
Cluster 4 of 4	0.018372348	34	-48	-15	Right Cerebrum	Temporal Lobe	Fusiform Gyrus

Table 4

Descriptive Statistics for Centroid Clusters Found in Studies using ASD Subjects for fMRI Face-processing Tasks involving Emotion

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 4	0.014462284	20.95584949	0.003368323	1449	1449
Cluster 2 of 4	0.012952438	8.678133257	0.001704941	670	670
Cluster 3 of 4	0.012563825	8.141358558	0.001770714	648	648
Cluster 4 of 4	0.013281105	8.114755212	0.002059487	611	611

Table 5

Centroid Clusters Found in Studies using Healthy Control Subjects for fMRI Face-processing Tasks involving Emotion

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 8	0.067872094	19	-5	-9	Right Cerebrum	Limbic Lobe	Parahippocampus
Cluster 2 of 8	0.027352347	36	-61	-13	Right Cerebrum	Posterior	
Cluster 3 of 8	0.085201254	-21	-5	-11	Cerebellum	Lobe	Declive
					Left Cerebrum	Limbic Lobe	Parahippocampus
						Temporal	
Cluster 4 of 8	0.027864022	-42	-58	-13	Left Cerebrum	Lobe	Fusiform Gyrus
Cluster 5 of 8	0.023619759	47	13	26	Right Cerebrum	Frontal Lobe	Mid Frontal Gyrus
							Med Frontal
Cluster 6 of 8	0.031477987	0	52	3	Right Cerebrum	Frontal Lobe	Gyrus
						Temporal	Sup Temporal
Cluster 7 of 8	0.031658747	-51	-54	7	Left Cerebrum	Lobe	Gyr
Cluster 8 of 8	0.034568602	8	-52	27	Right Cerebrum	Limbic Lobe	Cingulate Gyrus

Table 6

Descriptive Statistics for Centroid Clusters Found in Studies using Healthy Control Subjects for fMRI Face-processing Tasks involving Emotion

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 8	0.034803041	222.3566301	0.01316367	6389	6389
Cluster 2 of 8	0.028545188	155.6569125	0.007374002	5453	5453
Cluster 3 of 8	0.039981781	206.2260267	0.016169308	5158	5158
Cluster 4 of 8	0.026797505	90.49517479	0.005110585	3377	3377
Cluster 5 of 8	0.022987505	49.03234842	0.002238733	2133	2133
Cluster 6 of 8	0.026830074	42.76713819	0.004282879	1594	1594
Cluster 7 of 8	0.02513206	15.23002822	0.003510269	606	606
Cluster 8 of 8	0.026253477	14.93822857	0.003775043	569	569

Table 7

Descriptive Statistics for Centroid Clusters Found in Healthy Controls but not in ASD Subjects for fMRI Face-processing Tasks involving Emotion

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 3	2.134800236	4542.854902	0.61228564	2128	2128
Cluster 2 of 3	2.236855666	4048.708756	0.662883922	1810	1810
Cluster 3 of 3	1.893760815	1293.438636	0.629490671	683	683

Conjunction of ASD and Normal Subjects using Emotion-based Face Processing fMRI Tasks

Table 8

Centroid Clusters Found in Both Healthy Controls and ASD Subjects for fMRI Face-processing Tasks involving Emotion

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 2	0.013159479	36	-59	-12	Right Cerebellum	Posterior Lobe	Declive
Cluster 2 of 2	0.002894194	-39	-63	-15	Left Cerebellum	Posterior Lobe	Declive

Table 9

Descriptive Statistics for Centroid Clusters Found in Both Healthy Controls and ASD Subjects for fMRI Face-processing Tasks involving Emotion

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 2	0.013513544	52.20281892	0.003721877	3863	3863
Cluster 2 of 2	0.012123673	19.85857634	0.002961349	1638	1638

Contrast of Healthy Controls > ASD using Emotion-based Face Processing fMRI Tasks

Table 10

Centroid Clusters that are Active in Healthy Controls but not in ASD Subjects during fMRI Face-processing Tasks involving Emotion

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 3	2.5491575	0	53	2	Left Cerebrum	Frontal Lobe	Med Frontal Gyrus
Cluster 2 of 3	2.847963333	19	-8	-16	Right Cerebrum	Limbic Lobe	Para-hippocampus
Cluster 3 of 3	2.582873344	-24	6	-11	Left Cerebrum	Frontal Lobe	Subcallosal Gyrus

Meta-Analysis of fMRI studies using Passive Viewing Face Tasks with ASD and Healthy Subjects

Table 11

Passive Viewing Face Tasks with ASD Subjects. Centroid Clusters Found in ASD Subjects for fMRI Face Processing Tasks Involving Passive Viewing

Cluster	Value	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 2	0.013159479	36	-59	-12	Right Cerebellum	Posterior Lobe	Declive
Cluster 2 of 2	0.011979814	-37	-62	-14	Left Cerebellum	Posterior Lobe	Declive

Table 12

Descriptive Statistics for Centroid Clusters Found in Studies of ASD subjects for fMRI Face-processing Tasks involving Passive Viewing

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 2	0.014288512	50.49560315	0.003197737	3534	3534
Cluster 2 of 2	0.013265406	23.02874415	0.002238552	1736	1736

Table 13

Descriptive Statistics for Centroid Clusters Found in Studies using Healthy Controls for fMRI Face-processing Tasks involving Passive Viewing

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 8	0.035339418	364.5967759	0.014906349	10317	10317
Cluster 2 of 8	0.036350898	332.6107154	0.015033061	9150	9150
Cluster 3 of 8	0.025699871	121.4318895	0.005634875	4725	4725
Cluster 4 of 8	0.034013501	113.5030522	0.012624947	3337	3337
Cluster 5 of 8	0.036962989	122.3474921	0.014863261	3310	3310
Cluster 6 of 8	0.024275614	50.34762359	0.004207237	2074	2074
Cluster 7 of 8	0.027644055	37.84471179	0.00629148	1369	1369
Cluster 8 of 8	0.024742845	28.28107128	0.005096761	1143	1143
Cluster 1 of 8	0.035339418	364.5967759	0.014906349	10317	10317
Cluster 2 of 8	0.036350898	332.6107154	0.015033061	9150	9150
Cluster 3 of 8	0.025699871	121.4318895	0.005634875	4725	4725
Cluster 4 of 8	0.034013501	113.5030522	0.012624947	3337	3337
Cluster 5 of 8	0.036962989	122.3474921	0.014863261	3310	3310
Cluster 6 of 8	0.024275614	50.34762359	0.004207237	2074	2074
Cluster 7 of 8	0.027644055	37.84471179	0.00629148	1369	1369
Cluster 8 of 8	0.024742845	28.28107128	0.005096761	1143	1143

Table 14

Centroid Clusters Found in Healthy Control Subjects for fMRI Face-processing Tasks involving Passive Viewing

Centroid	ALE	X	Y	Z	Hemisphere	Lobe	Region
Cluster 1 of 8	0.042513127	37	-58	-14	Right Cerebellum	Posterior Lobe	Declive
Cluster 2 of 8	0.037815968	-40	-59	-15	Left Cerebellum	Posterior Lobe	Declive
Cluster 3 of 8	0	40	16	21	Right Cerebrum	Frontal Lobe	Mid Frontal Gyrus
Cluster 4 of 8	0.060722576	-21	-6	-11	Left Cerebrum	Limbic Lobe	Parahippocampus
Cluster 5 of 8	0.079494085	20	-6	-11	Right Cerebrum	Limbic Lobe	Parahippocampus
Cluster 6 of 8	0.026413429	1	11	51	Right Cerebrum	Frontal Lobe	Sup Frontal Gyrus
Cluster 7 of 8	0.04382704	31	-54	42	Right Cerebrum	Parietal Lobe	Sup Parietal Lob
Cluster 8 of 8	0.031601854	-41	6	30	Left Cerebrum	Frontal Lobe	Inf Frontal Gyrus

Conjunction of ASD and Normal Subjects using Emotion-based Face Processing fMRI Tasks involving Passive Viewing

Table 15

Centroid Clusters Found in Both Healthy Control Subjects and ASD Subjects for fMRI Face-processing Tasks involving Passive Viewing

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 2	0.013159479	36	-59	-12	Right Cerebellum	Posterior Lobe	Declive
Cluster 2 of 2	0.002894194	-39	-63	-15	Left Cerebellum	Posterior Lobe	Declive

Table 16

Descriptive Statistics for Centroid Clusters Found in Both Healthy Controls and ASD Subjects using fMRI Face-processing Tasks involving Passive Viewing

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 2	0.013513544	52.20281892	0.003721877	3863	3863
Cluster 2 of 2	0.012123673	19.85857634	0.002961349	1638	1638

Contrast of Healthy Controls > ASD using Face Processing fMRI Tasks involving Passive Viewing

Table 17

*Descriptive Statistics for Centroid Clusters Found in Healthy Controls but not ASD
Subjects using fMRI Face-processing Tasks involving Passive Viewing*

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 2	2.032840717	3307.431846	0.60913892	1627	1627
Cluster 2 of 2	1.990276828	1522.561774	0.631526645	765	765

Contrast of ASD > Healthy Controls using Face Processing fMRI Tasks involving Passive Viewing

Table 18

Centroid Clusters Found Activated in ASD Subjects but not Healthy Controls for fMRI Face-processing Tasks involving Passive Viewing

Cluster	ALE	X	Y	Z	Hemisphere	Lobe	ROI
Cluster 1 of 2	2.526053309	3	12	52	Right Cerebrum	Frontal Lobe	Sup Frontal Gyrus
Cluster 2 of 2	2.890951633	22	-7	-13	Right Cerebrum	Limbic Lobe	Parahippocampus

Table 19

Descriptive Statistics for Centroid Clusters Found in ASD Subjects but not Healthy Controls using fMRI Face-processing Tasks involving Passive Viewing

Description	Mean	Sum	SD	Size (mm)	Voxels
Cluster 1 of 2	2.017333362	3294.305381	0.600033243	1633	1633
Cluster 2 of 2	2.032179218	1566.810177	0.667864155	771	771

Figure 1. Healthy Control Subjects Using Face-processing Tasks Involving Emotion

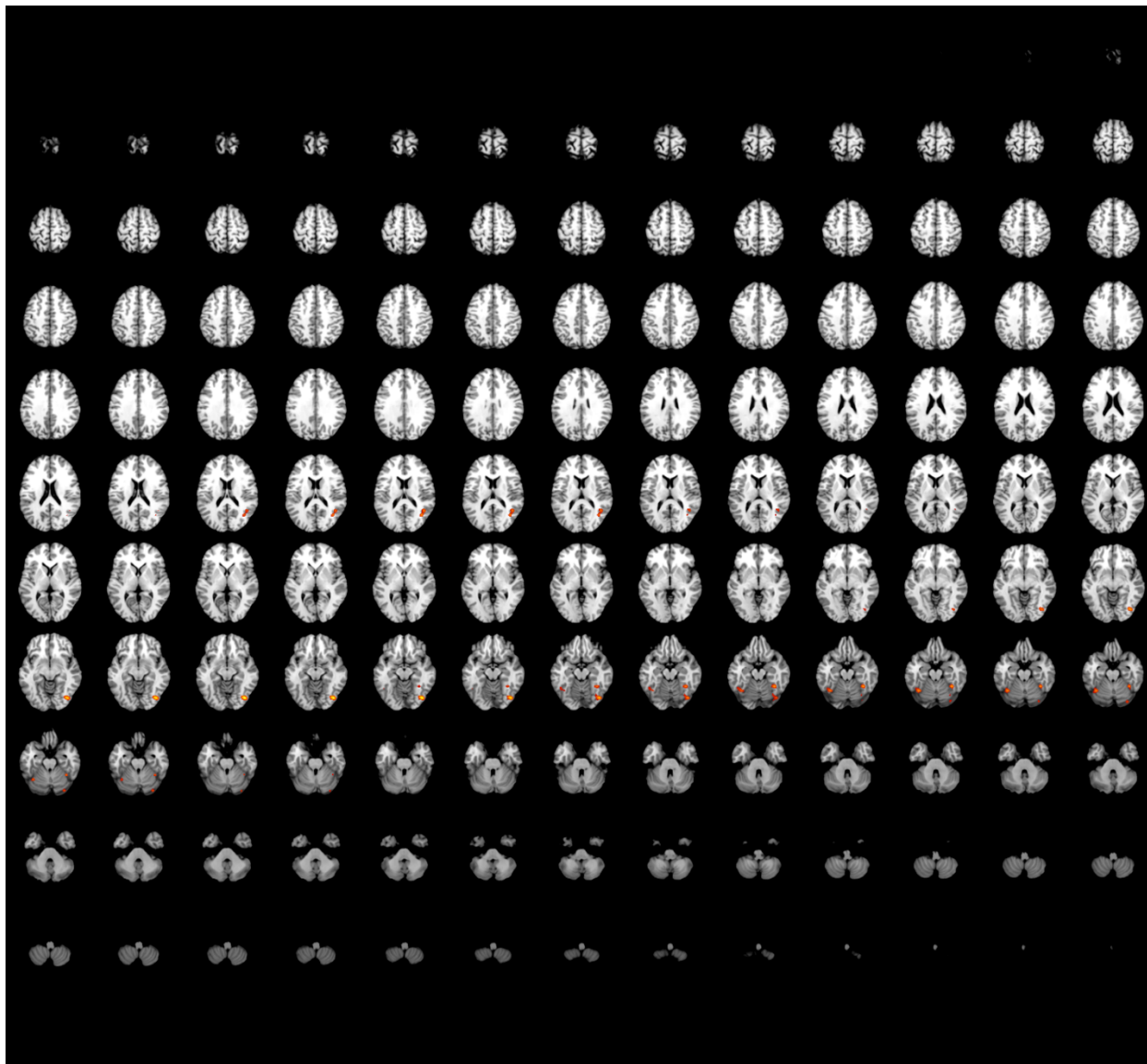


Figure 2. Contrast of ASD and Normal Subjects using Emotion-based Face-processing fMRI Tasks: Areas that are active in ASD Subjects but not in Healthy Controls. There were no areas active in ASD subjects, which were not active in Healthy Control Subjects in fMRI studies using emotion-based face-processing tasks.

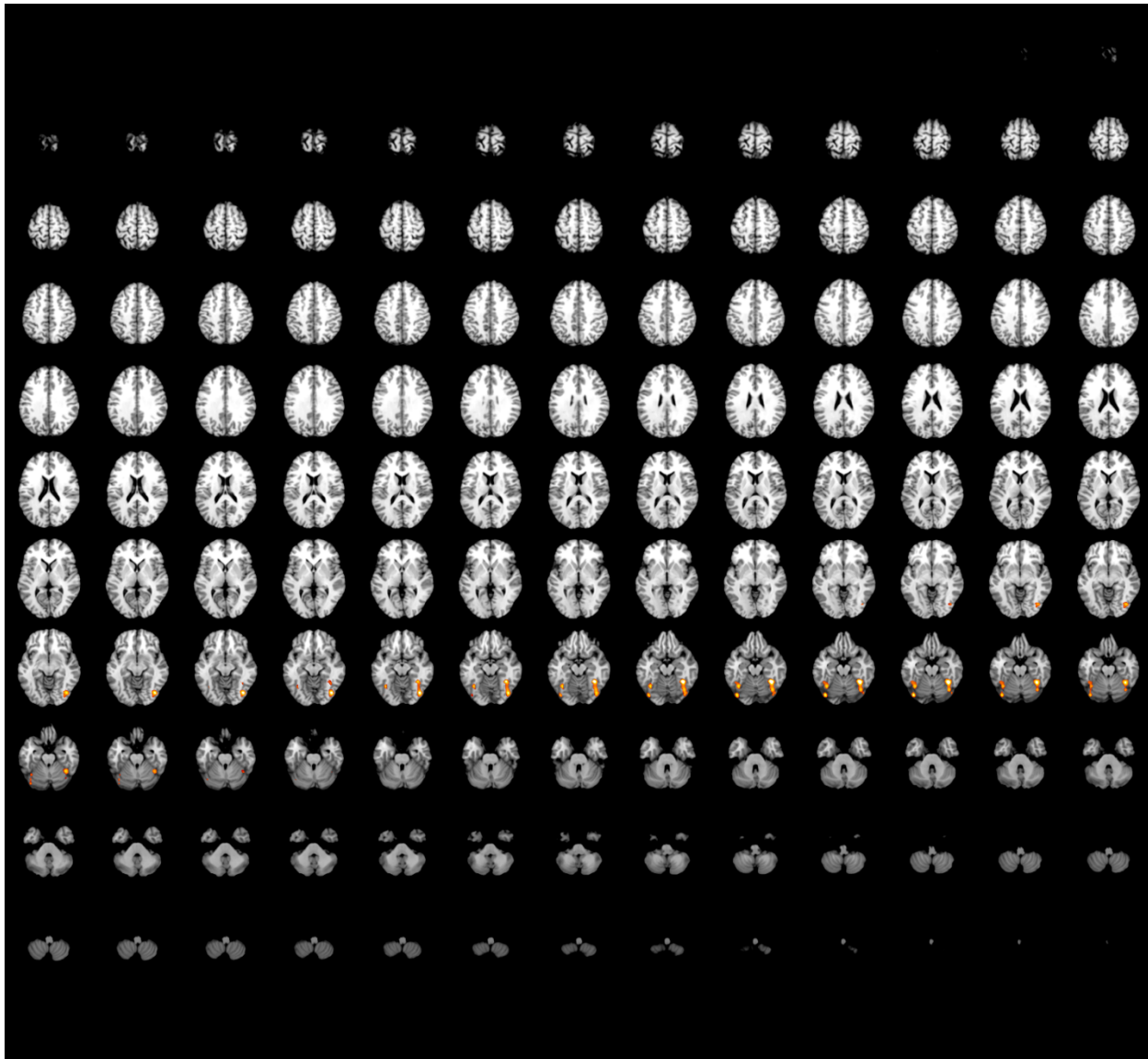


Figure 3. Contrast of Normal and ASD Subjects using Emotion-based Face Processing fMRI Tasks: Areas, which are active in Healthy Controls but not in ASD Subjects

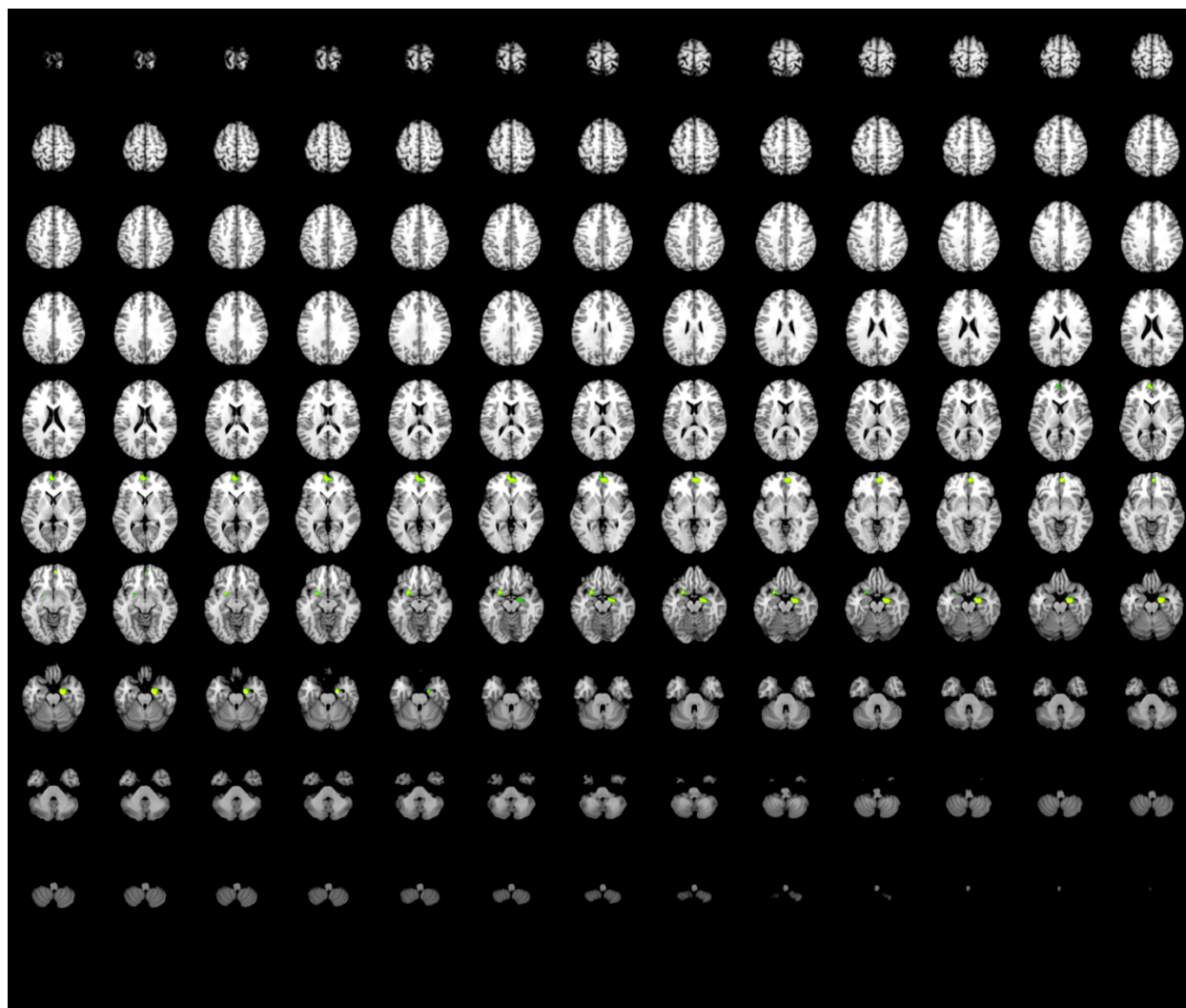


Figure 4.

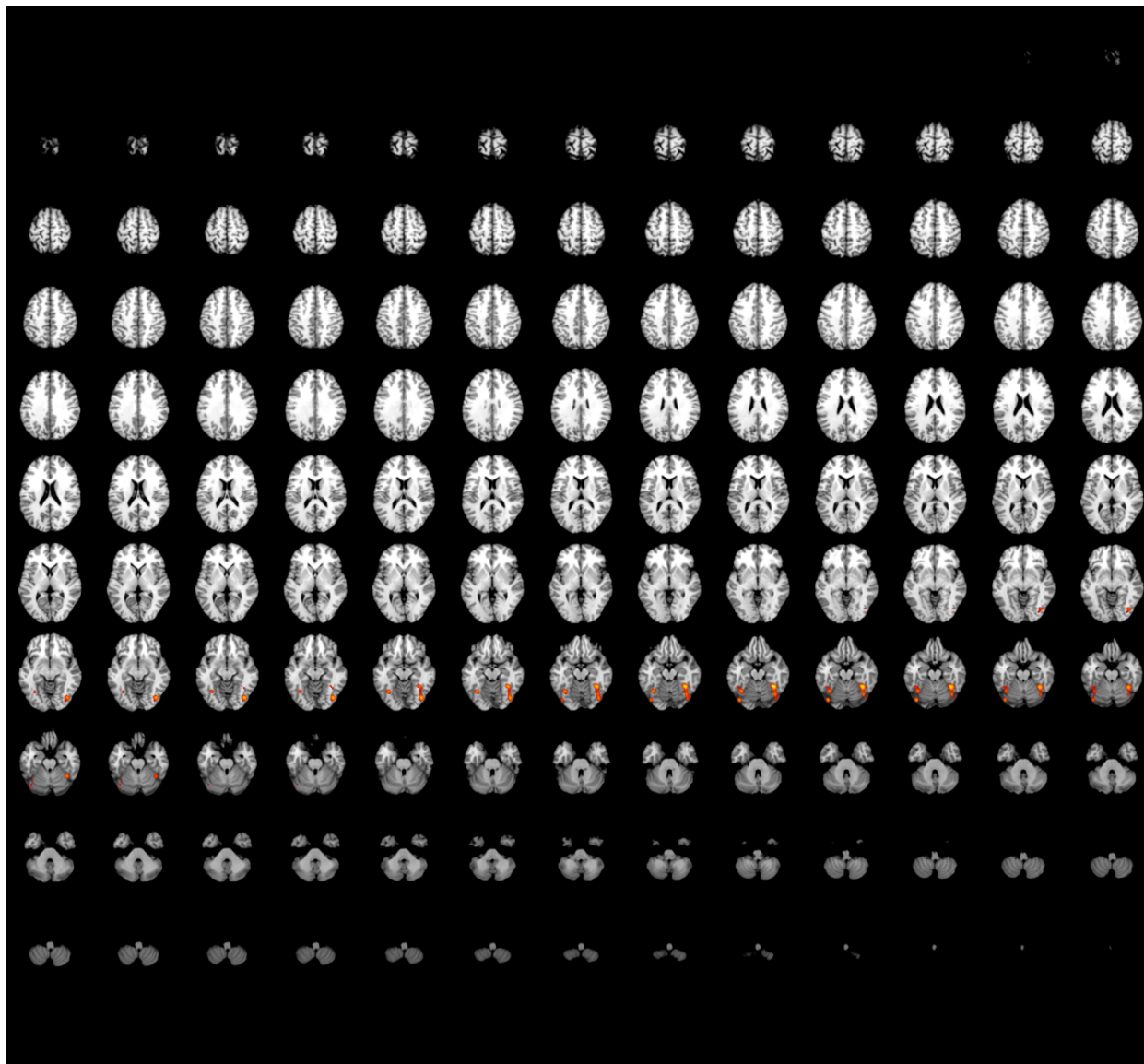


Figure 5.

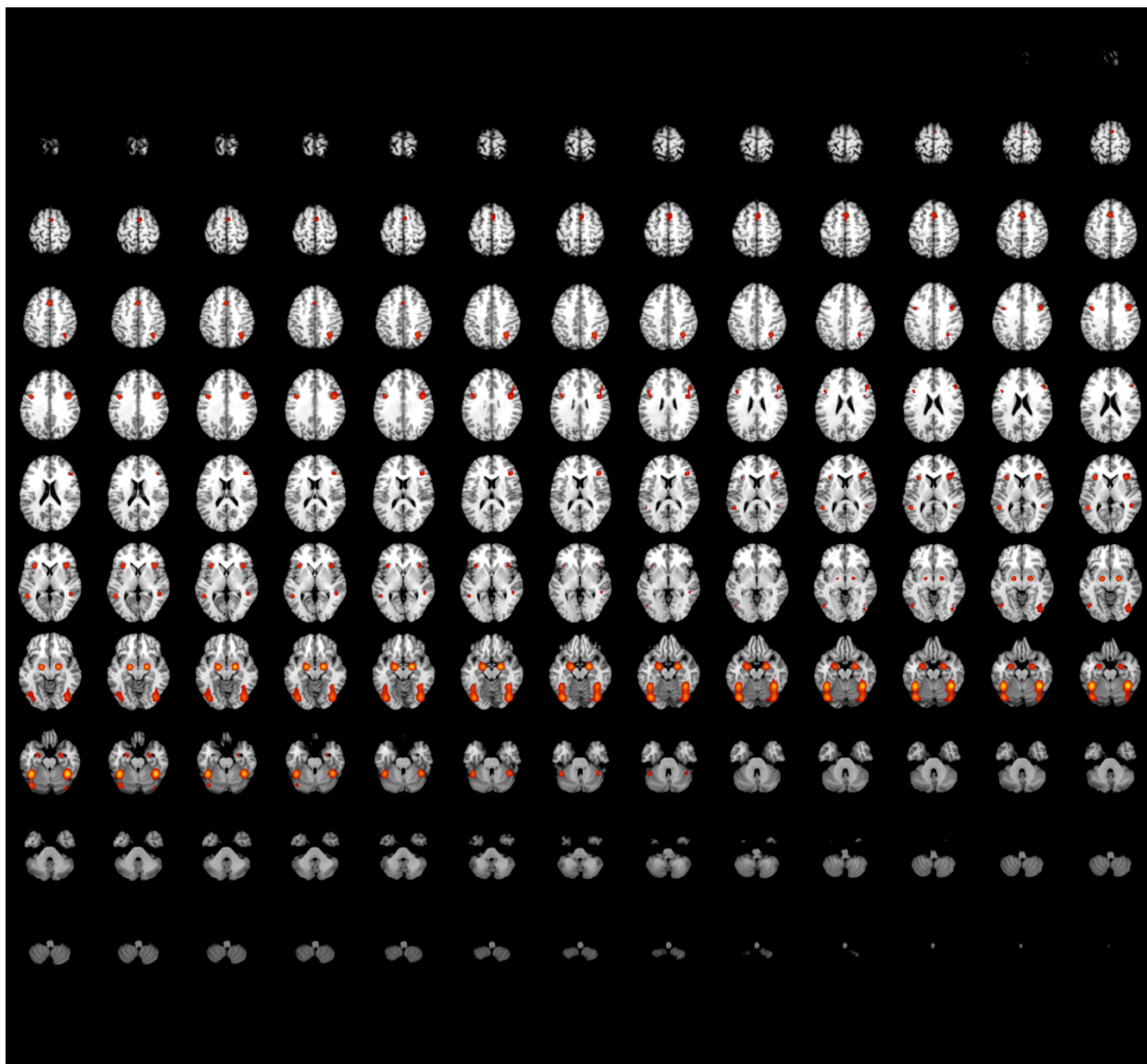


Figure 6. Contrast of Normal and ASD Subjects Using Passive Viewing Based Face Processing fMRI Tasks: Areas that are active in ASD Subjects but not Healthy Controls

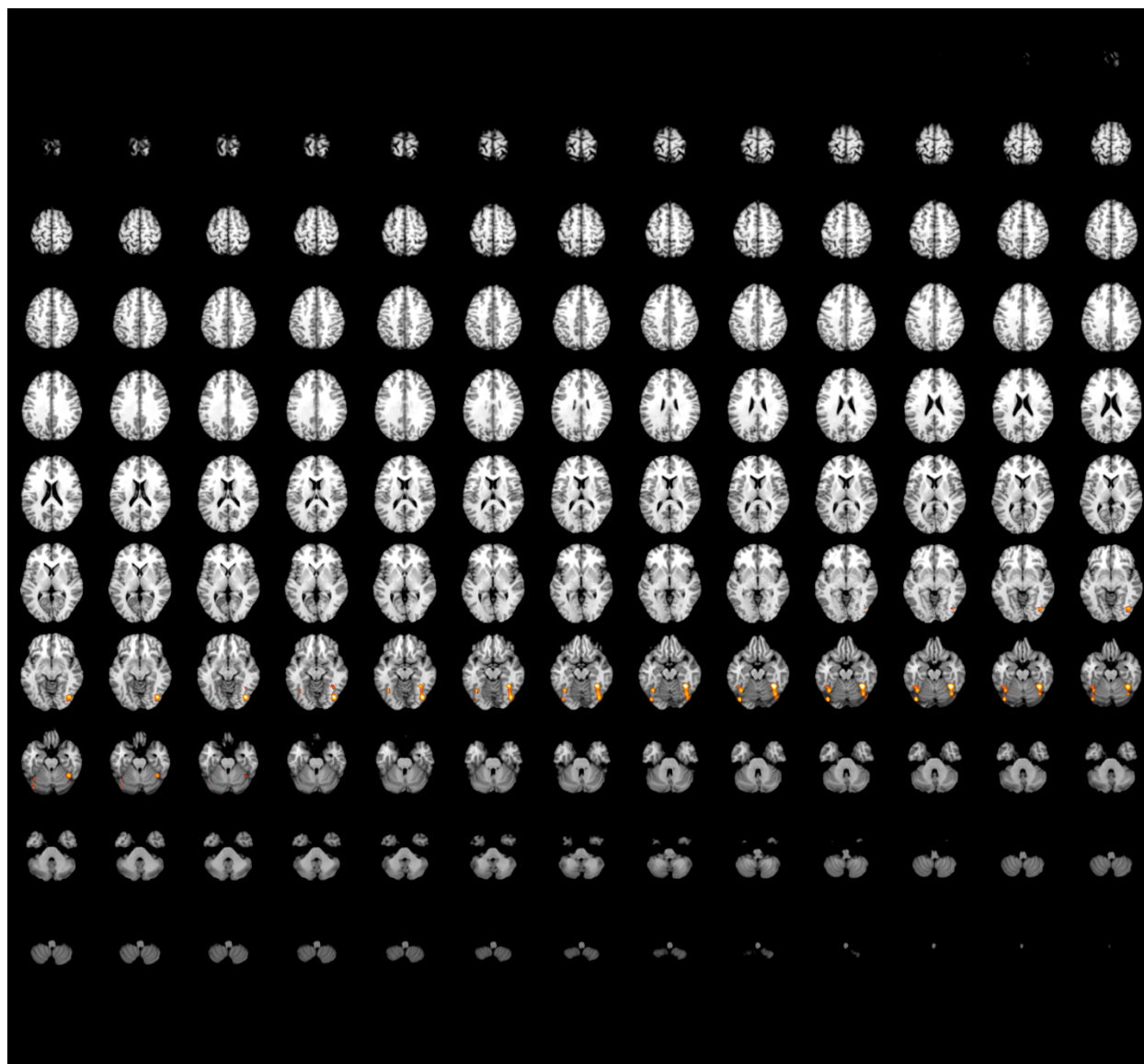


Figure 7.

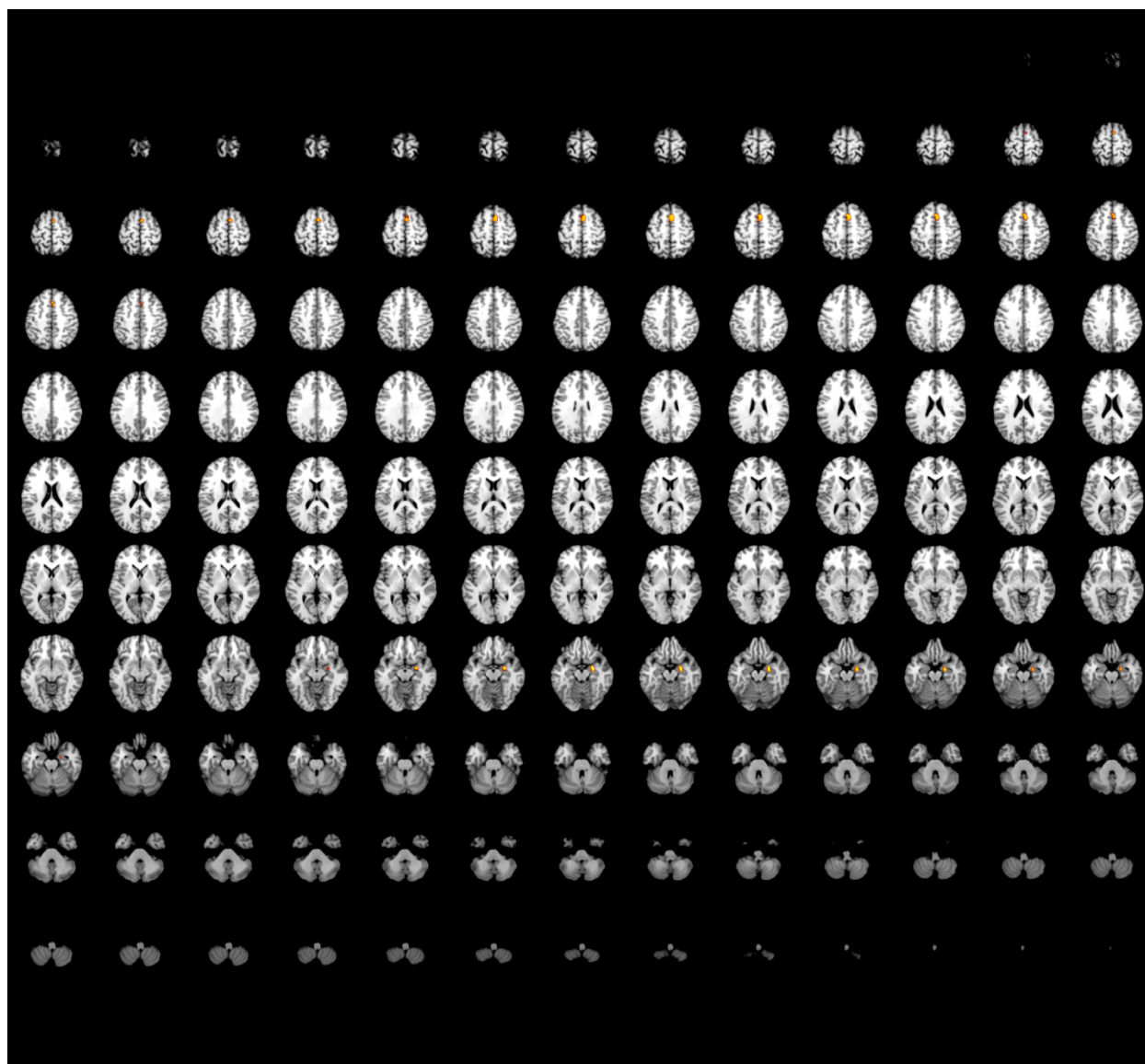
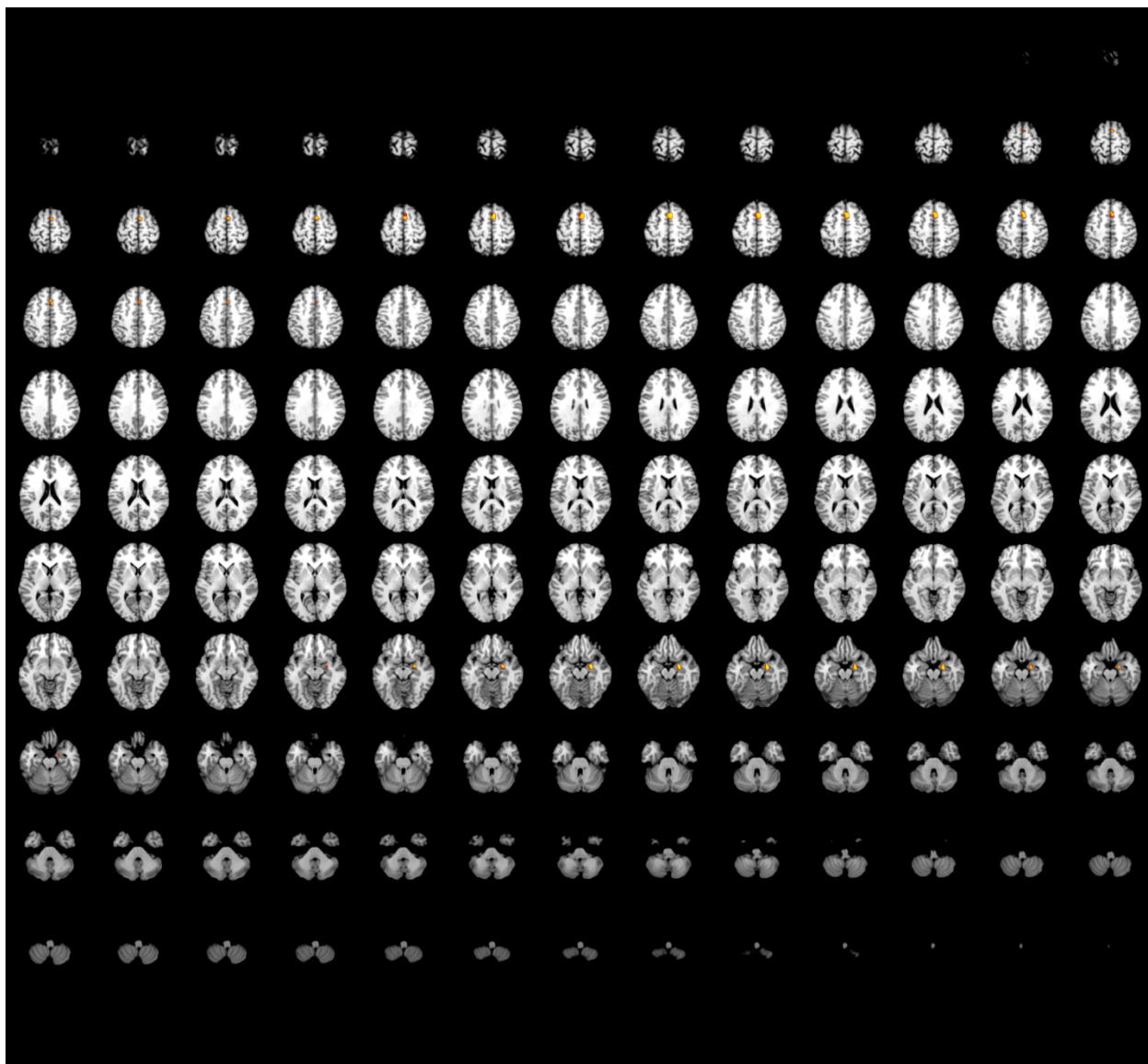


Figure 8.



The Hippocampal Network Model: A Transdiagnostic Metaconnectomic Approach

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Number of Text Pages: 19

Text word count: 6371

Figures: 8 **Number of Pages:** 7

Tables: 6 **Number of Pages:** 3

Key Words: Anatomic Likelihood Estimation, ALE, BrainMap, Functional Covariance, Functional MRI, Gray Matter Density, Hippocampal Network Model, Hippocampus, Magnetic Resonance Imaging, MRI, Meta-Analysis, Meta-Analytic Connectivity Modeling, MACM, Structural Covariance, Structural MRI, Voxel-Based Morphometry, VBM.

ABSTRACT

Purpose: The hippocampus plays a central role in cognitive and affective processes and is commonly implicated in neurodegenerative diseases. Our study aimed to identify and describe a hippocampal network model (HNM) using trans-diagnostic MRI data from the BrainMap® database. We used meta-analysis to test the network degeneration hypothesis (NDH) (Seeley et al., 2009) by identifying structural and functional covariance in this hippocampal network.

Methods: To generate our network model, we used BrainMap's VBM database to perform a region-to-whole-brain (RtWB) meta-analysis of 269 VBM experiments from 165 published studies across a range of 38 psychiatric and neurological diseases reporting hippocampal gray matter density alterations. This step identified 11 significant gray matter foci, or nodes. We subsequently used meta-analytic connectivity modeling (MACM) to define edges of structural covariance between nodes from VBM data as well as functional covariance using the functional task-activation database, also from BrainMap. Finally, we applied a correlation analysis using Pearson's r to assess the similarities and differences between the structural and functional covariance models.

Key Findings: Our hippocampal RtWB meta-analysis reported consistent and significant structural covariance in 11 key regions. The subsequent structural and functional MACMs showed a strong correlation between HNM nodes with a significant structural-functional covariance correlation of $r = 0.377$ ($p = 0.000049$).

Significance: This novel method of studying network covariance using VBM and functional meta-analytic techniques allows for the identification of generalizable patterns of functional and structural abnormalities pertaining to the hippocampus. In accordance with the NDH, this framework could have major implications in studying and predicting spatial disease patterns using network-based assays.

1. INTRODUCTION

The hippocampus is arguably the most well studied sub-cortical region in both humans and animals due in large part to its functional role in the cognition of learning and memory. When compromised, symptoms of hippocampal dysfunction are distinguished by impairments in memory, attention, emotion, spatial navigation, and executive function. Pathologically, hippocampal disease is characterized by neuronal degeneration progressing to structural atrophy detectable by magnetic resonance imaging (MRI), as in the cases of Alzheimer's disease (AD) (Schröder & Pantel, 2016), mild cognitive impairment (MCI) (Huijbers et al., 2014), mesial temporal lobe epilepsy (MTLE) (Mumoli et al., 2013), and schizophrenia (Radulescu et al., 2014). In terms of network topology, the hippocampus has been characterized as a hub, exhibiting structural covariance with multiple other brain regions, in keeping with its central role in multiple cognitive processes. It has been suggested that metabolic demands of hubs make such structures selectively vulnerable to neuropsychiatric diseases (Goodkind et al., 2015; Crossley et al., 2014), arguing for converging structural and functional network abnormalities. Advances in resting state functional MRI (fMRI) and sophisticated meta-analytic methodologies have allowed researchers to exhaustively map and quantify functional covariance networks (Fox and Raichle, 2007; Smith et al., 2009; Crossley et al., 2013). Nevertheless, our understanding of the relationships between functional and structural networks in the human brain, as can be studied using MRI, remains in its infancy. In 2009, Seeley et al., postulated the “network degeneration hypothesis” (NDH), which predicts that disease atrophy patterns should recapitulate healthy functional network architecture with recent studies beginning to address this question in the context of disease-specific network changes (Lefort-Besnard et al., 2018). Our aim in this study was to test the NDH meta-analytically and trans-diagnostically using the hippocampus as the central hub, thereby creating a hippocampal network model (HNM) that should be applicable in multiple neuropsychiatric and systemic disorders.

Structural and functional connectivity are two procedurally distinct, but conceptually linked constructs, both exhibiting network properties. Functional connectivity networks can be extracted by functional covariances, either at rest or during task performance, and exhibit interconnected sets of brain regions that interact to perform specific perceptual, motor, cognitive, and affective functions (Bressler & Menon,

2010). Structural covariance networks are inferred from inter-regional morphometric covariances across subjects (e.g. gray matter atrophy, cortical thinning). The notion that structural covariance is fundamental to functional network connectivity is based on the expectation that functional processes can exert trophic influences that, over time, modify gray matter volume enough to be detected as structural covariance patterns (Seeley et al., 2009; Gong et al., 2012). Multiple competing and converging hypotheses have been put forward to explain disease-related structural covariance, these include: 1) transneuronal spread, 2) nodal stress, 3) trophic failure, and 4) shared vulnerability (Zhou et al., 2012). For this reason, structural covariance has been extensively studied in the characterization of neurocognitive development (Alexander-Bloch et al., 2013; Lerch et al., 2006), aging (Marstaller et al., 2015; Montembeault et al., 2013), and in neurodegenerative disorders (Seeley et al., 2009; Spreng and Turner, 2013). The NDH suggests a close relationship between structure and function whereby abnormalities in structural covariance, functional covariance and behavior will be mutually predictive in brain disorders.

Meta-analytic computation of functional covariance is well-established (Smith et al., 2009; Crossley, et al., 2013). In assessing functional connectivity networks, activation likelihood estimation (ALE) is an extensively validated technique used in meta-analyses that pools 3D coordinates in stereotactic space from a number of like studies applied to functional task-activation studies (Laird et al., 2005; Turkeltaub et al., 2012). It achieves this by analyzing voxel-wise, univariate effects across experiments and generates a probability distribution centered at the respective coordinates. A natural extension of ALE, meta-analytic connectivity modeling (MACM) is a study-wise multivariate approach used to generate functional covariance networks from activation patterns reported across a range of experimental neuroimaging tasks and paradigms (Laird et al., 2009a; Robinson et al., 2010; Eickhoff et al., 2010a). In MACM, an ALE score is generated for every voxel, which are then converted into *P* values to identify areas of significance with scores higher than empirically-derived null distributions (Turkeltaub et al., 2012; Laird et al., 2005; Eickhoff et al., 2012). This technique has been found to correspond well with numerous mathematical computational formalisms including seed-based resting state (Jiang, et al., 2015), independent components analyses (Smith, et al., 2009), and graph theory (Crossley et al., 2013). Although MACM and ALE have been validated and replicated considerably in functional studies and, recently, using structural

data (Langner et al., 2014; Reid et al., 2017), the present study aims to adopt these methods for investigating structural covariance using a meta-analytical and trans-diagnostic approach with VBM.

Voxel-based morphometry (VBM) is a widely-used technique to identify subtle, disease-related structural changes that cannot be easily observed on visual analysis. VBM achieves this by standard space brain registration and group-averaging, comparing gray matter densities between patients and controls, producing disease-specific atrophy patterns computed in a univariate, voxel-wise manner. VBM studies have reported regional gray matter atrophy and hypertrophy patterns in thousands of peer-reviewed publications spanning over one hundred diseases. Indeed, VBM studies constitute a large body of quantitative literature reporting a vast number of areas of focal structural change in the brain (Ashburner & Friston, 2000). Coordinate-based reporting and whole-brain coverage are *sine qua non* for meta-analysis; VBM meets both criteria. Using VBM, then, meta-analytic methods 1) can compute convergent patterns of atrophy and hypertrophy in a cross-study manner; 2) can compute structural covariance network, using between-study, co-atrophy patterns. The multiple reports of VBM studies conducted within diseases and across diseases using a standardized coordinate space makes it well suited for coordinate-based meta-analytic structural covariance analyses studies (Glahn et al., 2008; Fox et al., 2014; Crossley et al., 2015).

A transdiagnostic approach, as opposed to disease-specific, for studying structural covariance networks can most readily be achieved through meta-analysis. In recent years, a growing literature of transdiagnostic neuroimaging has been used in the meta-analytic investigation of neuropsychiatric pathology. Numerous reports indicate that diseases of the brain tend to exhibit patterns of convergence, both structurally and functionally (Seeley et al., 2009; Crossley et al., 2013; Goodkind et al., 2015; McTeague et al., 2016). This new approach – grouping studies by neurobiological effects rather than by diagnostic category – corresponds closely to the Research Domain Criteria (RDoC) initiative set forth in 2010 to “create a new kind of taxonomy for mental disorders by bringing the power of modern research and approaches in genetics, neuroscience, and behavioral science to the problems of mental illness.” (Insel, et al., 2010). Clinical and neurobiological data has also suggested that psychiatric disorders are more comorbid than previously thought. They share common imaging and genetic markers, and

demonstrate alterations across neural networks that mediate cognition and other mental processes (Etkin and Cuthbert, 2014). Moreover, there is much interest and support within the neuroscience community in leveraging large brain imaging databases for the purpose gaining deeper insight into neuroscientific phenomena (Crossley et al., 2016; Bzdok et al., 2017).

BrainMap (Fox et al., 1994; Fox and Lancaster, 2002) is a neuroimaging database of published neuroimaging experiments with coordinate-based results in standard space. Its collection of functional task-based activation and structural gray matter atrophy enables investigators to study human brain function and structure in healthy and disease subjects meta-analytically. Its functional database currently contains 3,197 functional publications spanning over one hundred paradigms with 15,834 experiments and 69,727 subjects. Additionally, the VBM database contains 993 publications spanning over one hundred diseases with 3,150 experiments and 75,709 subjects (Laird et al., 2011; Laird et al., 2009b). In our study, we utilized MACM, a study-wise multivariate method to assess covariance across structural networks using BrainMap's VBM transdiagnostic literature (Eickhoff et al., 2010b). Previously, MACM has been used to investigate functional covariance between brain regions that are functionally connected across task-activation experiments (Fox et al., 2005a; Robinson et al., 2010; Laird et al., 2013). To our knowledge this paper is the first to employ MACM to generate a structural covariance model using BrainMap's transdiagnostic VBM database. In our endeavor to test the NDH, we believe that using the MACM method is well suited to investigate anatomic/activation likelihood estimate correlations found between structural and functional covariance models.

In this study, we computed a structural covariance model of the hippocampus – the HNM – beginning with a region-to-whole brain trans-diagnostic VBM meta-analysis (also known as a single-seed MACM analysis). We identified 11 significant nodes using a rigorous voxel-level family-wise error (FWE) of 0.01. These 11 nodes of interest were then re-seeded into the BrainMap database as standardized spherical ROIs to generate two MACM models: 1) structural covariance (significant regions of gray matter density changes), from the VBM database, and 2) coactivation (significant blood-oxygen level dependency signal changes in task studies), from the functional database in the form of ALE values and *P* statistics. We hypothesized that using MACM, nodes derived from our RtWB meta-analysis will reveal covariance

patterns in the form of edges for both structural and functional covariance analyses. Finally, in accordance with the NDH, we postulated that our data-driven meta-analytic structural and functional covariance models generated from the HNM will show a significant degree of concordance.

2. MATERIALS & METHODS

2.1. Region-to-Whole Brain (RtWB) Meta-Analysis:

The BrainMap VBM database included, at the time the experiment was conducted, a total of 980 VBM studies comprising 3091 experiments and 74,013 subjects and spanning a total of 143 different ICD-10 codable neurological and psychiatric diseases (supplementary table 1) as well as 23 non-ICD-10 classifications. We searched this database for papers reporting hippocampal gray matter alterations using a region-based approach, with the hippocampus as the region of interest. Hippocampal volumetric masks, including both anterior and posterior sections of the hippocampus, were derived from the Harvard-Oxford Structural Probability Atlas (Jenkinson, 2012) and subsequently binarized and transformed into Talairach space for further analysis. The VBM database was searched using BrainMap's Sleuth 2.4 software (Fox et al., 2005b) to identify voxel-wise associated clusters with the hippocampal volumetric seed across all VBM studies (search performed on 15 April 2017). Sleuth search: Locations → Talairach Image is Binarized Hippocampus Volume Mask; Experiments → Contrast is Gray Matter (Fig. 1). The search criteria included experiments with gray matter contrast and locations found to co-occur with the binarized hippocampal volumes. Although the vast majority of VBM studies address changes in the form of gray matter atrophy (Controls > Patients), we chose to include in our analysis all studies involved hippocampal structural change, these include studies demonstrating both atrophy and hypertrophy. Using a broad filter encompassing all structural covariance studies present in the database serves to provide a more robust and statistically powerful sampling of studies addressing hippocampal structural covariance. The initial search yielded a total of 166 papers comprising 274 experiments, 10,695 subjects, and 3156 locations. We used additional manual filtering for data non-redundancy to avoid within-lab and sample-specific bias, this brought down our samples to 165 papers, 269 experiments, 10,653 subjects, and 3123 locations. According to Eickhoff et al. (2016), a cluster- or voxel-level FWE correction presents the most appropriate

method of statistical inference. In addition, Eickhoff recommends at least 20 experiments be included in an ALE meta-analysis to achieve sufficient statistical power for reporting moderate effects. Our experiment exemplifies some of the most conservative (voxel-level FWE) and robust (269 experiments) parameters set forth by Eickhoff's recommendations.

An ALE map of the filtered workspace containing 269 experiments, 10,653 subjects, and 38 diseases was performed using GingerALE 2.3.6 (brainmap.org/ale/index.html) (Eickhoff et al., 2009) with the following parameters: voxel-level family-wise error (FWE) of 0.01, threshold of 1000 permutations, and minimum cluster volume of 50mm³ (Table 1). Spatial concordance among the reported VBM foci was computed with the modified anatomic likelihood estimation (ALE) algorithm (Eickhoff et al., 2012). Previous methods papers (Eickhoff et al., 2009; Turkeltaub et al., 2012) have described how to report spatial uncertainty in VBM foci where ALE describes each VBM focus as a Gaussian probability distribution. Three-dimensional Gaussian distributions were pooled in a voxel-wise manner first within experimental contrasts and then across contrasts within a group to create a whole-brain ALE probability cluster map. Each voxel was essentially assigned a unique ALE value that represents the likelihood of experimental effects, such as gray matter structural change in the case of VBM, present within that voxel. ALE maps were also tested against a null distribution to reflect random spatial associations between different experiments at a set threshold of permutations. Voxels that survived this statistical threshold were then reported as ALE clusters reflecting significance in meta-analytic convergence of peak voxels. These voxels reflect significant changes in gray matter within and across experiments. ALE also represents an analytic, data-driven technique in creating the null-distribution used in statistical inference, and uses a Monte-Carlo based approach to permit more accurate cluster-level inference (Eickhoff et al., 2012).

2.3 Meta-Analytic Connectivity Modeling

MACM investigates whole-brain connectivity patterns by assessing the covariance between two or more nodes quantitatively using ALE, with ALE values being defined as the probability estimate that an activation (or “atrophy”) exists within a particular coordinate across experiments (Robinson et al., 2010;

Robinson et al., 2012). MACM analyses resulting in ALE maps have been validated with diffusion tensor imaging (DTI) and connectivity atlases (CocoMac) (Robinson et al., 2010) and have been demonstrated to be the meta-analytic equivalent of resting-state functional connectivity maps (Laird et al., 2009b; Smith et al., 2009). Further, MACM has also been validated as a method for functional connectivity by recovering known, microscopically distinguishable compartments within a same brain region in a process known as connectivity-based parcellation (Bzdok et al., 2012, Barron et al. 2015). A step-by-step visualization of the MACM method is provided in Fig. 2.

Covariance between nodes can be measured as structural covariance, using gray matter VBM contrasts, or as functional covariance, using hemodynamic response contrasts from task-activation paradigms in normal subjects. From our RtWB meta-analysis of the hippocampus, which yielded an ALE map of 11 significant foci, or nodes, located within 7 clusters reporting structural covariance transdiagnostically (Table 1, Fig. 3), we proceeded to conduct a structural and a functional MACM experiment. We first performed a structural MACM (sMACM) for each of the 11 reported nodes identified as the peak foci from the RtWB meta-analysis (Table 1). Spherical 8mm diameter ROIs were created and centered on the coordinates of the peak ALE voxel at each cluster. Each of the 11 ROIs was then seeded into the VBM database (a separate analysis for each ROI) in a seed-to-whole brain (StWB) meta-analysis (also known as a network MACM analysis), similar to how we derived our nodes using a RtWB meta-analysis of the hippocampus. We used the same criteria as the RtWB analysis for our seeds in Sleuth 2.4 whereby only gray matter contrasts and defined regions (spherical ROIs) were used in the search. Manual filtering for data non-redundancy was also performed for each ROI to avoid within-lab and sample-specific bias for each search. The newly filtered workspace containing the experiments and coordinates of studies reporting StWB structural covariance (Table 2) were processed using GingerALE 2.3.6 (voxel-level FWE of 0.01, thresholded to 1000 permutations, and minimum cluster volume of 50mm³). ALE values were derived for each node in the HNM from each ROI's StWB meta-analysis and reported in a seed-to-projection table of ALE values (Table 3). A seed-to-projection coefficient (i.e. edge) is the ALE value obtained from the center voxel, or center coordinate, of each HNM node from a seed node's ALE analysis (e.g. If node 1 is the seed for an ALE analysis, a seed-to-projection coefficient is

obtained from the ALE value representing the center voxel of nodes 2 through 11). Figure 4 shows Bonferroni-corrected (0.01) statistical p values reported from the seed-to-projection Uncorrected P output file from GingerALE. If reciprocal significance was present (i.e. $N1 \rightarrow N2$ and $N2 \rightarrow N1$) then co-directionality of edges was determined (Fig. 5).

This MACM strategy was replicated in the functional database to produce a functional MACM of the 11 nodes derived from the VBM hippocampal RtWB meta-analysis. One noteworthy difference between the two MACMs is the sizes of the seeds used in the analysis. For the functional MACM, 12mm diameter ROIs were used. The reason for this is because a larger ROI is required to obtain comparable numbers of coactivation clusters from the functional database in BrainMap. The selection of 8mm diameter ROIs for sMACM and 12mm diameter ROIs for fMACM were chosen to account for differences in cluster number and size between the structural and functional database, allowing for the balancing of ALE clusters between datasets using spatial filtering. ROI diameters were thus obtained iteratively within lab through evaluating the number and location of the pertinent voxels against the VBM and functional databases. As in the structural MACM, a non-redundancy filtered table of StWB studies from BrainMap's functional dataset was generated (Table 4), with its corresponding seed-to-projection ALE value table (Table 5). Our ability to perform both structural and functional MACMs allows us to integrate whole-brain structural covariance and whole-brain functional coactivation patterns from BrainMap in a common numerical form of anatomic likelihood estimates. This allows us to run statistics on the ALE matrices (Tables 3 & 5) comparing structure and function.

2.4 Statistical Analysis of Functional and Structural HNMs

A Pearson's correlation was used to evaluate the ALE seed-to-projection coefficients derived from the fMACM and sMACM of the 11 individual nodes from the hippocampal RtWB brain VBM meta-analysis. We use a node-and-edge model as a framework to illustrate the degree of covariance between the HNM nodes as determined by structural and functional MACM analyses. A Pearson's r and r^2 was calculated for each seed-to-projection ALE values comparing functional and structural values (e.g. ALE coefficients from the node 1 seed to nodes 2-11 projections in sMACM analysis were correlated to ALE coefficients

from the node 1 seed to nodes 2-11 projections in fMACM analysis). In addition, a Pearson's correlation was generated for the entire ALE coefficient matrix comparing all projections from all nodes in the sMACM analysis to all projections from all nodes in the fMACM analysis. 110 candidate paths, or edges, were identified with p values from the original ALE FWE-corrected analysis. Only paths meeting the significance threshold, a Bonferroni-adjusted p of 0.01 were deemed significant. Paths that met the Bonferroni correction threshold are thus represented as edges in the node-and-edge models in Figure 5.

2.5 Disease, Behavior, and Paradigm Analysis

Disease, behavior, and paradigm class were analyzed using the 11 nodes from the hippocampal analysis (Fig. 6). We used Lancaster's (2012) paradigm class analysis, which utilizes the BrainMap database to isolate activation foci for each behavioral sub-domain. This technique compares activations from the functional database, or atrophies from the VBM database, from within the ROI to the fraction expected without regional behavior, as if activations were uniformly distributed throughout the brain. Z-scores are generated for observed-minus-expected values for each behavior sub-domain, or disease sub-domain in the case of VBM, with the operational threshold z-score of 3.0 as comparable to a group p -value of 0.05. This analysis has been previously validated in both the behavior domain and paradigm class analyses (Lancaster et al., 2012). This study represents the first application of a disease paradigm analysis using VBM to identify diseases that are likely to be expressed in the specified regions of interest (Fig. 6).

3. RESULTS

3.1 Hippocampus Region-to-Whole Brain Meta-Analysis

The ALE results from the hippocampus RtWB meta-analysis (Table 1) shows 11 significant foci located within clusters representing extra-hippocampal gray matter density alterations across diagnoses as well as two distinct foci within each hippocampus (Fig. 3). For each focus, we reported location of maximum ALE values as (x, y, z) coordinates in Talairach space. The list of all 165 papers included in this meta-analysis are presented in a supplementary table.

3.2 Meta-Analytic Connectivity Modeling

We obtained significant results using structural (Table 2) and functional (Table 4) MACM of the resulting 11 ROIs from the HNM, reported as regions from the Talairach-Daemon (Lancaster et al., 2000). Two separate tables are reported for each MACM: ALE values from BrainMap's structural VBM database (Table 2) and task-activation functional database (Table 4) and Bonferroni corrected P 0.01 (Fig. 4). These corrected p -values, which represent covariance statistics between nodes and projections in Figure 4, were used to generate the edges in our node-and-edge model. Edges were deemed significant with a Bonferroni correction threshold, if only one edge between two nodes was significant, the connection was assigned as unidirectional (i.e. $N1 \rightarrow N2$ but not $N2 \rightarrow N1$); if both edges between two nodes were significant, then the connection was deemed bidirectional (i.e. $N1 \rightarrow N2$ and $N2 \rightarrow N1$) (Fig. 5). Figure 5 illustrates the presence of a number of significant nodes bearing structural bidirectional covariance properties. Among these are between the left anterior hippocampus (LAH, N1) and left posterior hippocampus (LPH, N2), LAH (N1) and right anterior hippocampus (RAH, N3), LPH (N2) and right posterior hippocampus (RPH, N4), left midline nucleus of the thalamus (LMN, N6) and RPH (N4), and left caudate head (LCH, N11) and right medial dorsal nucleus of the thalamus (RMDN, N5). Similarly, significant nodes bearing functional covariance bi-directional coactivation properties can be found between the LAH (N1) and RAH (N3), LPH (N2) and RPH (N4), left claustrum (LClaus, N8) and right claustrum (RClaus, N7), left insula (LIns, N9) and RClaus, LIns and right caudate body (RCB, N10), LIns (N9) and RMDN (N5), LIns (N9) and LMN (N6), LCH (N11) and RCB (N10), LCH (N11) and LMN (N6), LMN (N6) and RCB (N10), LMN (N6) and RClaus (N7), LMN (N6) and RMDN (N5), and RMDN (N5) and RClaus (N7). Significant unidirectional paths are also reported in both structural and functional MACM figures (Fig. 4 & 5).

3.3 Structural and Functional Correlation of HNM

The matrix correlation between sMACM and fMACM found a moderate but significant correlation of $r = 0.377$ ($p = 0.00005$) as defined by Cohen (1988) using Pearson Correlation. A similar finding was generated using the Mantel Test for matrix correlations (1967) whereby a moderate and significant correlation of $r = 0.397$ ($p = 0.0013$) was identified. We also reported r^2 to describe the variance explained (14.2%) by the association of structure and function between the nodes of the sHNM. The nodes, whose seed-to-projection ALE values demonstrate the greatest and most significant correlations between structural and functional covariance include: nodes 1 (left anterior hippocampus, $r = 0.942$ and $p = 4.83 \times 10^{-5}$), 2 (left posterior hippocampus, $r = 0.830$ and $p = 4.83 \times 10^{-5}$), and 3 (right anterior hippocampus, $r = 0.935$ and $p = 7.34 \times 10^{-5}$) (Table 6).

3.4 Disease, Behavior, and Paradigm Analysis

The 4 most significant diseases identified in the nodes from the RtWB meta-analysis include Alzheimer's Disease (AD), Mesial Temporal Lobe Epilepsy (MTLE), Mild Cognitive Impairment (MCI), and Schizophrenia. Likewise, an evaluation of these same 11 nodes using the behavioral domain paradigm from BrainMap's functional cohort of healthy subjects identified the emotional subdomains of fear and other emotion, the cognition subdomains of attention, explicit memory, semantic language, and other cognition, and the perception subdomain of pain somesthesia (Fig. 6).

4. DISCUSSION

The purpose of our study was to identify and define consistent gray matter structural abnormalities that co-exist with hippocampal atrophy, and address the network degeneration hypothesis (NDH) by testing and quantifying the correlation between structural and functional covariance. Our analysis found that indeed, a moderate correlation exists between meta-analytically derived structural and functional covariance models of nodes derived from a structurally-driven hippocampal network model (HNM). By applying the meta-analytic connectivity modeling (MACM) pipeline procedure (Fig. 2) to our HNM using BrainMap's voxel-based morphometry (VBM) and functional database, we were able to validate our hypothesis, that MACM can be applied to the VBM literature and generate structural covariance models

using the trans-diagnostic literature. Additionally, our resulting Pearson's correlation analysis using ALE values obtained from the structural and functional covariance networks of the HNM was found to support the NDH, establishing that the structural-functional relationship of interconnected brain regions is topographically correlated.

We interpret these structural covariances as related to four of the primary trophic influences outlined by Zhou et al., 2012. The transneuronal spread mechanism begins in an epicenter, where neuronal inclusions in the form of neurofibrillary tangles, cytoplasmic Lewy bodies, iron accumulation, prion diseases, viral inclusions, a diverse array of protein aggregates, etc. (Fornai et al., 2005) spread along axonal pathways to other groups of neurons located in more distant regions (Zhou, et al., 2012; Ahmed et al., 2016). The nodal stress mechanism suggests that brain hubs (i.e., regions with high levels of connectivity across the brain, more metabolic demand, and higher blood flow) are selectively susceptible to damage from oxidative stress and endothelial damage leading to impairments, such as a leaky blood brain barrier (Crossley et al., 2014). The mechanism of trophic failure involves the sub-cellular dysfunction of trophic factors, e.g. brain-derived neurotrophic factor (BDNF), which is involved in dendritic and axonal branching (Cohen-Cory et al., 2010). When trophic factor expression and regulation is impaired, trophic failure in the form of poor cellular and synaptic maintenance impairs structural connectivity (Fornito et al., 2015). Lastly, shared vulnerability is a mechanism whereby similar neuronal cell types across the brain are susceptible to disease-specific changes due to shared genetic and metabolic profiles (Cioli et al., 2014). Because our study is trans-diagnostic, it is impossible to identify which mechanisms predominate as different diseases exhibit differing and perhaps overlapping trophic influences.

4.1 HNM Connectivity

The functional and structural association of the hippocampus to multiple brain regions has been and continues to be an important area of research interest. The identification of hippocampal atrophy in normal aging as well as in diseases that differ in their symptomatology has generated interest in identifying network models explaining the associations between the hippocampus and other cortical and subcortical structures. The goal of developing a comprehensive hippocampal network model has its roots in the use of structural and functional biomarkers in specified brain regions that can be utilized to

investigate disease progression, treatment efficacy, and differences in normal aging (Marstaller et al., 2015).

Hippocampal network connectivity has been studied in other established networks, most notably the reward circuit (anterior cingulate cortex, orbital prefrontal cortex, ventral striatum, ventral pallidum, midbrain dopamine neurons, dorsal prefrontal cortex, amygdala, hippocampus, thalamus, lateral habenular nucleus, pedunculo pontine nucleus, and raphe nucleus) (Haber & Knutson, 2010) and the default mode network (posterior parietal cortex, precuneus, lateral temporal gyrus, posterior cingulate cortex, hippocampus, and cerebellum) (Laird et al., 2009a; Chang et al., 2015). Both networks provide empirically based models for the study of diseases that alter these networks' properties. Network modeling and structural equation modeling has also been used to predict behavioral and metabolic metrics using the reward circuit and DMN respectively (Laird et al., 2009a; Park et al., 2015; Lin et al., 2016).

Importantly, the most robust and well-described hippocampal connectivity profile is that which occurs between the contralateral hippocampi, validated in this present study both structurally and functionally (Fig. 5, Table 6). This association has long been established as both hippocampi share direct inter-hemispheric connections via the hippocampal commissure (Spencer et al., 1987). This contralateral structural connectivity can be observed using a visual sMACM of each hippocampus when seeded in the VBM database independently showing key points of difference as well as overlap (Fig. 7). Moreover, there is ample evidence that the hippocampus is a key component in networks relating to both normal functioning and pathology. In our analysis, we used a novel approach to answering the question of pathological significance relating to hippocampal structural covariance.

The hippocampus itself is not a monolithic structure. It is subdivided into histological regions (dentate gyrus, CA1-4, subiculum) and has been shown to differ in structural and functional properties along the longitudinal axis. Connectivity-based parcellation experiments of the hippocampus have recently defined this anterior-posterior differentiation of the hippocampus more precisely (Robinson et al., 2015). Other meta-analytic methods have shown functional differences between anterior and posterior hippocampal activation patterns (Chase et al., 2015). Importantly, seeding the hippocampi as volumetric binarized

regions in the present VBM database yields not only extra-hippocampal foci, but foci within the hippocampus itself. This lends credence to the aforementioned studies identifying distinct anterior-posterior functional and structural differentiation of the hippocampus in the form of focal atrophy. We identified two distinct ALE foci (Fig. 3) in each hippocampus that were subsequently regarded as independent nodes.

Indeed, our study also identifies several well-studied connections between the hippocampus and other brain structures. We found, unsurprisingly, that specific regions known to be structurally and functionally connected to the hippocampus also appeared in our meta-analysis: the claustrum, insula, MDN of the thalamus, and caudate. Tracer studies in the macaque brain have previously identified claustral projections to other subcortical structures found in our sHNM, specifically the dorsal thalamic nuclei, hippocampus, and caudate nucleus (Mathur, 2014). Crossley et al. (2014) found through DTI meta-analytic lesion mapping that there are a number of imaging connectome hubs relating to anatomical locations of MRI lesions, to which the bilateral hippocampi, thalamus, and insula belong. It has also been demonstrated that blood-brain barrier (BBB) breakdown in the human hippocampus, found to be correlated with normal aging as well as MCI, is also strongly associated with breakdown of the BBB in the caudate nucleus specifically (Montagne et al., 2015). The caudate-hippocampal connection has also been validated with a VBM-ALE meta-analysis study of gray matter atrophy in schizophrenia (Li et al., 2017). Thalamo-hippocampal connectivity is another well-established association in both animal and human models (Vertes et al., 2007; Barron et al., 2013). With regards to the thalamus, specific thalamic nuclei have been shown to be significantly associated with hippocampal pathology, namely the pulvinar, anterior nucleus, and medial dorsal nucleus (Rosenberg et al., 2009). This suggests that different subcortical structures may be differentially connected to the hippocampus by distinct structurally-related mechanisms across a range of diseases.

Our sMACM analysis demonstrate that the most consistent structural change in gray matter density across diseases implicating the hippocampus follows a distinct pattern involving regions previously identified as being implicitly associated with the hippocampus. Furthermore, our fMACM analysis supports the notion that structural and functional network properties are significantly correlated (Sui et al., 2014)

(Table 6). This validation can serve the purpose of using the present HNM and its nodes as biomarkers for the study of relevant pathologies (eg. AD, MTLE, MCI, Schizophrenia, aging, etc.).

4.2 Hippocampal Pathology:

Hippocampal pathology in Alzheimer's disease, mild cognitive impairment, epilepsy, and schizophrenia has been long established. Hippocampal volume loss is a common finding in imaging studies of individuals with AD, MCI and, normal aging (Apostolova et al., 2012), MTLE (Wei et al., 2016), and Schizophrenia (Koolschijn et al., 2010). Moreover, other studies have demonstrated that systemic pathologies like metabolic syndrome (Anand & Dikhav, 2012), type 2 diabetes mellitus and obesity (Wu et al., 2008; Wang et al., 2014; Stranahan, 2015), and normal aging (Apostolova et al., 2012) also report hippocampal atrophy. Recent studies have ascertained that volume loss in the hippocampus corresponds to neuronal cell death due in part to oxidative stress introduced by a leaky blood brain barrier (Montagne et al., 2015), along with sclerosis (Wei et al., 2016) and amyloid plaques and Tau protein tangles (Apostolova et al., 2010), etc. It is for this reason that a trans-diagnostically-driven HNM is justified as a tool to understand structural network abnormalities in the presence of hippocampal dysfunction.

This raises the question: what would the pattern of gray matter atrophy look like if the hippocampus were seeded and constrained only to specific diseases? We tested this by conducting a very similar RtWB analysis as the original trans-diagnostic study. By constraining our regional search to only the diseases that appear to be most strongly correlated to the sHNM based on the disease paradigm analysis (Fig. 6) and using a less stringent statistical threshold (Cluster-level 0.05, FDR pN 0.05, with 1000 threshold permutations) we were able to identify a number of significant regions of hippocampal structural covariance within these top four diseases. Figure 8 shows a visual comparison of the hippocampal structural covariance patterns for these diseases in order to illustrate that there are important similarities and differences across diseases, workspaces are available as supplementary data. We can conclude from this analysis that there are certain network pathways that are equally atrophogenic across diseases and co-vary significantly with damage to the hippocampus, whether that is due to sclerosis, plaques and tangles, or inflammatory infiltrates via a leaky BBB. Whatever the disease pathogenic onset that leads to

hippocampal cell loss, our sHNM model clearly shows that hippocampal gray matter density is markedly associated with at least 11 brain regions, which together are known to be associated with attention, emotion, reward, and memory, among others (Fig. 6).

4.3 Methodological Considerations

Meta-analysis has been defined as the post hoc combination of independently performed studies to better estimate a parameter of interest (Fox et al., 2005a). Several meta-analytic methods have since been developed. One of the earliest was the use of label-based meta-analysis whereby an investigator would assign labels from multiple studies and tally them without performing any statistical analysis (Keller & Roberts, 2008). This method was heavily criticized for being spatially imprecise and producing misleading results. With the advent of coordinate-based meta-analysis, studies began reporting peak activation or atrophy regions using an x, y, z coordinate system in a standardized brain space (e.g. Talairach and MNI). This method offers a statistically rigorous, and spatially precise alternative to the label-based and image-based methods. Therefore, coordinate-based meta-analysis makes it possible to use published peer-reviewed literature to conduct large scale, multi-laboratory, multi-contrast, and multi-study meta-analysis, as was done presently.

MACM is a tool that takes specific advantage of large volume of data from multiple labs, contrasts, subjects, and paradigms. Although the MACM technique has existed since Laird (2009a), its use has been limited to the study functional covariance. In recent years, it has been used to study functional covariance of specific brain regions such as the caudate (Robinson et al., 2012), nucleus accumbens (Cauda et al., 2011), insula (Cauda et al., 2012), left inferior parietal cortex (Müller et al., 2013), and amygdala (Robinson et al., 2010); specific brain processes such as emotion regulation (Kohn et al., 2014); and specific diseases such as spinocerebellar ataxia (Reetz et al., 2012), MTLE (Barron et al., 2013) and PTSD (Ramage et al., 2013) among others. To our knowledge, this study is the first to use BrainMap's VBM database to directly compare structural covariance with functional covariance using the same methodology.

Our study takes advantage of seven years of new and refined data uploaded into BrainMap since Robinson et al. (2010), providing greater statistical power to MACM analyses. We applied inclusion filters for whole-brain analyses and data non-redundancy. We conducted a RtWB meta-analysis by seeding the hippocampus and searching through the entire BrainMap VBM database to identify the most significant extra and intra-hippocampal foci associated with change in hippocampal gray matter density (Table 1 & Fig. 3). We used the Eickhoff et al. (2012) algorithm, which employs a data-driven approach to create the null-distribution used in statistical inference as well as a Monte-Carlo based approach permitting more accurate cluster-level and voxel-wise inferencing (Eickhoff et al., 2012). We then performed two separate MACM analyses (Tables 2-5, Figs. 4 & 5), following the most up-to-date approach as delineated in Langner et al. (2014) with minor improvements to account for differences in VBM and functional data (Fig. 2). These improvements to the meta-analytic process allows for a more statistically robust method of performing MACM analyses to determine both structural and functional covariance using coordinate-based meta-analytic methods. Using this method, we have also demonstrated that indeed, structural covariance and functional covariance are significantly correlated (Table 6). Future studies will no doubt benefit from using coordinate-based databases such as BrainMap to perform MACM analyses to derive preliminary biomarkers and network models as a strategy to inform studies using clinically-relevant resting state and T1 primary data (Biswal et al., 2010).

4.4 Clinical Purpose and Dividends

Behavioral characteristics (Fig. 6) have been shown to correspond to hippocampal function and dysfunction based on clinical behavior profiles of individuals with diseases of the hippocampus such as in Alzheimer's disease (Ballard et al., 2011) and schizophrenia (Tregellas et al., 2014). The paradigm class activation studies identified in the sHNM also validates the hippocampus' role in the reward circuit (Haber & Knutson, 2010) and its involvement in other tasks involving memory and attention (pain monitor-discrimination, face monitor-discrimination, semantic monitor-discrimination, and passive viewing). Furthermore, behavior characteristics are important features in the evaluation and analysis of individuals with hippocampal pathology.

Future analyses will aim to apply the sHNM to both structural (T1 weighted images) and functional (resting state fMRI) primary data and use statistical methods such as structural equation modeling, to define path coefficients with greater accuracy. We further hypothesize that structural equation modeling applied to primary data and restricted to nodes of the sHNM will increase our understanding of hippocampal pathology and introduce a novel approach to assessing its relationship to cognition, behavior, metabolism, and aging. We believe that a targeted analysis of the sHNM with primary data could subsequently bear prospective clinical dividends on the per-patient level by giving investigators and clinicians an objective anatomically derived method of assessing cognitive decline and improvement as it relates to disease progression and treatment.

5. CONCLUSION

In our region-to-whole brain meta-analysis of the hippocampi, we found consistent gray matter structural change across diseases in BrainMap's VBM database in 11 specific brain regions, termed the sHNM. These structures were found to show distinct patterns of structural and functional covariance using meta-analytic connectivity modeling. Functional and structural ALE values derived from MACM were found to be significantly correlated. Likewise, a paradigm analysis of behavior domains and paradigm class activation studies show that the sHNM corresponds to known hippocampal function in normal subjects (emotion, memory, attention) and known hippocampal atrophy in diseases subjects (AD, MCI, MTLE, schizophrenia). Our large sample size of VBM studies allowed us to use more conservative statistical thresholding in reporting the most significant ALE values in our structural and functional covariance studies. Hippocampal pathology is commonly observed in animals and humans, suggesting that a comprehensive structural hippocampal network model could serve as a clinically useful biomarker in the evaluation disease effects on cognitive function. These questions await further investigations.

ACKNOWLEDGMENTS:

We thank Dr. Amy Garrett for he valuable edits and Cheasequah J. Blevins for her neuroscience input and emotional support. This study was supported by funds from the National Institutes of Health (NIMH: R01 MH074457, NIMH: 3R01MH074457-11S1) and Congressionally Directed Medical Research Programs (CDMRP: W81WH-14-1-0316).

APPENDIX A. SUPPLEMENTARY DATA:

Supplementary data to this article can be found online at:

Table 1:

RtWB meta-analysis of BrainMap VBM Database Peak Foci: Voxel-level FWE 0.01, 1000 permutations, 50mm³ minimum cluster volume

Description	Size mm ³	Weighted center (x, y, z)			Hemisphere	Lobe	Region	Sub-Region
Node 1 - Left Anterior Hippocampus (LAH)	13065*	-26	-14	-14	Left Cerebrum	Limbic Lobe	Parahippocampus	Hippocampus
Node 2 - Left Posterior Hippocampus (LPH)	13065*	-26	-34	-4	Left Cerebrum	Limbic Lobe	Parahippocampus	Hippocampus
Node 3 - Right Anterior Hippocampus (RAH)	10672*	24	-12	-14	Right Cerebrum	Limbic Lobe	Parahippocampus	Hippocampus
Node 4 - Right Posterior Hippocampus (RPH)	10672*	28	-32	-4	Right Cerebrum	Limbic Lobe	Parahippocampus	Hippocampus
Node 5 - Right MDN of Thalamus (RMDN)	2659*	4	-18	12	Right Cerebrum	Sub-lobar	Thalamus	Med Dorsal Nucleus
Node 6 - Left Midline Nucleus of Thalamus (LMN)	2659*	-6	-16	14	Left Cerebrum	Sub-lobar	Thalamus	Midline Nucleus
Node 7 - Right Claustrum (RClaus)	464	36	6	4	Right Cerebrum	Sub-lobar	Claustrum	
Node 8 - Left Claustrum (LClaus)	292	-34	-8	0	Left Cerebrum	Sub-lobar	Claustrum	
Node 9 - Left Insula (LIns)	280	-34	16	2	Left Cerebrum	Sub-lobar	Insula	BA13
Node 10 - Right Caudate Body (RCB)	173	10	12	8	Right Cerebrum	Sub-lobar	Caudate	Caudate Body
Node 11 - Left Caudate Head (LCH)	64	-6	6	-2	Left Cerebrum	Sub-lobar	Caudate	Caudate Head

* Cluster containing two peak ALE foci: left anterior hippocampus and left posterior hippocampus, right anterior hippocampus and right posterior hippocampus, left MDN of the thalamus and right midline nucleus of the thalamus. All (x, y, z) foci are reported in Talairach space. All tissue labels are derived from the Talairach Daemon.

Table 2:

Structural MACM Workspace for 8mm Nodes

Description	Papers	Subjects	Experiments	Locations
Node 1 - Left Anterior Hippocampus (LAH)	21	1311	24	307
Node 2 - Left Posterior Hippocampus (LPH)	13	1123	18	314
Node 3 - Right Anterior Hippocampus (RAH)	20	1453	24	259
Node 4 - Right Posterior Hippocampus (RPH)	13	935	14	141
Node 5 - Right MDN of Thalamus (RMDN)	9	835	12	177
Node 6 - Left Midline Nucleus of Thalamus (LMN)	13	800	15	181
Node 7 - Right Claustrum (RClaus)	12	943	13	153
Node 8 - Left Claustrum (LClaus)	9	836	13	301
Node 9 - Left Insula (LIns)	17	1594	20	278
Node 10 - Right Caudate Body (RCB)	12	1140	12	137
Node 11 - Left Caudate Head (LCH)	11	1168	14	382

Table 3:

Structural MACM Seed-to-Whole Brain (FWE p01) Peak Centroid ALE Values – 8mm ROIs

<i>Projection ALE Values</i>											
<i>Seeds</i>	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
N1 (LAH)		0.01403	0.05461	0.00723	0.0128	0.0054	0.00675	0.00035	0.01187	0.0043	0.00094
N2 (LPH)	0.02246		0.02029	0.03482	0.00754	0.00842	0.00232	0.00244	0.00512	0.00988	0.01018
N3 (RAH)	0.04143	0.01117		0.01149	0.00154	0.00517	0.00415	0.0026	0.00276	0.00832	0.00595
N4 (RPH)	0.00968	0.02082	0.00724		0.00558	0.01549	0.00198	0.0009	0.00387	0	0
N5 (RMDN)	0.01371	0.01086	0.00945	0.00591		0.02623	0.00688	0.00005	0.00055	0.00522	0.01722
N6 (LMN)	0.00454	0.00448	0.00093	0.01939	0.03209		0.00041	0.0073	0.00061	0.00187	0.00561
N7 (RClaus)	0.01985	0.00365	0.01211	0.00137	0.00257	0.00139		0.00079	0.01025	0.01159	0.01187
N8 (LClaus)	0.0176	0.00503	0.00895	0.00395	0.01211	0.00879	0.01093		0.0017	0.00374	0.00294
N9 (LIns)	0.01058	0.00439	0.00523	0.00412	0.0048	0.01493	0.01988	0.00026		0.00432	0.00093
N10 (RCB)	0.00413	0.00084	0.00386	0	0.00667	0.00262	0.00167	0.00049	0.00113		0.00707
N11 (LCB)	0.00851	0.00619	0.00906	0.00095	0.01468	0.02224	0.01174	0.00244	0.02453	0.01704	

Table 4:

Functional MACM Workspace for 12mm Nodes

Description	Papers	Subjects	Experiments	Conditions	Locations
Node 1 - Left Anterior Hippocampus (LAH)	67	1071	76	207	1049
Node 2 - Left Posterior Hippocampus (LPH)	35	486	38	105	517
Node 3 - Right Anterior Hippocampus (RAH)	65	1133	80	164	1144
Node 4 - Right Posterior Hippocampus (RPH)	36	607	41	91	685
Node 5 - Right MDN of Thalamus (RMDN)	120	2102	148	328	2635
Node 6 - Left Midline Nucleus of Thalamus (LMN)	94	1358	103	254	2012
Node 7 - Right Claustrum (RClaus)	75	1068	85	192	1444
Node 8 - Left Claustrum (LClaus)	48	699	55	122	819
Node 9 - Left Insula (LIns)	214	3331	267	633	4235
Node 10 - Right Caudate Body (RCB)	73	1092	80	186	1256
Node 11 - Left Caudate Head (LCH)	66	1203	79	182	1045

Table 5:

Functional MACM Seed-to-Whole Brain (FWE p01) Peak Centroid ALE Values – 12mm ROIs

<i>Projection ALE Values</i>											
<i>Seeds</i>	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
N1 (LAH)		0.00976	0.06361	0.00716	0.01459	0.01571	0.00628	0.00672	0.02593	0.00552	0.01125
N2 (LPH)	0.00975		0.01893	0.01809	0.0084	0.00947	0.00338	0.00082	0.00567	0.00236	0.00717
N3 (RAH)	0.0699	0.01512		0.00896	0.00459	0.01134	0.01111	0.01543	0.00911	0.00662	0.02106
N4 (RPH)	0.00681	0.01748	0.00754		0.01054	0.00701	0.00567	0.00394	0.015	0.00999	0.01115
N5 (RMDN)	0.01561	0.01534	0.01576	0.00489		0.13813	0.0562	0.01643	0.09809	0.05815	0.02364
N6 (LMN)	0.0221	0.00731	0.00631	0.01082	0.13615		0.02388	0.00581	0.07941	0.02271	0.02435
N7 (RClaus)	0.0093	0.00288	0.0089	0.00485	0.03983	0.01945		0.01891	0.05811	0.01442	0.00377
N8 (LClaus)	0.00282	0.00076	0.01379	0.00056	0.0068	0.00631	0.02641		0.0123	0.00719	0.00446
N9 (LIns)	0.02258	0.00317	0.00559	0.0088	0.09499	0.07074	0.07888	0.00656		0.04675	0.02149
N10 (RCB)	0.00548	0.00115	0.00404	0.00813	0.05963	0.02721	0.01343	0.00595	0.04699		0.04322

N11 (LCB)	0.01253	0.00765	0.01574	0.0098	0.0208	0.01726	0.00599	0.00732	0.02634	0.03647	
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Table 6:

sMACM to fMACM statistical comparison of node-to-whole-brain (node to all other nodes) covariance using ALE values and sMACM to fMACM ALE matrix correlation.

sMACM to fMACM Statistical Comparisons			
Seed-to-projection	<i>r</i>	<i>r</i>²	<i>p</i>
N1 (LAH)	0.942	0.887	4.83e-5*
N2 (LPH)	0.830	0.688	4.83e-5*
N3 (RAH)	0.935	0.874	7.34e-5*
N4 (RPH)	0.379	0.144	0.280
N5 (RMDN)	0.347	0.120	0.326
N6 (LMN)	0.618	0.382	0.057
N7 (RClaus)	-0.096	0.009	0.792
N8 (LClaus)	0.143	0.020	0.694
N9 (LIns)	0.580	0.336	0.079
N10 (RCB)	0.579	0.335	0.080
N11 (LCB)	0.687	0.472	0.028

sMACM and fMACM ALE Matrix Statistical Comparisons			
Statistical Test	<i>r</i>	<i>r</i>²	<i>p</i>
Pearson Correlation	0.377	0.142	4.89e-5*
Mantel Test	0.397	0.158	0.001

* Values that survive a Bonferroni correction for multiple comparisons (11) threshold of 0.01, i.e. values < 0.00091

BrainMap VBM Database

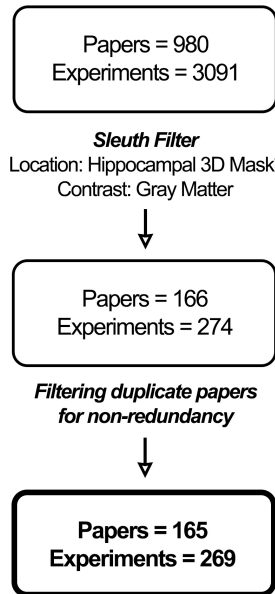


Fig. 1. Prisma Table: Pipeline demonstrating inclusion criteria for VBM studies incorporating hippocampal gray matter density changes across BrainMap's VBM database.

* Binarized hippocampal 3D mask in Talairach space was derived from the Harvard-Oxford Structural Probability Atlas (Jenkinson, 2012)

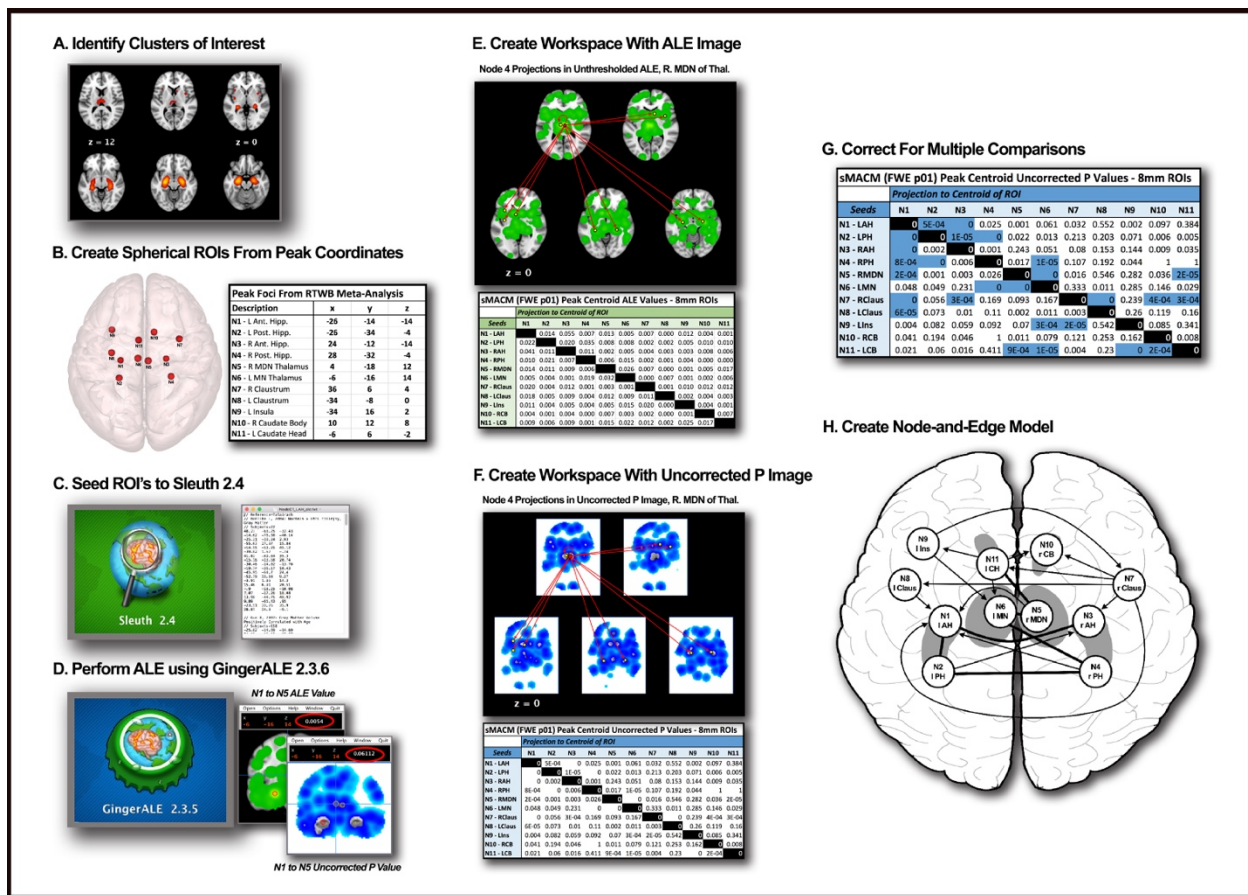


Fig. 2. MACM Pipeline: Pipeline showing a step-by-step process of using BrainMap and its corresponding software, Sleuth and GingerALE, to conduct a MACM analysis leading to the development of a node-and-edge model. A) Derive nodes from peak foci using region-to-whole brain meta-analysis. (Other methods for identifying nodes are also eligible for MACM analysis). B) Create spherical ROIs of nodes using peak foci coordinates. 8mm diameter for VBM studies, 12 mm diameter for functional studies and save as ROIs. C) Seed individual ROIs in BrainMap's Sleuth 2.4 to search database and develop a workspace. Filter appropriately for VBM or functional database searches. Use consistent brain space (i.e. Talairach, MNI). D) Perform ALE using GingerALE 2.3.6 using appropriate and consistent thresholds. E) Create workspace using Mango of spherical ROIs. Overlay raw ALE images derived from GingerALE unto workspace and record ALE values from the centroid of each node to create a table. F) Repeat process using Uncorrected P output file from GingerALE and record P values from the centroid of each node to create a table. G) Define appropriate statistical thresholds to correct the raw Uncorrected P value table. Presently, we used Bonferroni correction for multiple comparisons threshold and to define the most robust paths. H) Create a node-and-edge model where nodes are spherical representations of peak structural variance or activation foci (VBM or functional respectively). Dark edges represent bidirectional covariance, arrows represent unidirectional covariance.

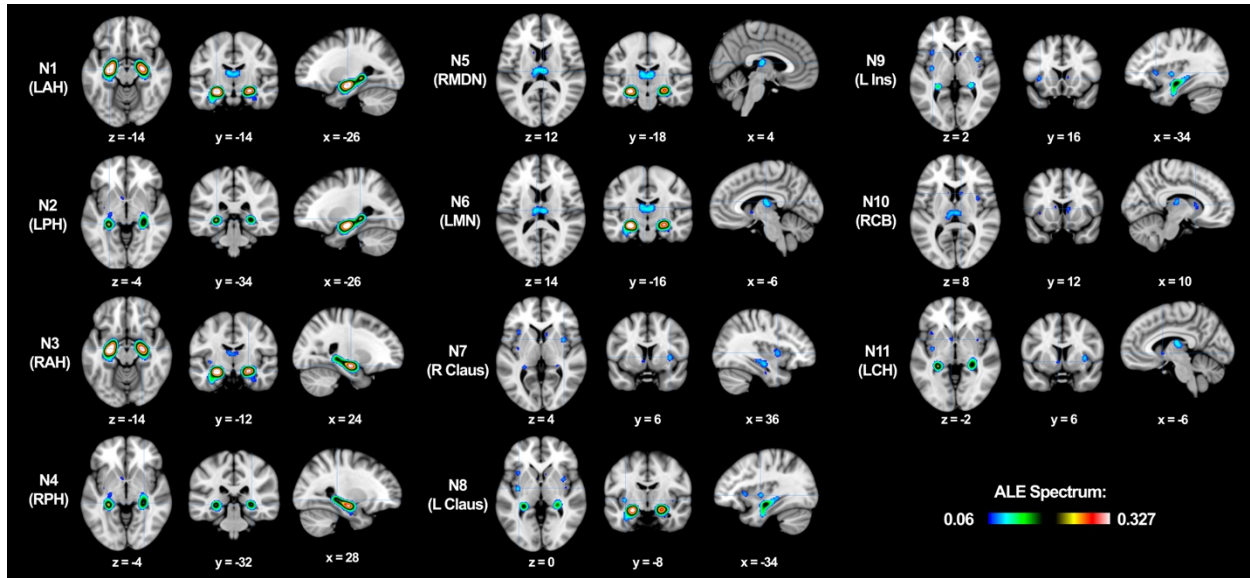


Fig. 3. Hippocampi Region to Whole Brain Meta-Analysis: Regions with specified peak foci showing significant structural covariance among trans-diagnostic VBM gray matter contrast studies (voxel-level FEW 0.01, thresholded at 1000 permutations and minimum reported cluster volume of 50mm³). LAH = left anterior hippocampus, LPH = left posterior hippocampus, RAH = right anterior hippocampus, RPH = right posterior hippocampus, RMDN = right medial dorsal nucleus of the thalamus, LMN = left midline nucleus of the thalamus, R Claus = right claustrum, L Claus = left claustrum, L Ins = left insula, RCB = right caudate body, LCH = left caudate head.

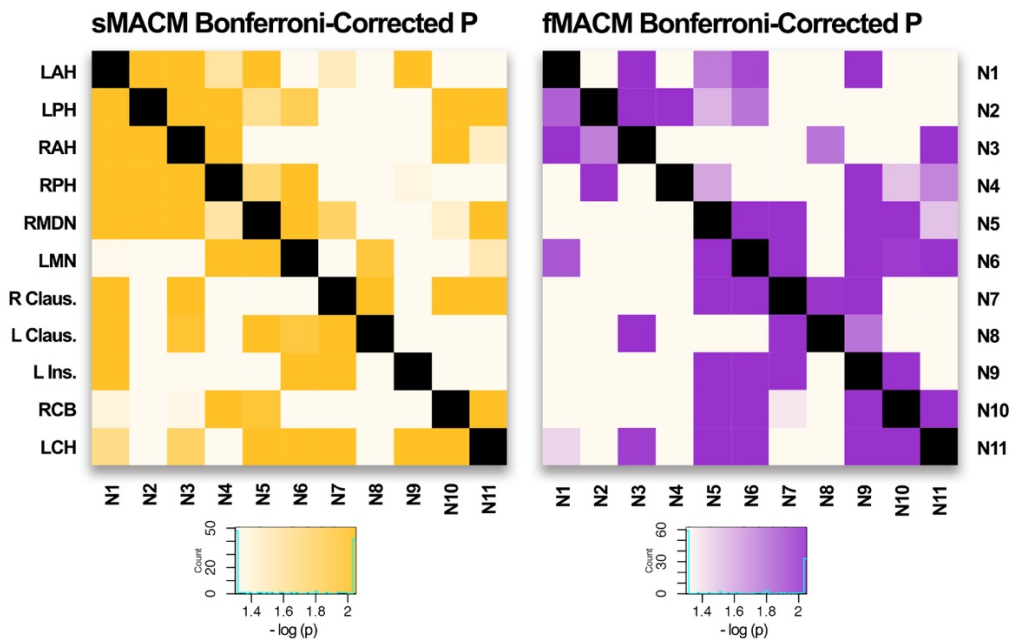
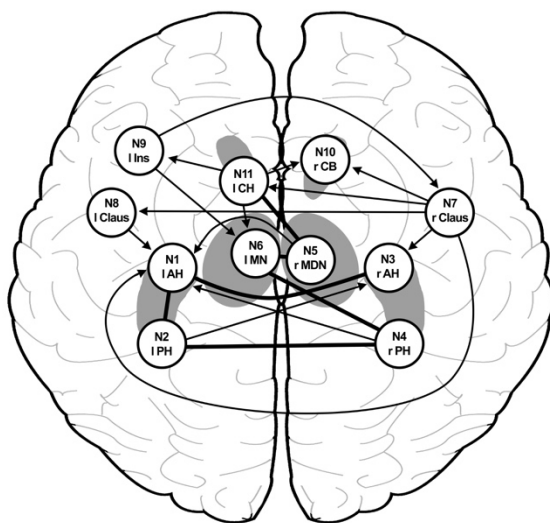
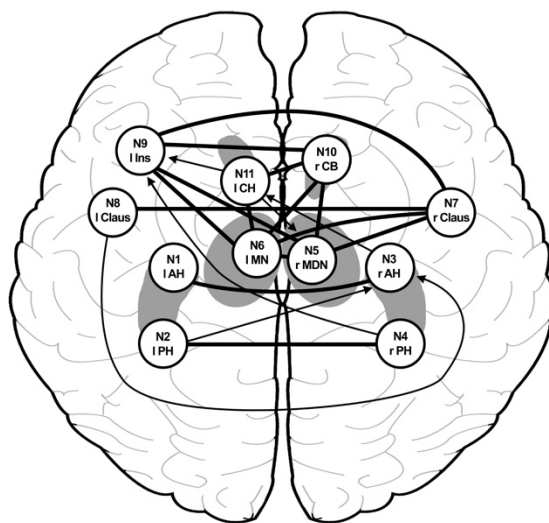


Fig. 4. Heat Map of Bonferroni-Corrected P Values in sMACM and fMACM of sHNM: Histogram color values are reported in $-\log_{10}(p)$. Values greater than or equal to 2.04 are darkest and represent regions of covariance with a Bonferroni-Corrected $P \leq 0.01$ (≤ 0.00091) for 11 nodes. Values less than or equal to 1.30 are lightest and represent regions of least covariance ($p > 0.05$).



sMACM Node-and-Edge Model of sHNM



fMACM Node-and-Edge Model of sHNM

Fig. 5. Node-and-Edge Diagrams of MACMs: Each diagram delineates paths from the Bonferroni-Corrected P values used in assessing inter-nodal covariance. Bolded lines represent bi-directionality, indicating that variance in two nodes are predictive of variance in each other. Arrows represent uni-directionality, indicating that variance in one node is predictive of variance in another, but not vice versa.

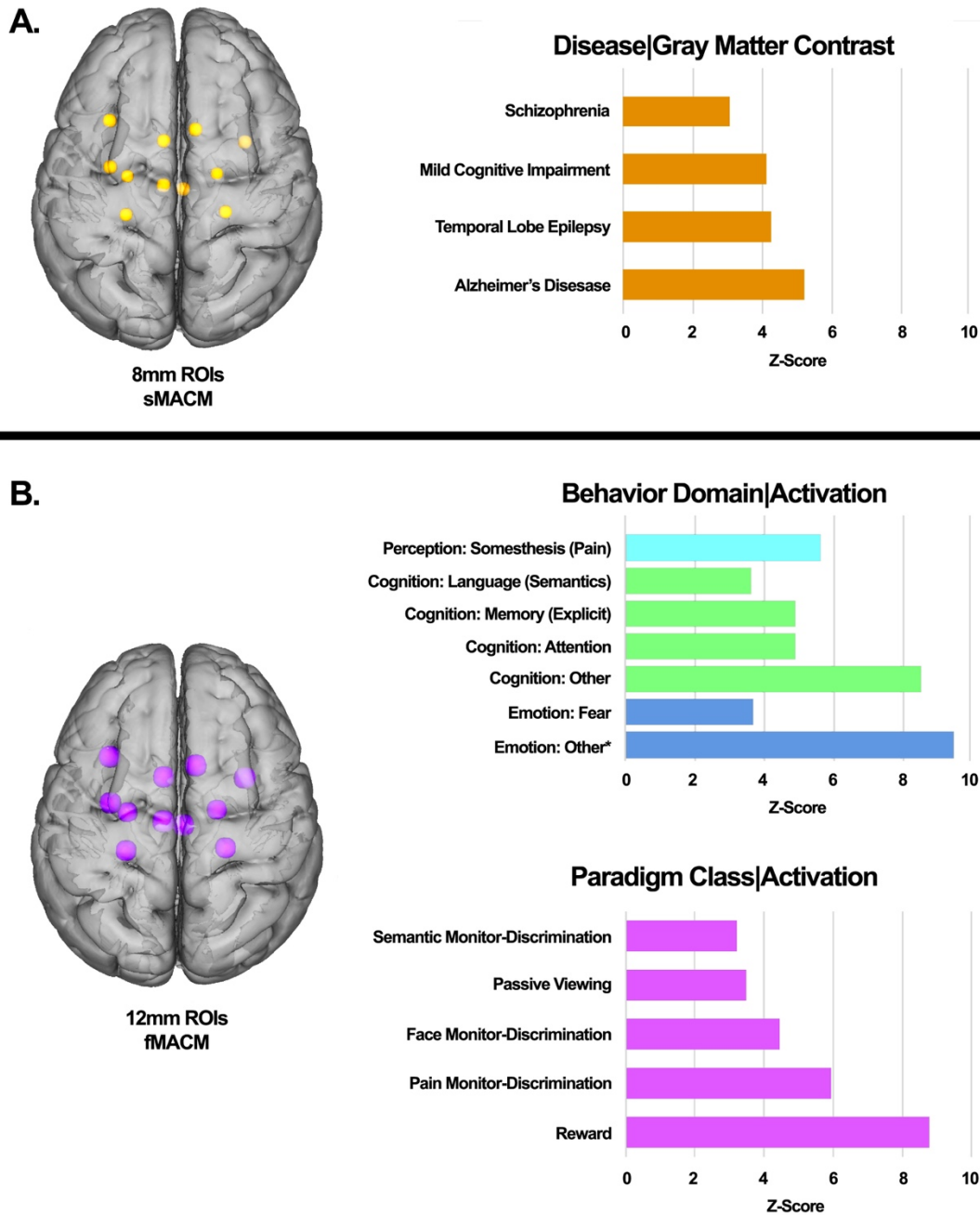


Fig. 6. Specific behavioral, paradigm class, and disease weightings on the structural hippocampal network model.

- A. Structural characterization of sHNM based on Disease Classification meta-data of the BrainMap VBM structural database representing peak structural MACM disease classes.
- B. Functional characterization of sHNM based on the Behavioral Domain and Paradigm Class meta-data of the BrainMap functional database representing peak functional MACM behavior domains and task paradigms.

Only paradigms fulfilling the minimal threshold of $z \geq 3.0$ are reported.

* The designation “other” indicates an emotion experimental contrast that does not meet the eligibility criteria for pre-selected emotions in the BrainMap database: anger, anxiety, disgust, fear, happiness, humor, sadness.

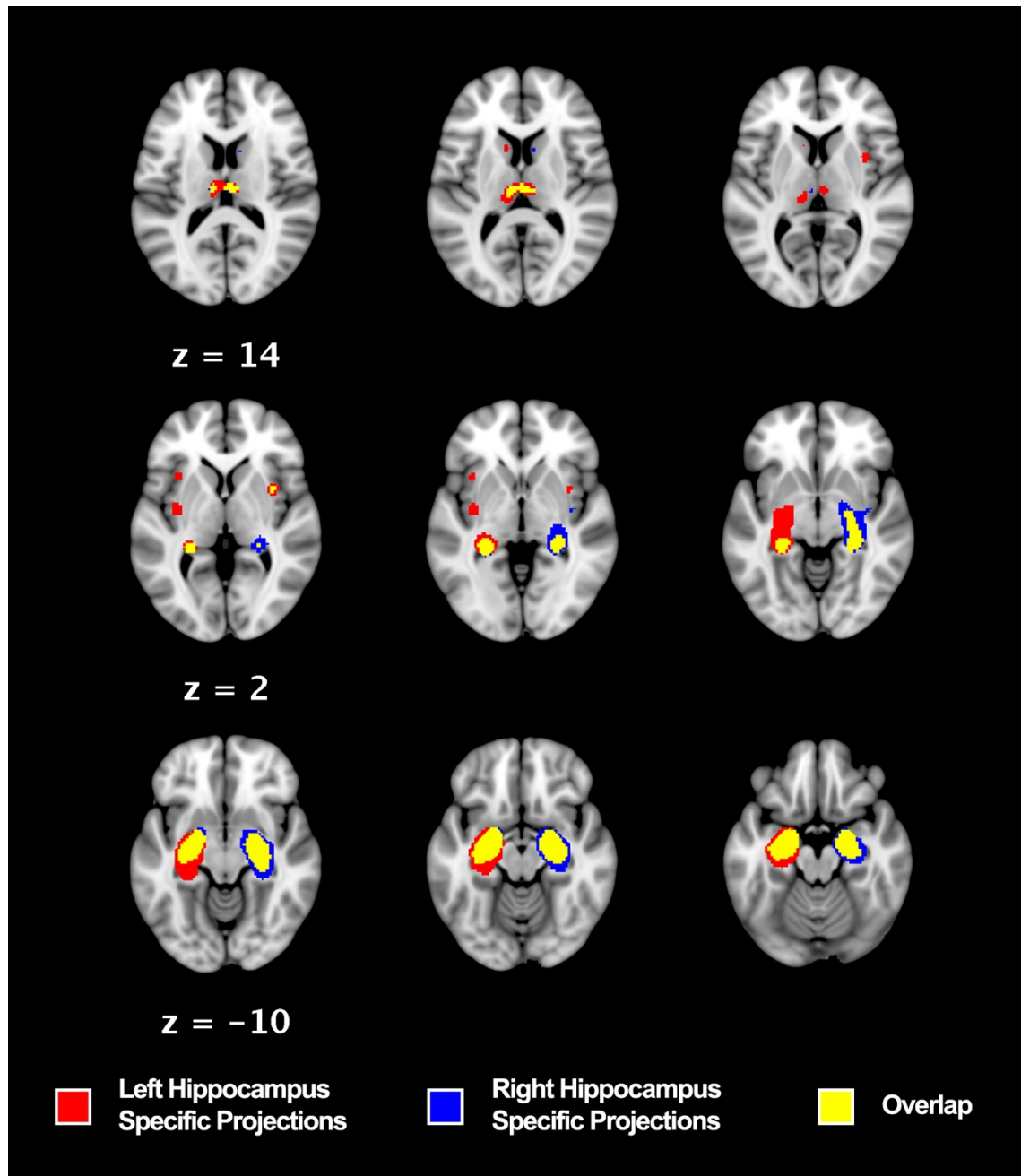


Fig. 7. Laterality of structural covariance between right and left hippocampi: Regions in red are those that co-vary significantly with the left hippocampus seeded in a RtWB meta-analysis. Regions in blue are those that co-vary significantly with the right hippocampus seeded in a RtWB meta-analysis. Regions in yellow represent the overlapping structures of the right and left hippocampus RtWB meta-analyses. All analyses were conducted using a voxel-level FEW 0.01, thresholded to 1000 permutations, and reporting only minimal cluster volumes of 50mm³. Left Hippocampus Specific Projections: left caudate head, left insula, left claustrum. Right Hippocampus Specific Projections: right caudate body, right claustrum (different focus than overlap right claustrum). Overlap: left anterior hippocampus, left posterior hippocampus, right anterior hippocampus, right posterior hippocampus, right MDN of thalamus, left MDN of thalamus, right claustrum (different focus than right hippocampus specific projection).

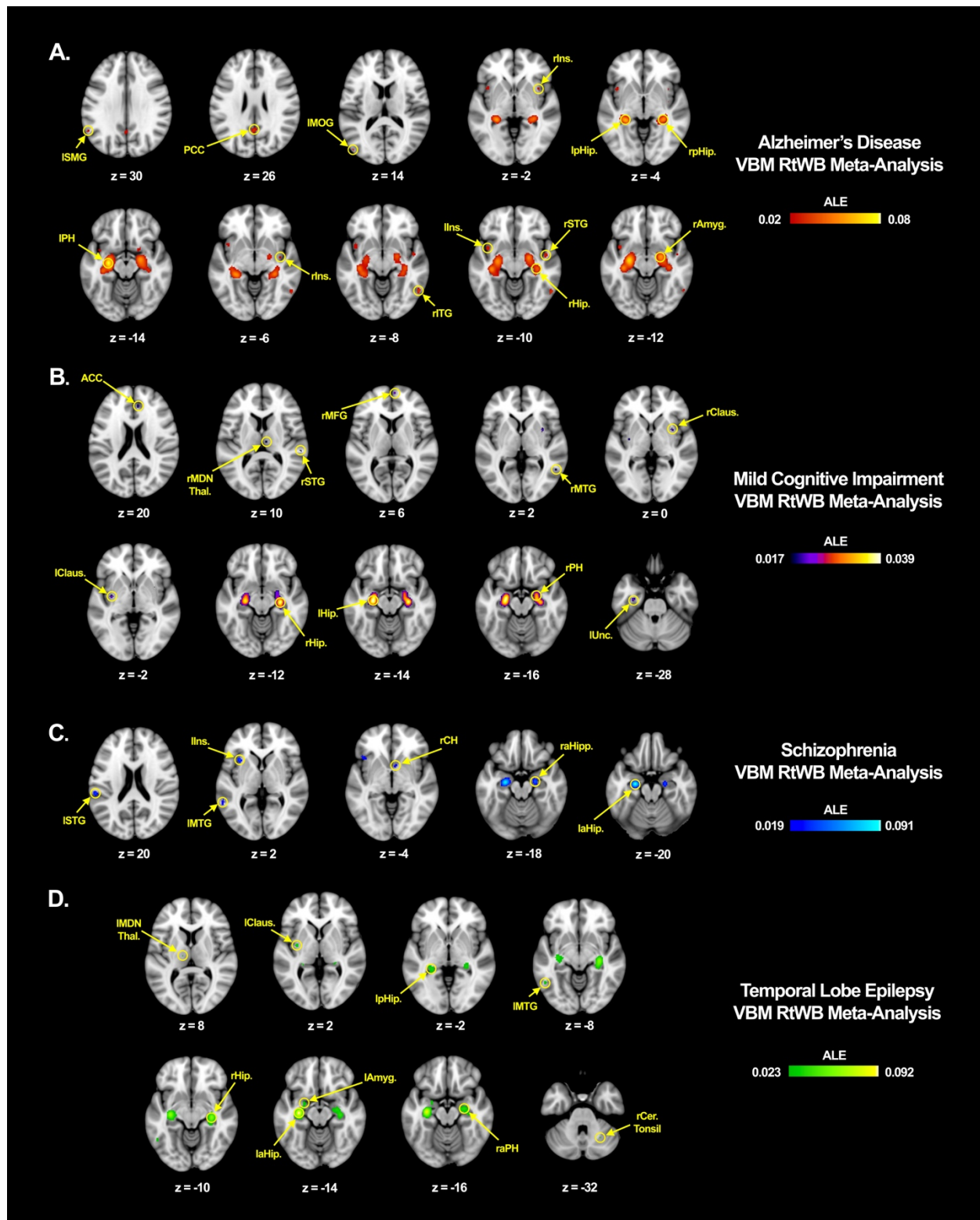


Fig. 8. Hippocampal Region-to-Whole Brain Within-Disease Meta-Analysis: All RtWB within-disease meta-analyses were conducted using GingerALE's Cluster-Level 0.05 analysis with FDR pN 0.05 at 1000 threshold permutations.

- A. The hippocampus was seeded BrainMap's VBM database constrained only to AD VBM studies. 11 significant foci were identified: left supramarginal gyrus (ISMG), posterior cingulate cortex

(PCC), left middle occipital gyrus (IMOG), right insula (rIns.) in two locations, left posterior hippocampus (lpHip.), right posterior hippocampus (rpHip.), left parahippocampus (IPH), right inferior temporal gyrus (rITG), left insula (lIns.), rSTG (right superior temporal gyrus), right hippocampus (rHip.), and right amygdala (rAmyg.). Study consisted of 23 papers, 1350 subjects, 39 experiments, and 443 locations.

- B. The hippocampus was seeded BrainMap's VBM database constrained only to MCI VBM studies. 11 significant foci were identified: Anterior Cingulate Cortex (ACC), right medial dorsal nucleus of the thalamus (rMDN Thal.), right superior temporal gyrus (rSTG), right medial frontal gyrus (rMFG), right middle temporal gyrus (rMTG), right claustrum (rClaus.), left claustrum (lClaus.), right hippocampus (rHip.), left hippocampus (lHip.), right parahippocampus (rPH), and left uncus (lUnc.). Study consisted of 14 papers, 995 subjects, 23 experiments, and 287 locations.
- C. The hippocampus was seeded BrainMap's VBM database constrained only to Schizophrenia VBM studies. 6 significant foci were identified: left superior temporal gyrus (lSTG), left middle temporal gyrus (lMTG), left insula (lIns.), right caudate head (rCH), right anterior hippocampus (raHip.), and left anterior hippocampus (laHip.). Study consisted of 15 papers, 1119 subjects, 20 experiments, and 269 locations.
- D. The hippocampus was seeded BrainMap's VBM database constrained only to temporal lobe epilepsy and mesial temporal lobe epilepsy VBM studies. 9 significant foci were identified: left medial dorsal nucleus of the thalamus (lMDN Thal.), left claustrum (lClaus.), left posterior hippocampus (lpHip.), left middle temporal gyrus (lMTG), right hippocampus (rHip.), left anterior hippocampus (laHip.), left amygdala (lAmyg.), right anterior parahippocampus (raPH), and right cerebellar tonsil (rCer. Tonsil). Study consisted of 18 papers, 1571 subjects, 44 experiments, and 461 locations.

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BrainMap VBM: An Environment for Structural Meta-analysis

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Running Title: BrainMap VBM

Keywords: voxel-based morphometry, structural covariance, structural magnetic resonance imaging, independent components analysis, ICA, **pattern analysis**,

30 transdiagnostic, data-mining, networks, atrophy

ABSTRACT

BrainMap (www.brainmap.org) is a community accessible database of peer-reviewed, coordinate-based neuroimaging literature created to promote the use of coordinate-based meta-analytic (CBMA) methods in human neuroimaging. In prior descriptions of this resource, BrainMap only contained the functional, task-activation literature. Herein we describe the extension of BrainMap to include published reports of structural brain changes obtained using the widely-applied method of voxel-based morphometry (VBM). VBM is a highly automated, whole-brain, voxel-wise analysis that reports the locations of statistically significant between-group and within-group differences as x-y-z coordinates (cluster center-of-mass or peak voxel) in a standardized coordinate space. As with any mass-univariate approach, correction for multiple comparisons is approximate, allowing false positive (type I error) and false negative (type II error) results to appear in the literature. Meta-analysis—computing convergence across multiple studies—is a robust approach for retaining true positive and excluding false positive findings. Here we report the meta-data structure, current data volume, and automated **reverse inference** functions (region-to-disease profile) of this new community resource. Further, we report transdiagnostic structural covariance networks (SCov) obtained through independent components analysis (ICA) of a massive portion of the BrainMap VBM sector **to fully illustrate its content and utility**. We also describe the influence of two data-filtering approaches to reduce data-redundancy effects. Finally, we apply hierarchical clustering analysis (HCA) to measure the disease specificity of each network. With HCA, we find that ICA-derived VBM networks clearly distinguish psychiatric from neurological diseases; psychiatric diseases show markedly weaker network-weighting.

INTRODUCTION

The BrainMap project (www.brainmap.org) has provided a freely accessible, online environment for neuroscientists to compile and analyze coordinate results linked to experimental metadata of published functional neuroimaging studies since 1987 {Fox:1994cx, Gibbons:1992wn}. Experiments using functional magnetic resonance imaging (fMRI) populate most of the database, but other modalities include positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Here, a separate sector of BrainMap is introduced for structural MRI studies that employ voxel-based morphometry (VBM), titled: BrainMap VBM. VBM is a mass-univariate, whole-brain analysis of local grey or white matter tissue volume across or within subject groups, where locations of statistical significance are reported as x-y-z coordinates (cluster center-of-mass or peak voxel) in a standardized coordinate space (Talairach or MNI) [Ashburner and Friston, 2000]. Here, we comprehensively describe BrainMap VBM's novel design, current data volume, quality assurance, and multi-purpose utility (e.g. region-to-disease inference). The unique capacity of this new community resource is then illustrated by employing independent components analysis (ICA)—an exploratory, multivariate strategy that has not previously been applied to VBM metadata.

BrainMap is one of multiple neuroimaging databases currently available, and its distinction from others is useful to discuss. Because BrainMap accumulates x-y-z coordinates, it is considered a coordinate-based meta-analysis (CBMA) resource. An alternative database, Neurovault (www.neurovault.org), stores 3-D unthresholded statistical parametric images (SPI) from each study rather than significant coordinates; this

methodology is defined as image-based meta-analysis (IBMA) [Gorgolewski et al., 2015].

While IBMA incorporates sub-significant data that can prove to be statistically meaningful in aggregation, one persistent and fundamental drawback is the sparsity of SPIs shared.

Significant, standardized x-y-z coordinates are reliably reported. BrainMap is an accruing

community resource, and relies on user submission and quality review by BrainMap's

managing team. Manual coding and review enable high-quality data organization and

characterization, a complementary approach to the fully automated coordinate- and text-

mining CBMA environment, Neurosynth (www.neurosynth.org), which is intrinsically more

prone to error but contains a substantial volume of data [Yarkoni et al., 2011]. Along with

x-y-z coordinates, BrainMap curates extensive experimental meta-data, and provides a

software suite with three cross-platform Java applications for data entry (Scribe), filtered

data retrieval (Sleuth) and statistical analysis (GingerALE) that can be downloaded at

www.brainmap.org/software [Fox and Lancaster, 2002; Fox et al., 2014].

CBMA collectively represents a “powerful, rapidly evolving family of methods for mining

and synthesizing the human neuroscience imaging literature” (for review, see [Fox et al.,

2014]). CBMA is most often used to localize consistently significant regions in a defined set

of studies that are conceptually related (e.g. functional Stroop tasks) or identically designed

(e.g. Alzheimer's vs. Healthy Control VBM). Numerous univariate methods exist for this

purpose, and they are each facilitated using BrainMap VBM. Activation likelihood

estimation (ALE)—referred to as *anatomical* likelihood estimation in the context of VBM

studies—is a parametric methodology which uses a 3-D Gaussian smoothing kernel of x-y-z

coordinates (adjusted according to the sample size per experiment) to model the

probability that a coordinate actually lies within a particular voxel [Turkeltaub et al., 2002].

This smoothing process accounts for **inter-subject and inter-laboratory variability**

typically observed in neuroimaging experiments {Eickhoff:2009dp}. Each voxel-wise

probability image per experiment, referred to as a “modelled activation” (MA) map, is

5 iteratively combined via a probability union for a resultant ALE statistic image [Eickhoff et

al., 2012]. The ALE methodology has advanced in a variety of ways, and can be easily

implemented with common statistical inference strategies in the GingerALE software

[Eickhoff et al., 2009; Eickhoff et al., 2016; Laird et al., 2005; Turkeltaub et al., 2011].

Similar, but conceptually distinct, univariate CBMA methods include multi-level kernel

10 density analysis (MKDA) and signed differential mapping (SDM). MKDA uses a spherical

indicator function (radius = 10-15 mm) to smooth coordinates and produce a 3-D

histogram of nearby peaks in each voxel [Wager et al., 2007]. **While ALE and MKDA both model peak activity convergence, SDM aims to recreate statistical parametric images**

and focuses on local effect sizes. In SDM, coordinates are smoothed with large FWHM

15 kernels (20-25 mm), and both increased and decreased effect sizes—not probabilities—are

plotted on the same map [Radua and Mataix-Cols, 2012]. Also, meta-regression of external

assessments like symptom scores and genetic load have been explored in both SDM and

ALE [Dogan et al., 2013; Lansley et al., 2013].

20 **ALE, MKDA, and SDM each address a salient topic in the current neuroimaging**

environment: reproducibility {Mueller:2017hp, Poldrack:2017gx}. In a highly

publicized study, Eklund et al. [2016] demonstrated inflated false-positive rates in massive

null-fMRI datasets due to faulty cluster-based thresholding by popular software packages.

They concluded that cluster-based inference is more sensitive to statistical assumptions (e.g. ‘uniform smoothness’, where local variations in image smoothness aren’t accounted for) which is corroborated by several VBM studies [Salmond et al., 2002; Scarpazza et al., 2013; Scarpazza et al., 2015; Silver et al., 2011]. Silver et al. [2011] reported inflated false-positives in a VBM null-dataset when applying lower cluster-forming thresholds ($\alpha_c = 0.01$, 0.05) and smaller smoothing kernels (6mm). Sample size also contributes to varying VBM results, as larger sample sizes introduce more power and higher sensitivity which reduces type-II error. Fusar Poli et al [2014] analyzed 324 VBM studies and indeed found a positive, but weak relationship between number of foci reported and sample size. They suggested that reporting biases are more prevalent in smaller studies, which would account for their result. Along with the revaluation of cluster-based statistical methodology, Eklund et al. [2016] recognized that “metaanalysis can play an important role in teasing apart false-positive findings from consistent results.”

Many multivariate methods—which go beyond statistical tests per voxel and can measure inter-regional functional covariance (FCov), or “connectivity”—have demonstrated clear applicability to the coordinate-based literature, an important finding that has delivered a host of CBMA tools. To avoid confusion of terminology, the reader may refer to {Bzdok:2017cl}; the author discusses the semantic differences between the traditional definition of “multivariate” and that in use by the general neuroimaging community. Multivariate CBMA tools, from the neuroimaging perspective, include meta-analytic connectivity modeling (MACM), a seed-to-whole-brain or seed-to-target CBMA approach that utilizes BrainMap’s diverse task-activation collection

to identify patterns of co-activation of an *a priori* ROI [Robinson et al., 2010]. MACM has been applied by Torta et al. [2011], Zald et al. [2012], and Ramage et al. [2013] among many others to characterize the connectomic and behavioral associations of brain regions.

The same principle has been used on a smaller scale to parcellate subregions of

canonical anatomical designations, for example, the pulvinar thalamus

{Barron:2015ih}. This CBMA approach has added value to a family of methods known as Connectivity-based Parcellation (CBP) {Eickhoff:2015fm}. Using graph theory,

Crossley et al. [2013] compared the relative frequency at which each pair of 638 ROIs **across the whole-brain** was co-activated by multiple tasks in BrainMap and found

occipital, central, and default-mode modules that were behaviorally specialized as well as rich clubs that were diversely co-activated by tasks requiring both action and cognition

{vandenHeuvel:2011he}. In a particularly innovative strategy, ICA was extended to the functional sector of the BrainMap database by Smith et al. [2009]. Treating each modelled activation (MA) image as an effective “time-point” in arbitrary order, they established 10

canonical networks that show correspondence both during task and resting-state, and attributed behavioral characteristics to each using BrainMap metadata. Finally, several studies have established system-level structural equation models using nodes derived from BrainMap to study effective connectivity in primary datasets [Laird et al., 2008; Li et al., 2016; Price et al., 2009].

BrainMap VBM is a new resource that can offer an equivalent potential of research in structural covariance (SCov), an analog to FCov. SCov is defined as inter-individual differences in regional brain structure, e.g. cortical thickness or grey matter density,

covarying with other brain regions across a population [Alexander-Bloch et al., 2013]. SCov has proven to be a sensitive method in studying disease, and has shown alterations in a range of symptomatologies beyond neurodegenerative disorders [Coppen et al., 2016; Minkova et al., 2016] including schizophrenia [Palaniyappan et al., 2014], autism [Dziobek et al., 2010], major depressive disorder (MDD) [Wu et al., 2017], and even chemotherapy-related cognitive impairment [Hosseini et al., 2012] to name a few. Conceptually, MACM is equally applicable to SCov as it is to FCov, although it is not yet widely used. A seed-to-whole-brain and seed-to-target CBMA SCov **application was recently published** by Kotkowski et al. [2018] **with promising results**.

Since the primary motivation for this work is exhibiting the contents and utility of BrainMap VBM, we propose independent components analysis (ICA) as well-suited toward this end. ICA isn't limited to manually selected regions of interest, but instead decomposes a set of whole-brain signals into spatial component maps of maximal statistical independence [Beckmann:2004fe]. Here, the multivariate and exploratory nature of ICA is fully leveraged with BrainMap VBM in that many diseases (43) showing grey matter morphology are processed together in a pseudo time-series for pattern identification. ICA has shown success in disseminating SCov components from T1, inter-subject covariance data in healthy and diseased populations [Coppen et al., 2016; Eckert, 2010; Hafkemeijer et al., 2014; Segall et al., 2012; Xu et al., 2009]. In this study, we demonstrate that ICA of BrainMap VBM coordinates—blind to any diagnostic information—can extract components of inter-experiment SCov and can comprehensively inform disease specificity through reverse inference (i.e. region-to-disease) methodology presented here. While ICA of

functional metadata has a strong literature {Laird:2011ep, Smith:2009bh, Ray:2013ed}, it has not previously been applied to VBM metadata.

Error and artifact naturally occur in massive meta-analytic datasets like BrainMap, and can stem from experiment mischaracterization, incorrect coordinate documentation, or—of which we address here—within-group effects. Within-group effects impact the results of ALE and other CBMA methods when groups of subjects with multiple experiments in a dataset influence results more than groups with only one experiment [Turkeltaub et al., 2011]. Here we notice a non-trivial number of VBM studies that report experiments with varying statistical thresholds, sub-group analyses, or follow-up experiments which resulted in similar or identical coordinate(s) results being reported, i.e. data-redundancy (within-group and data-redundancy effects are used here interchangeably). Such experiments are removed in an intensive workspace review by an experimenter performing a well-designed meta-analysis {Muller:2017ip, Fox:1998vl}. Large-scale analyses of the entire database (e.g. MACM, ALE), however, employ limited filters which inherently restrict rigorous review. Here we report an automated and semi-automated approach to identify and exclude experiments for large-scale meta-analysis in accordance with the standards regarding incidental findings recommended by the Committee on Best Practices in Data Analysis and Sharing (COBIDAS) [Nichols et al., 2016]. Importantly, these methods are adaptable to large-scale CBMA methods beyond ICA and advance the integrity of these analyses.

This study: 1) presents the meta-data structure, existing data volume, automated data-interpretation functions, and multi-purpose utility of the community-accessible BrainMap VBM database; 2) reports 21 SCov networks computed by applying ICA to data representing 30,218 diagnosed subjects (and 23,007 healthy control subjects) across 43
5 different diagnoses; 3) assesses an automated and semi-automated approach to detection and elimination of data-redundancy; and, 4) applies hierarchical clustering analysis (HCA) to investigate the organizational architecture of SCov networks with respect to disease specificity.

METHODS

Meta-data Structure & Coding

Basic criteria for BrainMap eligibility is whole-brain analysis (i.e. not region-of-interest methods), coordinate results reported in standardized space, and publication in an English-language journal. The BrainMap VBM hierarchical database design is illustrated in Figure 1, and can be separated into Paper-level, Experiment-level, and Location-level tiers. Paper-level descriptors include—but are not limited to—basic citation information such as the journal, authors, keywords, and institution; an abstract summarizing the paper; each subject-groups' size, average age, gender ratio, specific inclusion-exclusion criteria, and relevant diagnosis (or diagnoses) according to the current version of International Classification of Disease Codes (ICD-10) managed by the World Health Organization [1992] per subject-group; any *External Assessments* that were used to evaluate subjects (e.g. Clinician Administered PTSD Scale, Body-Mass Index, etc.); *Session* information including the number of scans and the time interval apart (e.g. pre- vs. post-treatment, 3 months); the imaging modality used (e.g. 3T MRI) along with software packages, pre-processing protocol, and standardized space applied (i.e. MNI or Talairach); and a feedback field for any questions or comments for the BrainMap reviewing team.

In BrainMap, an *Experiment* is defined operationally by the production of a statistical parametric image (SPI) [Fox et al., 2005]. A *Paper* usually reports multiple *Experiments*. Each *Experiment* is generated based on criteria defining specific subsets of the subject-groups, *Sessions*, *External Assessments* (e.g. symptom score correlation), or statistical protocol—which Experiment-level taxonomy accounts for. Once a paper is coded via the

Scribe software and submitted, it is verified for quality assurance by a taxonomy expert who has had extensive training. In addition, the user-interface that is implemented to code papers, Scribe, is regularly evaluated and updated to meet the needs of a burgeoning neuroimaging field. This includes additional meta-data fields for proper characterization, e.g. new software packages.

Independent Component Analysis

To investigate SCov of grey matter in disease, two filters were applied to the BrainMap VBM database in preparation for ICA; only (1) 'Grey Matter' *Contrast* and (2) 'Disease' *Context* experiments were included (Figure 2). These criteria encompassed most of the VBM database (Table I). The established method of Independent Component Analysis in BrainMap metadata is shown in the Experiment ICA, (Figure 3, a) [Laird et al., 2011; Ray et al., 2013; Smith et al., 2009]. Peak coordinates in the VBM BrainMap database were smoothed using a Gaussian distribution (FWHM = 12 mm) to for "Modeled Activation" (MA) images with 2x2x2-mm resolution. ICA was then applied to the **2-D (vectorized voxel values x Experiment-ID)** dataset using MELODIC (multivariate exploratory linear optimized decomposition into independent components; [Beckmann et al., 2005]) in FSL (FMRIB Software Library; [Smith et al., 2004; Woolrich et al., 2009]). **In the current literature of ICA in T1-weighted data, the dimensionality has ranged considerably across studies. Values chosen include 7 {Eckert:2010it}, 9 {Xu:2009ke, Hafkemeijer:2014ed}, 10 {Coppens:2016hw}, and 75 {Segall:2012bg}.** We selected a dimensionality of 20, which matches that of Smith et al. [2009], where canonical, large-scale functional networks using BrainMap metadata were established. **We recognize the**

fundamental differences between functional and structural datasets, but we presume many readers are familiar with a dimensionality of 20. The primary purpose of this analysis is to demonstrate that SCov components can be extracted from BrainMap VBM metadata, and to display the massive, transdiagnostic nature of this resource. Future work can investigate varying dimensionality, as was done by Ray et al. (2013) in the functional database.

Incidental findings found in Experiment ICA from coordinate redundancy in two separate papers (Sup. Figure 1) spurred two approaches in filtering the database for large-scale analysis. The modified Paper ICA was performed by grouping the MA images by Paper-level to create the **2-D** dataset (**vectorized voxel values** x Paper-ID) resulting in $M = 757$ “time-points” (Figure 3, b). This approach was an expedient solution from a programming perspective and eliminated both data-redundancy artifact components. However, collapsing the dataset this way reduced our data volume/statistical power and in some cases combined multiple biologically distinct statistical contrasts. We therefore investigated a separate strategy, the Experiment-filtered ICA (Figure 3, c). This required the removal of experiments that were data-redundant. To identify these **outlier** papers, we queried the database for papers that reported the same x-y-z coordinate in multiple experiments. A total of 28 papers were identified with a collective experiment count of 212. This represented 4% of publications in the VBM database. Filter criteria in “cleaning” experiments are contained in the Supporting Information.

Region-to-Disease Association

Two reverse inference methods were employed to measure the association, i.e. weighting, of a given ROI or z-score image to distinct ICD-10 Diagnoses, i.e. $P(\text{Diagnosis} \mid \text{Region})$. The regional analysis method (Figure 3, d), extended from a region-to-function study by Lancaster et al. [2012], extracts coordinates for every ICD-10 Diagnosis separately; the

5 fraction of coordinates falling within the specified ROI was computed and compared with the fraction expected if coordinates of the diagnosis were not clustered, i.e. uniformly distributed. A significant disease association was determined if this discrepancy was large enough, i.e. producing a z-score ≥ 3.0 when corrected for multiple comparisons. Z-score calculation is provided below:

$$10 \quad z = \frac{p_0 - p_e}{\left(\frac{p_0(1 - p_0) + p_e(1 - p_e)}{N_b} \right)^{1/2}}$$

where observed probability (fraction of foci in ROI/outside of ROI) is p_0 , expected probability (fraction ROI/whole-brain volume) is p_e , and number of total foci (i.e. across the whole-brain) per distinct ICD-10 is N_b . This tool is frequently updated as studies accumulate in the database, and can be easily implemented as a plugin in the image-

15 analysis software, Mango, with millisecond processing times (www.ric.uthscsa.edu/mango/download).

In a separate reverse inference method using spatial correlation (Figure 3, e), we performed disease association measures using z-score ICA component images, i.e. not ROIs.

20 MA experiment images from each ICD-10 diagnosis were spatially correlated with z-score component images and averaged. This averaged correlation value, ranging from -1 to 1, represented the strength of disease association by similar spatial smoothness modeled

from coordinates. We confined our interest only in the positive values of the ICA components, masking components at $z > 0$ for spatial correlation. Because MA images only included positive values (i.e. modeled probabilities), negative z-scores extracted from ICA only result from mathematical artifacts associated with explicit and implicit data demeaning in ICA and are not derived from negative values in the original data {Laird:2011ep}. For more information discussing the motivation of this analysis, see Supporting Information.

10 Hierarchal Clustering Analysis

Hierarchal Clustering Analysis (HCA) was performed **on the (21x43) data matrix of network loadings** to identify clusters of components based on similar disease loading and, conversely, clusters of diseases according to their component loading. R Studio (www.r-project.org) was used for heatmap visualization and HCA analysis using the package gplots version 3.0.1. Pearson's correlation ($1 - r$) was used to calculate the 'distance' metric. With the distance matrix, we employed an "average linkage" algorithm that calculated the average distance between elements of each cluster. A similar method was used by Laird et al. [2011] and Ray et al. [2013] in their analyses of functional BrainMap ICA components. To identify **an appropriate** number of clusters **with HCA** in both diseases and components, **two separate statistical tests were applied evaluating each possible cluster size ($k = 1, 2, \dots, K$) measuring the "distinctness" of cluster groupings**: the silhouette **length** [Rousseeuw, 1987] **and the gap statistic {Tibshirani:2001fj}**. An average silhouette width is calculated from every object (i.e. each component or disease)

from its similarity to objects within its own cluster compared to other clusters. The silhouette ranges from -1 to 1, where a high value indicates that the object is well matched to its own cluster and poorly matched to neighboring clusters. **Similarly, the gap statistic is formed by comparing the change in within-cluster “dispersion” with that expected**

5 **under an appropriate reference null distribution {Tibshirani:2001fj}.**

RESULTS

Data Volume

The current data volume of the BrainMap VBM database is summarized in Table 1. Papers and experiments are sorted by the *Context* meta-data field, and further separated by

5 *Contrast* within the ‘Disease’ *Context* only. Some experiments are co-coded, i.e. an experiment is labelled both ‘Genetic’ and ‘Disease’. Experiments labelled in ‘Disease’ *Context* comprise most of the database, with ‘Normal Mapping’ and ‘Aging’ also considerably contributing. A PubMed search of (“Voxel-based Morphometry”) returned 4,237 publications, suggesting that BrainMap contains roughly 20% of the existing VBM
10 literature. The number of experiments varied per ICD-10 diagnosis (Sup. Figure 4), with a range from 10 to 245 and a median of 20 experiments/ICD-10 diagnosis. To determine the influence that diseases with more experiments had, a linear regression of experiment count vs. average cross correlation was performed. A significant association was found ($p < 0.03$), with a slope of 5.375×10^{-5} /experiment.

15

Components

The Experiment-filtered ICA and Paper ICA showed largely similar results, with 14 anatomically matched ($r > 0.4$, avg. $r = 0.61$) transdiagnostic SCov components. These components are displayed in Figure 4 (A – N), where overlap is colored yellow. In three of
20 these networks the Experiment-filtered ICA showed fractionation (G, J, K), i.e. two components corresponded to one Paper ICA component, and overlap is shown in white. Four networks proved to be unique to their respective method (O – R). Both the Paper ICA and Experiment-filtered ICA removed two artifacts produced by experiment redundancy

caused by two papers (Sup. Figure 1). The Experiment-filtered ICA thus only extracted one artifact, which contained entirely white matter—an expected result because parts of standard space involving “very few nonzero values in the input data, the combination of demeaning (of what was originally positive or zero data) and the variance normalization of voxels’ time series leads to meaningless components” [Smith et al., 2009]. The Paper ICA contained 4 artifact components; each artifact was anatomically diffuse with a low z-score distribution. The Paper ICA showed the most explained variance at 22%, while the Experiment-filtered ICA reported 17% explained variance (**Sup. Figure 3**). **A description of each component and its eight largest anatomical clusters are shown in Table II.**

Component visualization can be done online via the ANIMA database at www.anima.fz-juelich.de {Reid:2016eq}.

Region-to-Disease Analyses

A disease-component heatmap is shown in Figure 5; average spatial cross correlation was employed **per network to extract disease loadings**. Figure 5 includes 43 ICD-10 diagnoses across 21 VBM-ICA components for a total of 903 weights (**artifact components—as described in the preceding paragraph—were not included**). **For relevance, Figure 5 excludes network weights from ICD-10 diagnoses with a small sample size (< 10 experiments).** A histogram distribution of weights is also provided in Figure 5. The regional analysis and average spatial correlation region-to-disease methods (**Figure 3, d & e**) showed a significant association in a linear regression (Sup. Fig 2).

HCA Disease and Component Clusters

Psychiatric diseases (ICD-10 F codes) were clearly separated from neurological disorders (ICD-10 G codes) after applying HCA, as is evident in the middle portion of Figure 5. In the HCA analysis, total cluster numbers were specified at $k = 9$ for components (each color corresponds to a cluster on the x-axis in Figure 5) and $k = 11$ for diagnoses (y-axis), selected from local maxima in the average silhouette width **and gap statistic** for each possible cluster size ($k = 1, 2, \dots, \max$) (Sup. Figure 6). Component cluster labels are provided in the silhouette plot (Sup. Figure 7). Three component clusters (Clusters 1, 2, and 5) each showed high within-cluster similarity, i.e. they weighted similarly on diseases. We present these clusters of interest (Clusters 1, 2, 5) in more detail below; the Talairach Daemon atlas [Lancaster et al., 2000] is used for automated labeling.

Cluster 1 included Components P, I, K1, G2, and G1. Component P, unique to the Experiment-filtered ICA, was left-lateralized across the superior/middle temporal gyri and insula. It also incorporated the bilateral middle frontal gyri (BA 9) and medial frontal gyrus (BA 6). Component I peaked in the bilateral inferior frontal gyri (BA 47) and spread inferiorly. G1 and G2 were mostly confined to the left and right anterior hippocampus respectively. Component K1 included the amygdala, thalamus, and cingulate gyri among other regions. Each network significantly weighed on G30: Alzheimer's Disease (min: 0.04, max: 0.16, avg: 0.11), G31.84: Mild Cognitive Impairment (MCI) (min: 0.05, max: 0.13, avg: 0.08), and marginally on G20: Parkinson's Disease (min: 0.02, max: 0.05, avg: 0.03). Excluding Component P, each component loaded on G40.2: Temporal Lobe Epilepsy (avg: 0.07). Component K1 starkly loaded on Z81.8: Family History of Mental Disorder (0.10) and Component I on F60.2: Antisocial Personality Disorder (0.08).

Cluster 2 included components A, O, K2, and L, which shared topological similarity among the thalamus, caudate, and the insula. Component A was most significant in the caudate head and included the posterior insula. Component O was unique to the Experiment-
5 filtered ICA method, meaning it did not show enough inter-paper co-variance to be identified in the Paper ICA method. It peaked in the medial dorsal nucleus of the thalamus and contained the precentral gyrus (BA 9). Component K2 was most significant in the anterior insula, putamen, and included the anterior cingulate (BA 32). Component L peaked in the posterior insula and included the posterior cingulate/precuneus and anterior
10 cingulate. Each network heavily loaded on G10: Huntington's disease (avg: 0.22), G37.8: Other Specified Demyelinating Diseases (avg: 0.07), G35: Multiple Sclerosis (avg: 0.06), and G31.85: Corticobasal Degeneration (avg: 0.06). Excluding L, each loaded upon G24.9: Unspecified Dystonia (avg: 0.123). And excluding O, each network loaded upon G90.3: Multi-system Degeneration (0.09) and G31.0: Frontotemporal Dementia (0.06).
15 Individually, Network O especially loaded upon G31.85: Corticobasal Degeneration (0.09) and Temporal Lobe Epilepsy (0.06).

Cluster 5 contained components F and H. Both networks incorporated different aspects of the frontal lobe. Component F contained a large portion of the medial frontal lobe. It's
20 highest z-score was in the cingulate (BA 32); it also included the bilateral pre-central gyrus, insula and thalamus. Component H peaked in the medial frontal gyrus and the anterior cingulate, and contained the left thalamus/parahippocampus and right occipital gyrus. Both networks weighted most on M79.7: Fibromyalgia (avg: 0.054), F43.10: Post-

Traumatic Stress Disorder (avg: 0.037), Z91.49: Personal History of Psychological Trauma (0.033), and moderately on G31.0: Frontotemporal Dementia (avg: 0.023) and G89.2: Unclassified Chronic Pain (avg: 0.022).

DISCUSSION

An extension of the BrainMap database to include a separate sector for voxel-based morphometry experiments in addition to functional experiments has been introduced. To date, the VBM database contains coordinates from >3,000 experiments with detailed, hierarchical meta-data. The database is a community resource and can be utilized with a variety of univariate (e.g. ALE) and multivariate (e.g. MACM) meta-analytic approaches. For the first time, this study **leverages the** exploratory and multivariate capability of Independent Components Analysis (ICA) on VBM coordinates to extract transdiagnostic, inter-experiment SCov components. At the time of analysis, the BrainMap VBM database represented over 53,000 subjects across mainly 43 different ICD-10 diagnoses as well as healthy controls. An automated and semi-automated data-cleaning approach for ICA preparation was employed to appropriately handle data-redundancy effects, and can be adapted for other large-scale analyses. In addition, with disease loadings calculated from every network, hierarchical clustering was performed to investigate the organizational architecture of SCov across disease.

BrainMap VBM Coding & Region-to-Disease Inference Tools

The BrainMap meta-data coding scheme is a description system using mostly structured keywords that concisely capture experimental methods and research questions. In designing the functional BrainMap database, Fox et al. [2005] surveyed the neuroimaging literature and designated cogent, hierarchical *Behaviors* (e.g. Cognition:Working-Memory, Interoception:Sleep) and *Paradigm Classes* (e.g. n-back, Episodic Recall), as well as *Conditions* to describe the sensory stimulus applied (e.g., visually presented words), the

response made (e.g., words spoken aloud), and the instructions for each condition. The functional taxonomy of BrainMap was then validated by testing its coherence with data-filtering choices made by subject-matter experts carrying out meta-analyses [Fox et al., 2005]. Design of the VBM database was intrinsically simpler because of the straightforward experimental methods that encompass most of the VBM literature (i.e., disease vs. control group-wise contrast). Existing, BrainMap data-fields including *Behaviors*, *Paradigm Classes*, and *Conditions* were excluded in the VBM database, while International Classification of Disease (ICD-10) codes were implemented with the goal of performing analyses to localize and compare the morphological phenotypes of distinct brain disorders. A distinguishing feature of the present study was the broad inclusion of brain disorders across diagnostic category. ICA presented itself as an ideal, exploratory strategy to find **multivariate** patterns in the data **and to exhaustively exhibit its contents**. The analysis showed convincing results that provided a wealth of transdiagnostic knowledge (Figure 5).

The BrainMap workspace structure is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [Liberati et al., 2009]. PRISMA consists of a 27-item checklist and a four-phase flow diagram created by an international team of scientists and methodologists in response to poor reporting of systematic reviews. The meta-data structure of the VBM database, along with filtered search software (Sleuth), enable inclusion and exclusion criteria to be faithfully applied, reported, and—if the author chooses—shared via a workspace data file. The size of any neuroimaging meta-analysis varies and depends on the available literature per topic. In a recent study, Eickhoff et al.

[2016] performed extensive simulation analyses and recommended a minimum of 20 experiments to achieve sufficient power for moderate effects when using ALE.

The Disease Regional Analysis tool presented in this study utilizes the ICD-10 BrainMap meta-data. It is a freely-accessible plugin tool for the Mango GUI that extracts coordinates from the BrainMap VBM database, and assesses the association of a specified ROI across 39 ICD-10 diagnoses (Figure 3, d). The accumulation of coordinates in BrainMap allows the tool to be increasingly powerful, as it is intermittently synchronized to the most recent version of the database. The tool is conceptually straightforward, and provides comprehensive results in a short processing time (~1 second). Disease Regional Analysis showed a strong association with a separate, more computationally-expensive spatial correlation method (Sup. Figure 3).

Data-Redundancy

Following an Experiment ICA (Figure 3, a), two filtering protocols were tested to appropriately handle the observed data-redundancy artifacts (Sup. Figure 1). Paper ICA, while algorithmically expedient, incorporated less data volume because many experiments of the same paper were combined into one MA image (i.e. “time point”) to completely avoid coordinate redundancy from a single paper/subject-group. The Experiment-filtered ICA involved querying the database for **papers showing outlier influence** (> 2 x-y-z coordinate recurrences/paper), and subsequent experimenter review using inclusion-exclusion criterion to filter those 212 **outlier** experiments (see Supporting Information). This resulted in larger data volume for ICA input compared to the Paper ICA. We recognize

the complimentary nature of both methods in terms of noise artifacts vs. explained variance, which can be attributed to data input volume (i.e., more to data to model resulted in less explained variance). Each method, while expressing very similar results (**Figure 4**), gleaned some unique information. Paper ICA produced a cerebellar component (Q) that showed extremely specific weighting on ataxias. Experiment-filtered ICA generated a left-hemispheric, temporal component (P) involving language, and predictably weighted on aphasia. The same data-cleaning principles employed here are recommended for other large-scale, minimally filtered CBMA applications.

HCA Component Clustering & Disease Specificity

Psychiatric and neurological diseases were clearly separated by HCA—an unsupervised learning algorithm that organizes diagnostic categories and independent components into separate dendrograms (Figure 5). As conveyed in the middle portion of the Figure 5, psychiatric diseases did not show robust component association. In a post-hoc analysis supporting this conclusion, we performed a non-parametric Wilcoxon rank sum test on network loadings of the neurological sample (F code, 13 diseases x 21 networks = 273 sample size) and psychiatric sample (G code, 21 diseases x 21 networks = 441 sample size). We found a significant difference between samples ($p = 0.012$); the neurological sample showed a higher mean rank. Neurological diseases indeed induce more atrophy compared to psychiatric disorders, i.e. more coordinates [Fusar Poli et al., 2014], but that doesn't entirely explain the substantially weaker loadings observed here. Instead, these findings suggest that psychiatric diseases show a consistently weaker spatial pattern of morphometric change across studies in comparison to neurological diseases. In Figure 6,

we display three component clusters of interest. These clusters (Cluster 1,2, and 5) show high within-cluster similarity (avg. silhouette > 0.43), i.e. weight similarly on diseases.

Previous computational approaches toward understanding the network architecture of

VBM coordinate data compliment the present analysis. An atrophic pattern matching Component K2 (anterior insula and dorsal anterior cingulate) was reported in a VBM meta-analysis combining schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety by Goodkind et al. [2015]. They found that decreased gray matter in those regions is associated with worse executive functioning and sustained attention. Component K2 in the present analysis shared the same topology, and provides more evidence of a shared endophenotype across psychiatric disorders, which Goodkind et al. [2015] points out, “is not currently an explicit component of psychiatric nosology”.

Disease non-specificity was also observed in Component L, which had the highest median disease score (0.022). Component L included the posterior and anterior cingulate, as well as the posterior insula. Consistent with this finding, Crossley et al. [2014] performed graph analysis of VBM coordinates and primary diffusion tensor imaging (DTI) data of healthy subjects and found that disease lesions most frequently target ‘hub’ regions, i.e. grey matter nodes with the highest number of fiber tract connections. One of the most structurally connected nodes of DTI data included the posterior cingulate cortex.

20

Structural Covariance in Disease

The transdiagnostic SCov networks reported here replicate other disease-related SCov networks published. In an ICA of T1-weighted images of schizophrenia patients and

controls combined, Xu et al. [2009] found that the most significant component showing diminished network integrity (i.e. atrophy) included the superior temporal gyri, insula, and medial frontal gyrus. This topology mirrored Component E in this analysis, which weighted highest on schizophrenia. Seeley et al. [2009] found that Alzheimer's disease, behavioral variant frontotemporal dementia, semantic dementia, progressive nonfluent aphasia, and corticobasal syndrome each atrophied distinct anatomical regions that reflected seed-based structural covariance among healthy subjects. The present investigation indeed found SCov networks accentuated in Alzheimer's disease (Component J2), aphasia (Component P), and corticobasal degeneration (Components C and O) when comparing against one another.

Coppen et al. [2016] combined T1 images from premanifest gene carriers of Huntington's disease, manifest Huntington's disease, and healthy controls to perform structural ICA. Two networks—a caudate nucleus network and a hippocampal network—showed reduced network integrity in both Huntington's disease gene carrier groups compared to controls. Here we report a network (Component A) with similar topology extending beyond the caudate with extreme loading on Huntington's disease. In a separate study, Wu et al. [2017] investigated SCov in MDD within functional networks involved in emotion regulation. They observed a SCov increase of the right amygdala and right angular gyrus in MDD.

Component K1 contained both regions ($z > 3$), and was MDD's highest network weighting. Considering that Component K1 was associated with many diseases, however, this connection could be non-specific to MDD.

The mechanisms driving long-distance SCov are an active area of research [for review, see Evans et al., 2013], and multiple hypotheses have been put forward to understand the network-based atrophy observed in brain disorders; these include: 1) transneuronal

spread, 2) nodal stress, 3) trophic failure, and 4) shared vulnerability. 1) The

transneuronal spread mechanism begins in an epicenter, often a hub (i.e. the hippocampus, insula, etc.), where alterations spread along axonal pathways in a “prion-like” manner

[Ahmed et al., 2016; Zhou et al., 2012]. 2) The nodal stress mechanism suggests that brain

hubs are selectively susceptible to damage from oxidative stress and endothelial damage

leading to impairments, such as a leaky blood brain barrier [Crossley et al., 2014]. 3) The

dysfunction of trophic factors includes brain-derived neurotrophic factor (BDNF), which is involved in dendritic and axonal branching [Cohen-Cory et al., 2010]. When trophic factor

expression and regulation is impaired, trophic failure in the form of poor cellular and

synaptic maintenance impairs structural connectivity [Fornito et al., 2015]. 4) Lastly,

shared vulnerability is a mechanism whereby similar neuronal cell types across the brain

are susceptible to disease-specific changes due to shared genetic and metabolic profiles

[Cioli et al., 2014]. Future work can quantitatively compare the transdiagnostic SCov

networks reported here to functional networks to investigate the plausibility of these

hypotheses. Such an analysis could also compare the network degeneration effectiveness

across diseases. Segall et al. [2012] performed a spatial comparison between structural and

functional ICA components in healthy subjects, and proposed further efforts toward

understanding how neurodegenerative syndromes play a role in the structural and

functional connectome interaction.

Structural Covariance in Healthy Aging

Healthy, aging subjects have also been studied using structural ICA. Hafkemeijer et al.

[2014] performed ICA on 370 T1-weighted, grey-matter segmented MRI images in middle-aged to older adults from 45 to 85 years-old. They found strong age-related atrophy in

5 subcortical, sensorimotor, and posterior/anterior cingulate networks. Upon visual inspection, those SCov networks showed similarity to Components A, M, and L respectively.

Segall et al. [2012] also performed structural ICA on 603 healthy subjects, and found the largest age effect on a motor network similar to Component M. **Although the dataset in**

the present analysis incorporates mechanistically diverse disease processes across

10 **the age spectrum (e.g. Parkinson's disease and preterm birth), some components may be influenced by age-related factors such as oxidative stress and inflammation.**

Alternatively, some diseases could selectively target neuroprotective factors defending against age-related detriment {Eckert:2011fl}.

15 **To better interpret our components and their association with age, we utilized the full scope of BrainMap VBM in a post-hoc analysis and queried** for experiments in the

'Age' *Context*. We further excluded positive associations (i.e. hypertrophy), and used 43 experiments representing 3,684 healthy and diseased subjects for analysis. The 43

experiments were compiled in an unthresholded ALE image, and spatially compared to the

20 VBM ICA components. Component M (postcentral gyrus, middle/inferior frontal gyrus), A (caudate, posterior insula), and L (anterior/posterior cingulate, posterior insula)

significantly correlated with the age-related atrophy ALE—representing different aspects of its topology, $p < 5 \times 10^{-4}$ (Sup. Figure 5). Component M showed the highest spatial

correlation to the age-associated ALE ($r = 0.28$), and included brain regions involved in primary sensorimotor function (BA 2/3/4) and cognitive-control (BA 9). Motor deficits in aging adults include coordination difficulty, slowing of movement, and difficulties with balance and gait [Seidler et al., 2010]. These results suggest that certain neurodegenerative diseases may exacerbate distinct structural networks that strongly atrophy with age.

Further analyses are necessary to substantiate this claim.

ICA included some VBM experiments measuring age effects in diseased populations, which could in part explain the age-related networks. Hafkemeijer et al. [2014] reported that age was not significantly associated with gray matter volume in an inferior temporal and three cerebellar networks. These networks matched to Components I and Q respectively, and did not show significant age-association in this analysis.

CONCLUSION

The BrainMap VBM database is a new, accruing CBMA resource for structural neuroimaging. Here, we **extract** transdiagnostic, inter-experiment SCov networks **which exhaustively illustrate the content of the database and its region-to-disease**

5 **capability.** Some networks replicate previously published inter-subject ICA SCov components from Alzheimer's, schizophrenia, aphasia, and Huntington's disease, as well in healthy, aging subjects [Coppen et al., 2016; Hafkemeijer et al., 2014; Seeley et al., 2009; Xu et al., 2009]. Components showing non-specific disease weighting compliment previous work suggesting a shared endophenotype across psychiatric diseases [Goodkind et al.,
10 2015]. The **significantly** weaker psychiatric network loading reiterates the need to better distinguish mental disease according to neurobiological principles [Insel et al., 2010]. **We hope this resource facilitates reproducibility in the field of structural neuroimaging. And as BrainMap VBM becomes more populated, we anticipate larger data-mining activities for more definitive conclusions to be drawn.** Future work can use the
15 components reported here in primary datasets as the NIFTI files are freely available for download at www.brainmap.org/icns and the Archive of Neuroimaging Meta-analyses (ANIMA) database at www.anima.fz-juelich.de [Reid et al., 2016].

LIMITATIONS

The experiments in the BrainMap VBM database across the 43 ICD-10 diagnoses analyzed varied considerably (Sup. Figure 4). The total number of experiments per disease ranged from 10 to 245 (median: 20). Every experiment was included in the ICA analysis to

5 incorporate as much data as possible for the data-mining experiment. This limitation was explored with a regression analysis of each weight (in Figure 2) vs. experiment-count per disease, and a significant ($p < 0.03$), but small association was found (slope: 5.375×10^{-5} /experiment). This suggested that diseases with many experiments in the database (e.g. schizophrenia) **indeed had more influence than diseases with less experiments (e.g.**
10 **temporal sclerosis), but only a small effect was observed.**

ACKNOWLEDGMENTS

This work was supported by awards from the National Institutes of Health (MH74457, RR024387, MH084812, NS062254, AA019691, EB015314) and the Congressionally Directed Medical Research Program (W81XWH0820112, **W81XWH-14-1-0316**).

CONFLICTS OF INTEREST

Nothing to report.

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FIGURE LEGENDS

Figure 1. Hierarchical structure of the VBM database. (Top right) BrainMap meta-analysis workflow of coding a paper with Scribe, compiling and filtering a workspace with Sleuth, and performing statistical analysis with GingerALE—each cross-platform Java application is available at (www.brainmap.org/software). (SPI – Statistical parametric image, CAPS – Clinician Administered PTSD Scale, MNI – Montreal Neurological Institute, ICD-10 – International Classification of Disease version 10). Not all data fields are shown for demonstration.

Figure 2. PRISMA Flowchart. PRISMA Flowchart for selecting studies for transdiagnostic ICA analyses.

Figure 3. Transdiagnostic ICA of the VBM database. (a) ICA input of BrainMap coordinates per experiment, along with the modified data-filtering approaches of (b) Paper ICA and (c) Experiment-Filtered ICA to reduce data-redundancy influence for large-scale analysis. Each image shows smoothed VBM coordinates corresponding to an effective “time point” (in arbitrary order) for ICA. The bottom panel refers to separate reverse inference methods of associating an a priori (d) binary mask or (e) positive z-score image to a disease using BrainMap’s extracted coordinate data. G23.1: Progressive Supranuclear Palsy is demonstrated as an example—which contains 14 experiments in the database. The Regional Disease Analysis tool freely available as a plugin at www.ric.uthscsa.edu/mango/download.

Figure 4. VBM ICA Components. 14 spatially matched components among the Experiment-filtered ICA (green) and the Paper ICA (red) where overlap is yellow. Each ICA was performed at a pre-set dimensionality of 20. Images with white show the similarity between a single Paper ICA component (red) and two fractionated Experiment-filtered ICA components (green & blue). Four spatially unique components to each method are shown in the bottom (O – R). Artifact components aren't displayed.

Figure 5. Heatmap of Component & Disease Weighting. Heatmap includes weighting of 43 International Classification of Disease (ICD-10) codes with ≥ 10 experiments in the BrainMap database (average spatial correlation, see Methods). HCA orders x and y-axes by similarity between components according to Disease weighting, and Diseases according to component weighting. The labels 'F' and 'G' represent psychiatric and neurological ICD-10 disease codes respectively, which were clustered by the HCA analysis. Clustering was chosen at $k = 9$ and $k = 11$ for components and diseases respectively.

Figure 6. Clusters 1, 2, and 5 each showed high within-cluster similarity (avg. silhouette > 0.43). Each network is displayed at $z > 5$, and their strongest associated diseases are displayed at the bottom of the figure.

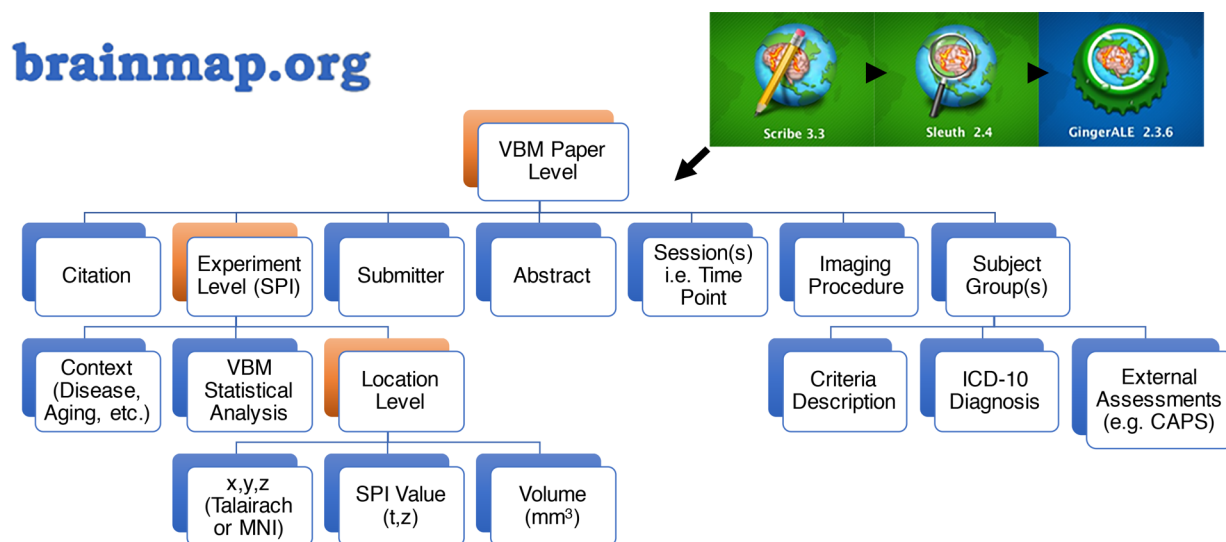


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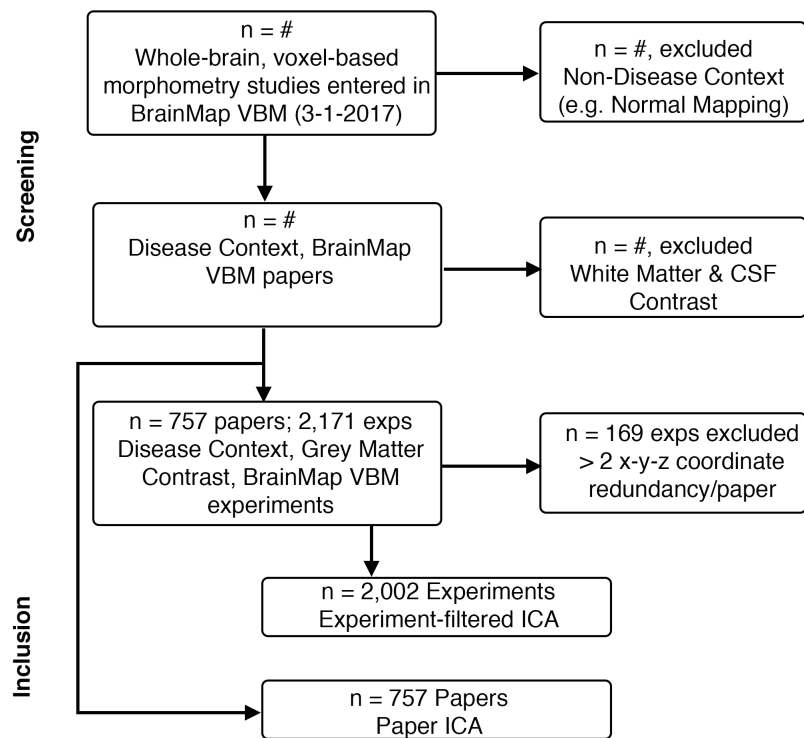


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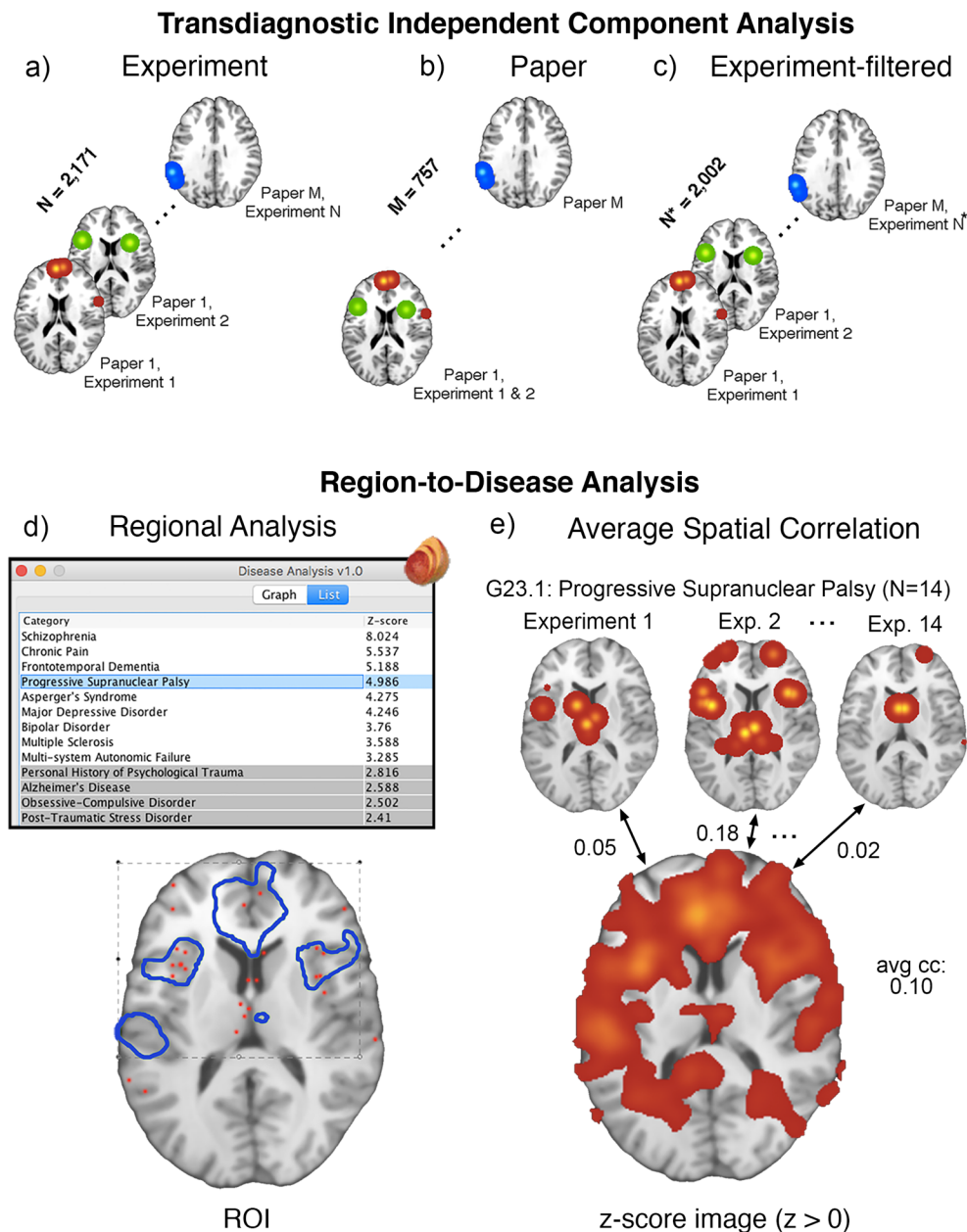


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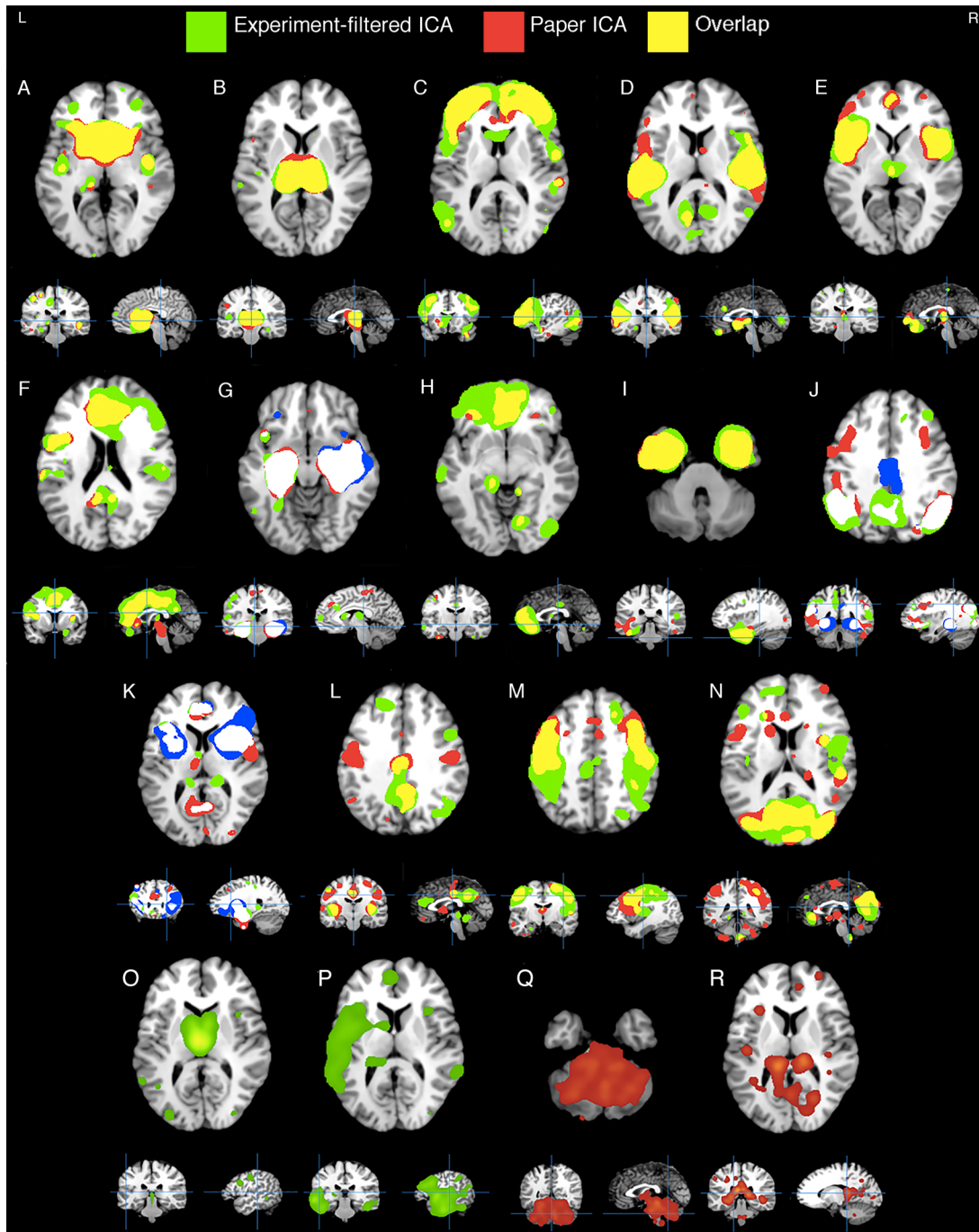


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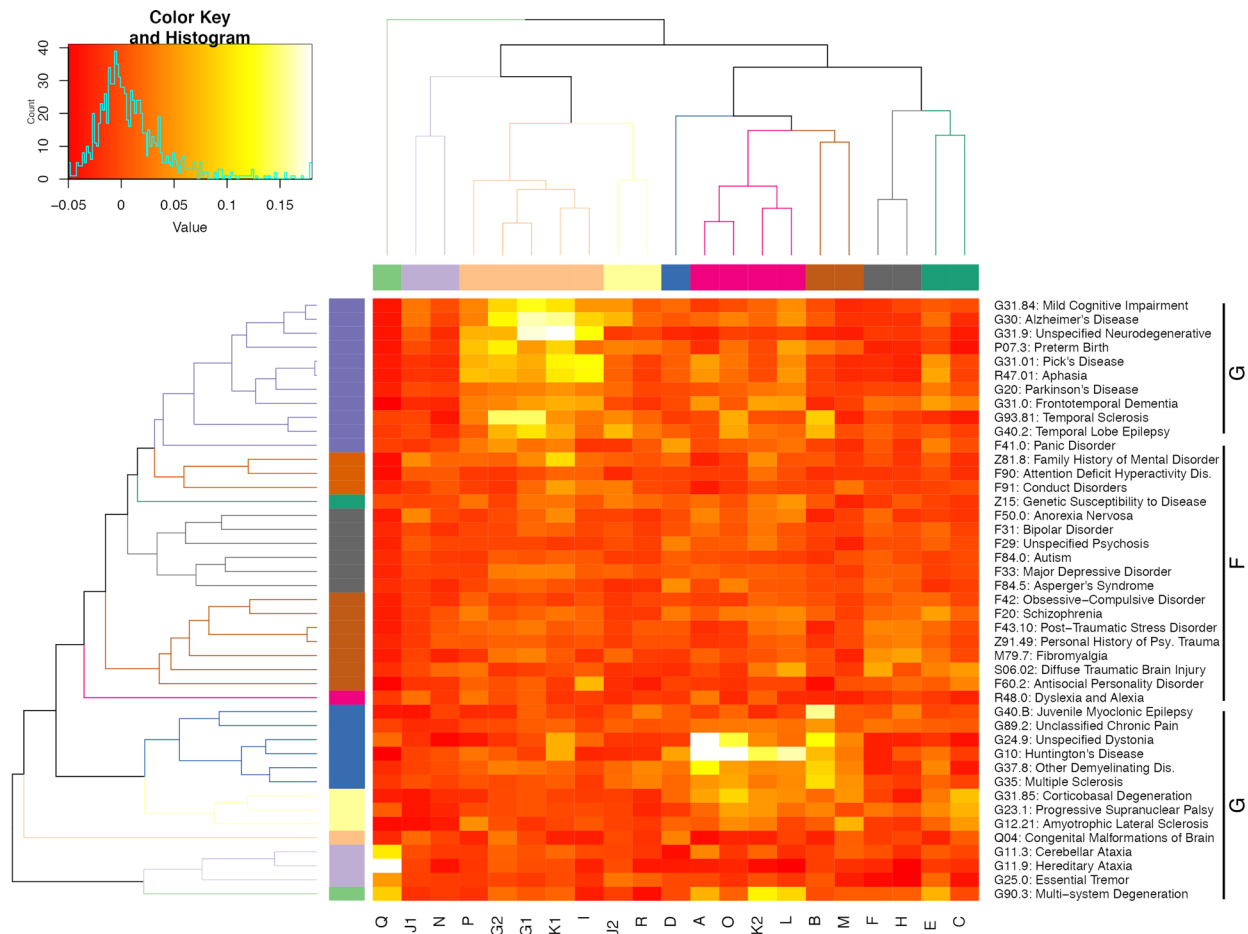


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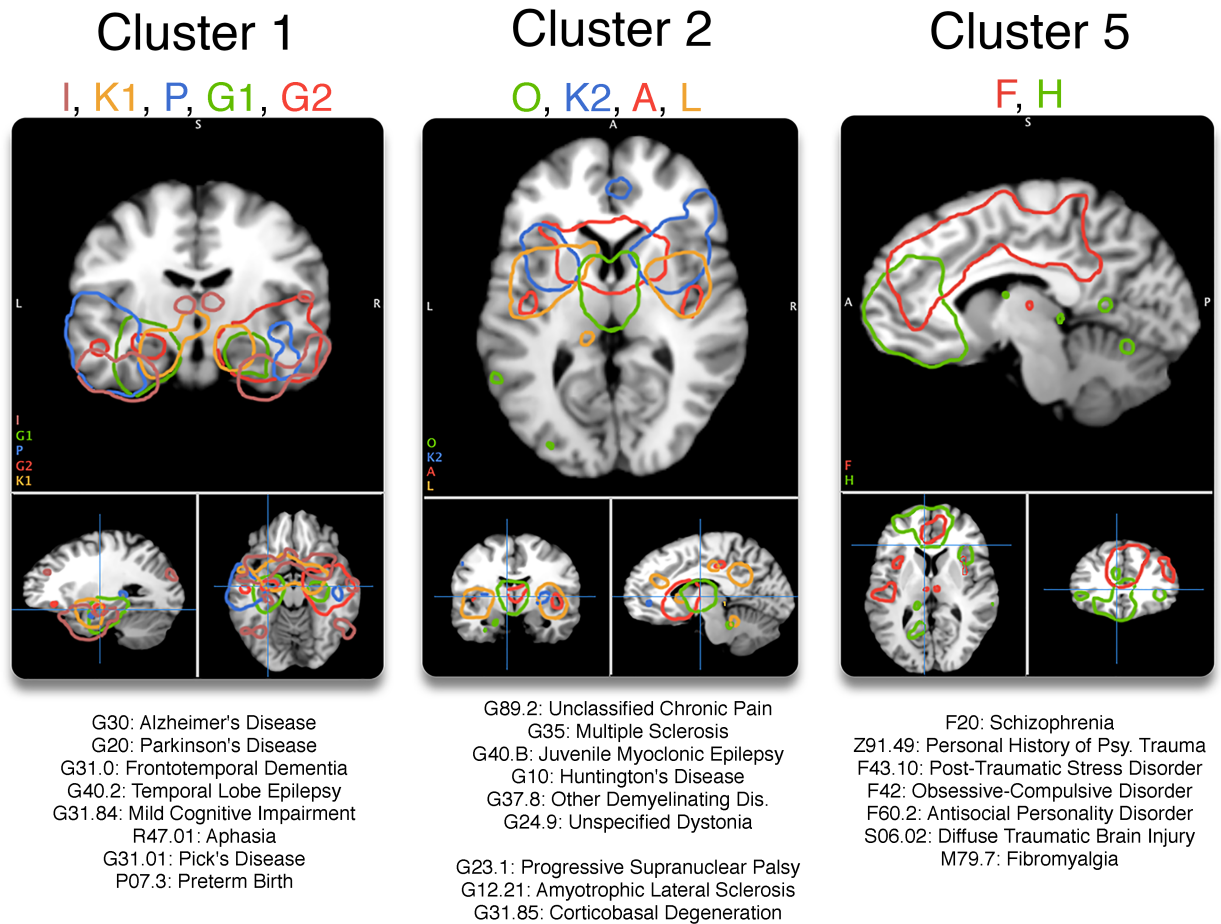


Figure 6. Clusters 1, 2, and 5 each showed high within-cluster similarity (avg. silhouette > 0.43). Each network is displayed at $z > 5$, and their strongest associated diseases are displayed at the bottom of the figure.

Table I. Data Volume of BrainMap VBM

BrainMap Context (Contrast)	Papers	Experiments	Coordinates
*Disease (Grey Matter)	757	2,171	15,876
Disease (White Matter)	207	458	2,644
Disease (CSF)	11	14	82
Normal Mapping	99	243	1,682
Aging	60	129	1,304
Pharmacology	46	100	632
Genetic	34	117	643
Gender	22	61	366
Treatment	19	59	449
Learning	9	15	49
Language	4	9	22
Handedness	2	9	81

Table I. Current data volume of BrainMap VBM sector by distinct *Contexts*. *Contrasts* are also designated for the Disease *Context*. *Only Disease *Context*/Grey Matter *Contrast* experiments were included for ICA analysis.

Table II. Anatomical Clusters of 21 VBM ICA Components

Talairach Daemon	Brodmann Area	Size (cm ³)	Max Z	x	y	z	Talairach Daemon	Brodmann Area	Size (cm ³)	Max Z	x	y	z
Component A							Component B						
Caudate		59.4	35.4	8	12	6	Thalamus		35.3	41.1	8	-22	10
Insula	BA 13	5.0	7.9	42	-8	2	Hippocampus		2.8	7.2	32	-16	-14
Sup Temporal Gyr	BA 38	2.7	6.3	32	18	-24	Putamen		1.8	6.0	-24	4	0
Postcentral Gyrus	BA 2	2.4	5.9	-42	-26	48	Caudate Head		0.9	7.1	12	18	2
Insula	BA 13	1.8	6.2	-44	-16	6	Insula	BA 13	0.8	5.3	-42	-20	12
Cingulate Gyrus	BA 31	1.2	6.9	-10	-28	40	Pyramis		0.5	6.0	24	-74	-30
Mid Frontal Gyrus	BA 10	0.3	4.8	-34	40	18	Caudate		0.3	5.4	12	8	20
Sub-Gyral		0.3	4.6	-30	44	2	Mid Temporal Gyr	BA 21	0.2	4.6	-46	-2	-18
Component C							Component D						
Mid Frontal Gyrus	BA 10	162.4	25.6	-26	52	20	Postcentral Gyrus	BA 40	57.7	24.1	52	-24	18
Mid Temporal Gyr	BA 39	9.7	6.8	-50	-70	12	Transverse Tem Gyr	BA 41	37.3	20.4	-48	-20	14
Precentral Gyrus	BA 6	6.3	7.7	54	-2	8	Anterior Cingulate	BA 25	8.7	11.9	2	4	-6
Subcallosal Gyrus	BA 34	3.5	7.5	-16	2	-12	Pos Cingulate	BA 30	3.3	8.5	-10	-62	12
Thalamus		2.8	8.3	-14	-28	0	Mid Occipital Gyr	BA 19	2.7	7.7	-50	-60	-4
Postcentral Gyrus	BA 2	1.5	6.6	48	-28	42	Med Frontal Gyrus	BA 9	2.5	9.0	-6	28	28
Mid Temporal Gyr	BA 21	1.1	6.5	-52	0	-12	Lingual Gyrus	BA 18	2.3	7.4	0	-82	2
Declive		1.0	6.1	-24	-74	-12	Pos Cingulate	BA 23	2.0	7.8	10	-58	14
Component E							Component F						
Insula	BA 13	39.0	29.9	-40	16	0	Cingulate Gyrus	BA 32	135.6	27.6	-4	30	28
Insula	BA 13	37.3	12.7	46	8	4	Inf Frontal Gyrus	BA 44	6.8	7.6	-48	6	22
Thalamus		2.6	8.5	2	-18	4	Transverse Tem Gyr	BA 41	6.0	7.3	-50	-20	12
Parahippocampus	BA 34	1.4	7.2	-20	-12	-14	Parahippocampus	BA 34	3.8	8.6	16	-8	-16
Precuneus	BA 7	0.8	5.3	12	-72	40	Postcentral Gyrus	BA 40	2.0	6.3	52	-24	18
Precuneus	BA 19	0.5	5.2	-28	-74	34	Insula	BA 13	1.3	6.1	32	14	10
Med Frontal Gyrus	BA 6	0.2	4.8	-6	-26	58	Thalamus		1.0	5.4	6	-14	10
Parahippocampus	BA 27	0.1	4.7	26	-32	-2	Med Frontal Gyrus	BA 11	0.9	6.0	0	36	-16
Component G1							Component G2						
Hippocampus		27.5	44.1	-26	-16	-14	Hippocampus		66.3	36.3	28	-14	-12
Hippocampus		7.8	15.3	26	-16	-12	Amygdala		5.1	10.1	-24	-12	-12
Inf Frontal Gyrus	BA 13	2.2	8.2	-34	22	6	Inf Frontal Gyrus	BA 47	0.7	6.1	-30	32	-6
Caudate		1.7	8.6	-10	12	12	Caudate		0.6	5.2	8	12	10
Thalamus		0.6	5.5	-6	-18	14	Mid Occipital Gyr	BA 19	0.6	5.1	30	-78	16
Insula	BA 13	0.6	4.8	-54	-32	20	Med Frontal Gyrus	BA 9	0.4	5.0	8	42	26
Postcentral Gyrus	BA 3	0.5	4.7	-40	-20	50	Inf Frontal Gyrus	BA 47	0.2	4.8	22	28	-8
Inf Frontal Gyrus	BA 47	0.4	5.4	34	28	-2	Mid Frontal Gyrus	BA 8	0.2	5.0	36	36	38
Component H							Component I						
Med Frontal Gyrus	BA 10	85.5	21.3	-6	56	6	Uncus	BA 28	97.1	28.3	24	6	-18
Thalamus		6.6	11.6	-14	-32	2	Sup Temporal Gyr	BA 22	8.0	9.5	-56	-54	6
Insula	BA 13	5.4	9.9	34	20	8	Sup Frontal Gyrus	BA 9	6.4	10.0	24	44	28
Mid Temporal Gyr	BA 21	3.5	10.2	-62	-22	-12	Inf Temporal Gyrus	BA 37	3.5	9.6	56	-60	-10
Inf Occipital Gyr	BA 19	3.3	8.7	42	-74	-2	Sup Temporal Gyr	BA 41	2.7	6.5	52	-28	14
Lingual Gyrus	BA 18	2.3	7.3	12	-70	-4	Mid Frontal Gyrus	BA 6	2.3	8.2	22	0	58
Precuneus	BA 19	1.9	6.0	34	-74	36	Thalamus		1.8	8.6	-6	-14	10
Cingulate Gyrus	BA 24	1.1	6.1	0	-20	34	Orbital Gyrus	BA 11	1.7	6.5	-6	38	-20
Component J1							Component J2						
Supramarginal Gyr	BA 40	67.6	15.8	-56	-52	28	Hippocampus		43.3	43.4	-26	-36	-2
Mid Temporal Gyr	BA 39	26.2	14.2	46	-64	30	Cingulate Gyrus	BA 24	6.9	6.9	0	-16	34
Inf Frontal Gyrus	BA 47	3.8	6.9	42	16	-8	Mid Frontal Gyrus	BA 6	4.2	7.5	-30	16	50
Hippocampus		3.7	8.3	-32	-30	-6	Mid Frontal Gyrus	BA 47	3.1	6.3	38	36	-2
Med Frontal Gyrus	BA 6	2.0	6.5	-10	-18	56	Insula	BA 13	2.2	6.2	-48	-38	22
Thalamus		1.9	8.3	6	-2	4	Sub-Gyral	BA 6	2.0	7.2	24	6	56
Inf Occipital Gyr	BA 19	1.5	6.9	38	-78	-4	Amygdala		1.2	6.5	22	-6	-12
Inf Frontal Gyrus	BA 47	1.4	6.1	-24	34	-8	Insula	BA 13	0.8	6.2	38	18	8
Component K1							Component K2						
Amygdala		49.3	50.8	-22	-2	-14	Insula	BA 13	50.4	23.9	36	10	8
Mid Frontal Gyrus	BA 46	4.4	8.4	-48	20	24	Clastrum		22.9	17.0	-30	8	6
Thalamus		1.6	6.6	16	-32	6	Anterior Cingulate	BA 32	6.8	9.6	2	38	22
Paracentral Lobule	BA 31	1.5	7.5	10	-32	40	Hippocampus		1.4	5.7	-32	-26	-8
Cingulate Gyrus	BA 31	1.5	6.7	-12	-32	40	Cingulate Gyrus	BA 32	1.1	6.6	6	8	42
Med Frontal Gyrus	BA 9	1.3	5.2	-8	40	16	Declive		1.0	6.3	-44	-56	-20
Mid Temporal Gyr	BA 21	0.7	6.3	-56	-20	-6	Inf Frontal Gyrus	BA 47	1.0	6.5	-30	32	-8
Thalamus		0.7	5.6	-14	-34	4	Pos Cingulate	BA 23	0.7	5.8	6	-60	16

Talairach Daemon	Brodman Area	Size (cm ³)	Max Z	x	y	z	Talairach Daemon	Brodman Area	Size (cm ³)	Max Z	x	y	z
Component L							Component M						
Clastrum		24.7	24.6	-38	0	2	Precentral Gyrus	BA 4	62.9	20.0	48	-12	42
Clastrum		23.6	26.0	38	-4	2	Postcentral Gyrus	BA 3	49.2	21.3	-46	-18	46
Precuneus	BA 31	13.9	10.4	2	-50	30	Caudate		3.9	7.6	10	10	18
Anterior Cingulate	BA 32	4.9	5.7	-6	32	22	Thalamus		3.6	14.3	12	-30	6
Thalamus		1.3	5.8	-16	-32	0	Thalamus		2.5	11.2	-16	-32	2
Culmen		0.7	5.2	8	-48	-8	Cuneus	BA 19	2.1	6.0	26	-84	22
Culmen		0.5	4.8	-6	-42	-18	Cingulate Gyrus	BA 31	1.6	5.8	-8	-24	42
Mid Frontal Gyrus	BA 9	0.5	5.8	48	10	34	Mid Frontal Gyrus	BA 8	1.5	7.0	20	32	40
Component N							Component O						
Cuneus	BA 7	96.2	15.7	12	-72	30	Thalamus		27.5	25.0	-4	-12	10
Anterior Cingulate	BA 32	13.3	10.7	-4	36	-4	Mid Frontal Gyrus	BA 6	4.2	8.9	40	2	38
Sub-Gyral	BA 6	6.2	8.6	28	2	56	Inf Frontal Gyrus	BA 9	2.6	8.6	-42	8	30
Precentral Gyrus	BA 6	5.1	10.5	52	0	8	Amygdala		2.1	6.2	-20	-4	-18
Sup Temporal Gyr	BA 22	4.3	14.1	-54	0	2	Culmen		1.9	5.8	-6	-38	-20
Fusiform Gyrus	BA 37	2.9	6.7	44	-52	-8	Mid Temporal Gyr	BA 21	1.4	6.0	-58	-50	6
Inf Parietal Lob	BA 40	2.1	6.3	50	-28	22	Angular Gyrus	BA 39	1.3	6.2	44	-66	34
Sup Parietal Lob	BA 7	1.4	6.7	-20	-54	64	Sup Frontal Gyrus	BA 9	0.9	5.2	30	34	30
Component P							Component Q						
Mid Temporal Gyr	BA 21	84.9	15.4	-58	-22	-4	Culmen		168.0	13.8	8	-36	-18
Sub-Gyral	BA 20	9.5	9.1	44	-16	-20	Insula	BA 13	4.7	5.5	38	-22	16
Sup Frontal Gyrus	BA 6	4.5	6.8	-2	6	60	Inf Frontal Gyrus	BA 47	1.5	5.6	34	30	-4
Thalamus		2.5	6.8	-14	-34	4	Med Frontal Gyrus	BA 10	1.4	4.9	-6	50	6
Mid Frontal Gyrus	BA 9	1.7	6.3	46	28	28	Clastrum		1.0	4.5	-28	-22	18
Med Frontal Gyrus	BA 10	1.1	6.3	-4	50	8	Inf Frontal Gyrus	BA 47	0.8	5.0	-48	30	2
Thalamus		0.8	5.7	0	-4	-2	Precentral Gyrus	BA 9	0.7	4.1	-42	6	32
Sup Temporal Gyr	BA 22	0.7	5.3	60	-42	14	Precentral Gyrus	BA 6	0.5	4.9	52	-8	34

Table II. Anatomical clusters were identified in Mango (www.ric.uthscsa.edu/mango/download) for each component using the “Find Overlay Cluster” tool. The Talairach Daemon Atlas was used for labelling, and x-y-z coordinates are reported in standardized Talairach space.