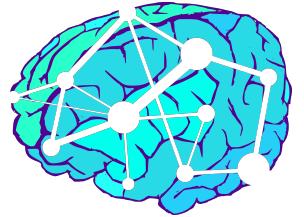


# NDMG: Reliable M3R Connectome Estimation at Scale



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## Abstract

We have produced a 1-click pipeline for reliable connectome estimation at scale and used it to process and release 1,000s of graphs across a range of scales to the public. Subsequently, we computed a mean and variance connectome from over 2200 individuals and 2800 sessions. By virtue of harmonized data processing, we show that while we can yield qualitatively similar graphs, results are meaningfully quantitatively different, making statistics such as p-values and clinical assays incomparable across datasets.

## 1 Introduction

just so I can see where non listed text will be

- O: mental health is a big problem. connectopathies are thought to be a subset of neurological disorders which derive from problems in connectivity within the brain
- S: estimating connectomes allows for the investigation of connectopathies and development of the understanding of their underlying causes, eventually leading to mechanisms for treatment
- C: many connectome estimation tools exist, either as partial- or complete-solutions. a current issue, however, is that there is no "standard" processing method, and not all methods produce equally reliable results; claims made from data processed one way may not be consistent with the claims made from the same data when processed differently.
- G: a consistent and reliable one-click connectome estimation pipeline which abstracts parameter selection and overfitting to their data has not been developed in the community, resulting in incongruent results across the community, and causes connectomics to suffer from a lack of reproducibility and repeatability.
- A: we have developed a turn-key solution for structural connectome estimation at scale

and packaged it to ship across any (Windows, Linux, OSx) modern platform.

- R: Our open-source scalable pipeline ndmg has been used to process +2,500 brain scans and generate +50,000 connectomes across a range of scales. We use these connectomes to illustrate the presence of batch effects in MRI, and have computed the largest known mean-and variance-connectomes to date.

The multi-level schematic of NDMG usage and operation can be seen in Figure 1. In the system-level diagram, we illustrate that NDMG is designed such that users are able to input minimally-processed DWI and T1w MR images (furthermore referred to as multimodal MR, or M3R), and receive a robust estimate of connectivity in return. NDMG is integrated with the BIDS [1] organization standard, and the Amazon Web Services (AWS) computing cloud, allowing it to serve as a turn-key solution for connectome estimation regardless of available local computational resources.

## 2 Methods

The NDMG pipeline has been developed by leveraging and interfacing existing tools, including FSL [2–4], DiPy [5], the MNI152 atlas [6], and a variety of parcellations defined in the MNI152 space [7–13]. All algorithms which required hyper-parameter selection were initially set to the suggested parameters for each tool, and tuned to improve the quality and

robustness of the results. Turning again to Figure 1, the lower-level schematic provides a glimpse at the

inner-workings of NDMG, breaking the pipeline into four key components: Registration, Tensor Estimation,

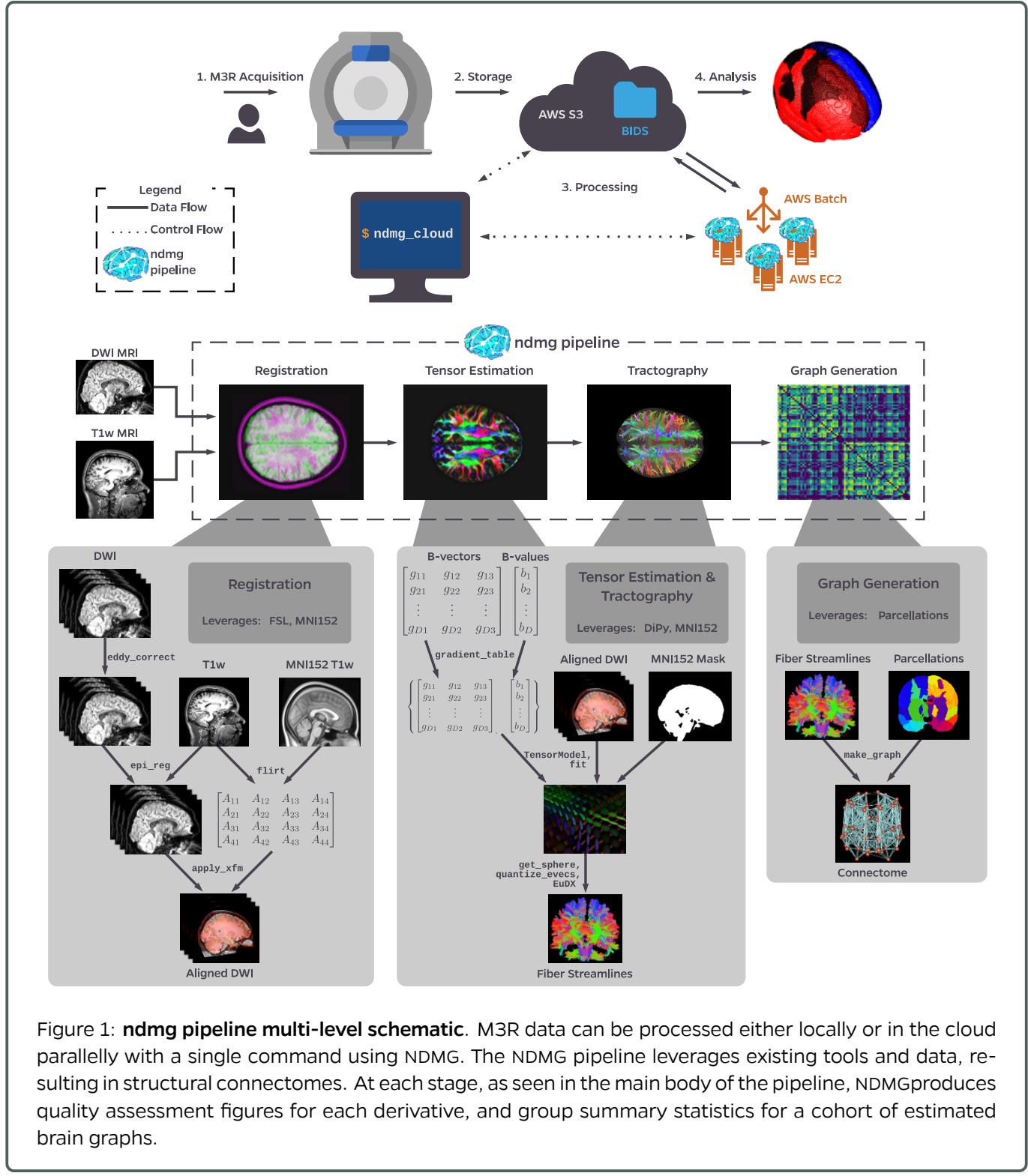


Figure 1: **ndmg pipeline multi-level schematic.** M3R data can be processed either locally or in the cloud parallelly with a single command using NDMG. The NDMG pipeline leverages existing tools and data, resulting in structural connectomes. At each stage, as seen in the main body of the pipeline, NDMG produces quality assessment figures for each derivative, and group summary statistics for a cohort of estimated brain graphs.

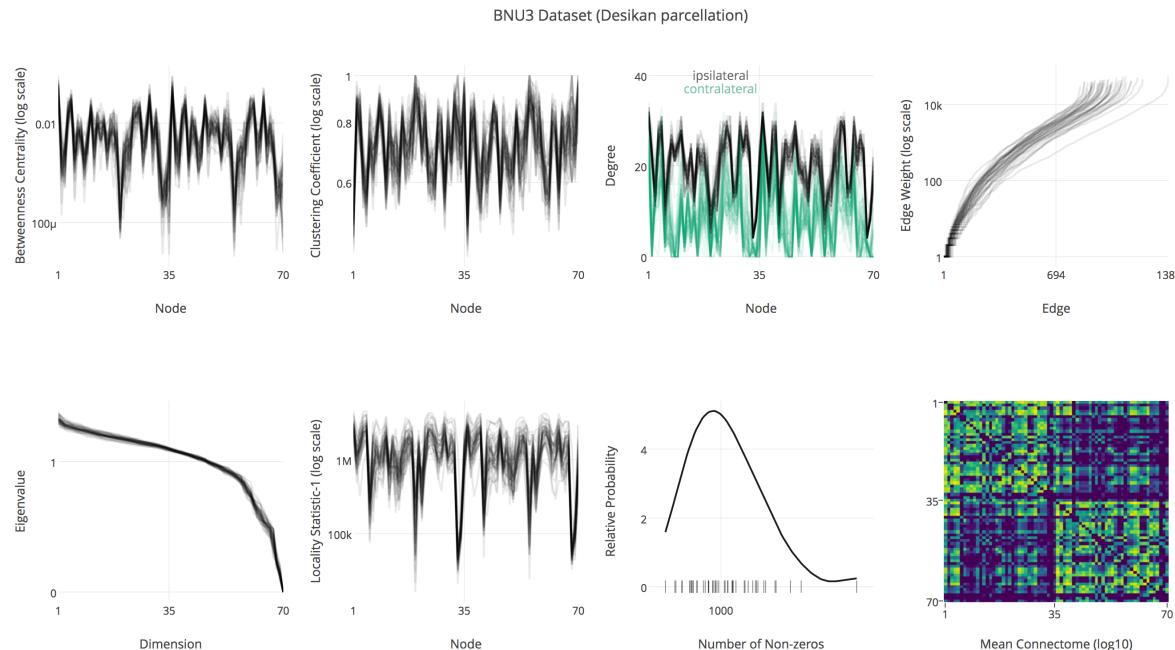
tion, Tractography, and Graph Generation. The process for each of these steps is described below, with an in depth look at the specific models and algorithms implemented at each stage contained within Appendix A.

**Registration** When generating connectomes, it is important that the derivatives from one scan can be compared to that of another. In order for the connectomes to align, they must be defined in a common space. To accomplish this, we transform the input M3R into the template MNI152 [6] space. Transforming the input data into the atlas space as opposed to the reverse enables connectomes that are acquired in different spaces or resolutions to be compared to one another reliably. Registration is done through FSL [2–4], and more detail can be found in Appendix A.1.

**Tensor Estimation & Tractography** Once the M3R data is aligned, we can use the gradient vectors and b-values accompanying the DWI scan to gener-

ate a voxelwise tensor image from the DWI image stack. Using DiPy [5] a simple 6-component tensor model is used. EuDX [14] performs deterministic tractography, an algorithm inspired by FACT [15], and streamlines are then traced from the tensors. For more information on tensor estimation and tractography, see Appendix A.2 and Appendix A.3, respectively.

**Graph Generation** Connectomes are created by mapping fibers through pre-made parcellations of the brain. These parcellations can be defined by neuroanatomists or generated by segmentation algorithms. Many of the parcellations, such as the HarvardOxford cortical atlas [10], JHU [9], and Talairach [11] atlases are packaged with FSL, while others were found from publications directly, such as the Desikan [7], AAL [8], Slab907 [12], and Slab1068 [13] parcellations, while the remaining were generated from segmentation algorithms, including CC200 [16] and 16 downsampled (DS) parcellations [17] ranging from 70 to 72,783 nodes. Tracing streamlines with



**Figure 2: Graph summary statistics.** Once a dataset is processed through NDMG, group analysis plots summary statistics of the graphs, serving as both quality assurance and a spring-board for exploratory analysis.

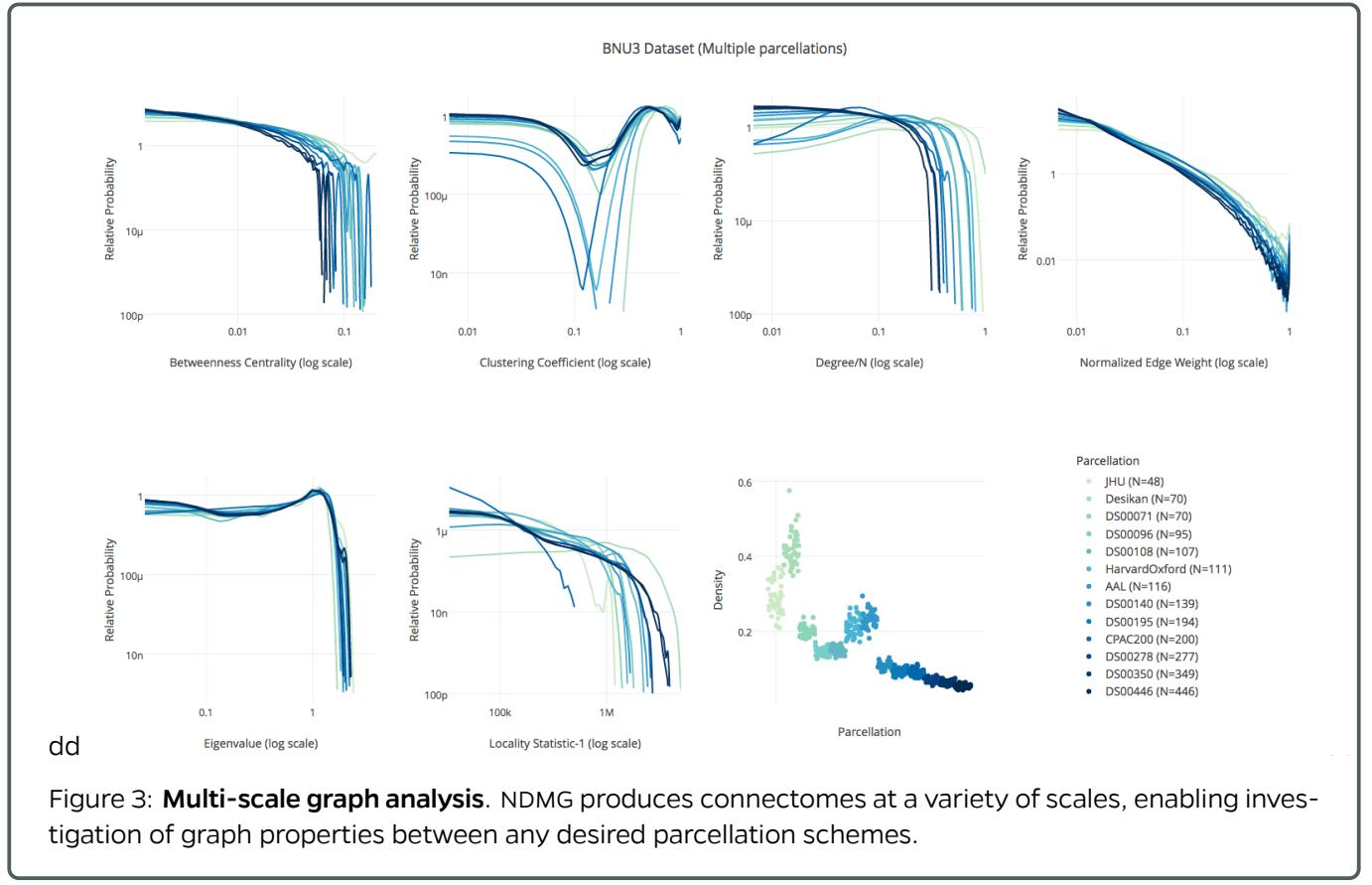
each parcellation, an edge is added to the corresponding graph for every pair of nodes along a fiber. The edges are undirected, and their weight is the total number of edges added between two nodes. See Appendix A.4 for more information.

## 2.1 Quality Assurance

As they are the final derivatives produced, connectomes, are far removed from the original imaging data. Importantly, we have developed quality assurance (QA) figures, enabling the user to easily detect whether or not the pipeline is producing expected results. QA for the intermediate derivatives in NDMG are shown in the main body of Figure 1. The QA plots have been designed to highlight likely problems that may occur within the pipeline. For registration, NDMG produces an overlay of the inputted DWI image and the MNI152 T1w template, which allows the user to verify that the brain boundary and higher-level structures of the input image have been

correctly aligned to the atlas. For tensor estimation, NDMG produces a fractional anisotropy (FA) map of the tensors, which allow the user to verify that the gradient table and the diffusion image are properly co-aligned. For tractography, NDMG visualizes a subset of the generated streamlines within a mask of the MNI152 brain, so that the user can verify that no fibers leave the brain and that their structure resembles that of the FA map generated in the previous step. Together, these figures provide a thorough inspection of the derivatives as they are being produced, so that if an error were to occur it would be more easily detectable by the user.

Once connectomes have been produced for an entire dataset, the user may then use NDMG to generate a plot of graph summary statistics to develop further understanding of the structure of their newly obtained brain graphs. Figure 2 shows the summary statistics plot for an exemplar dataset constructed with the Desikan [7] parcellation. The features of the graphs which NDMG computes are [17], clockwise



from top-left: betweenness centrality, clustering coefficient, hemisphere-separated degree sequence, edge weight, eigen values, locality statistic-1, number of non-zero edges, and the cohort mean connectome. These statistics enable detailed quality assessment of the graphs; for instance, enabling the user to confirm that edge density is higher ipsi-laterally than contra-laterally, and thus serve as a preliminary exploratory analysis of the processed data.

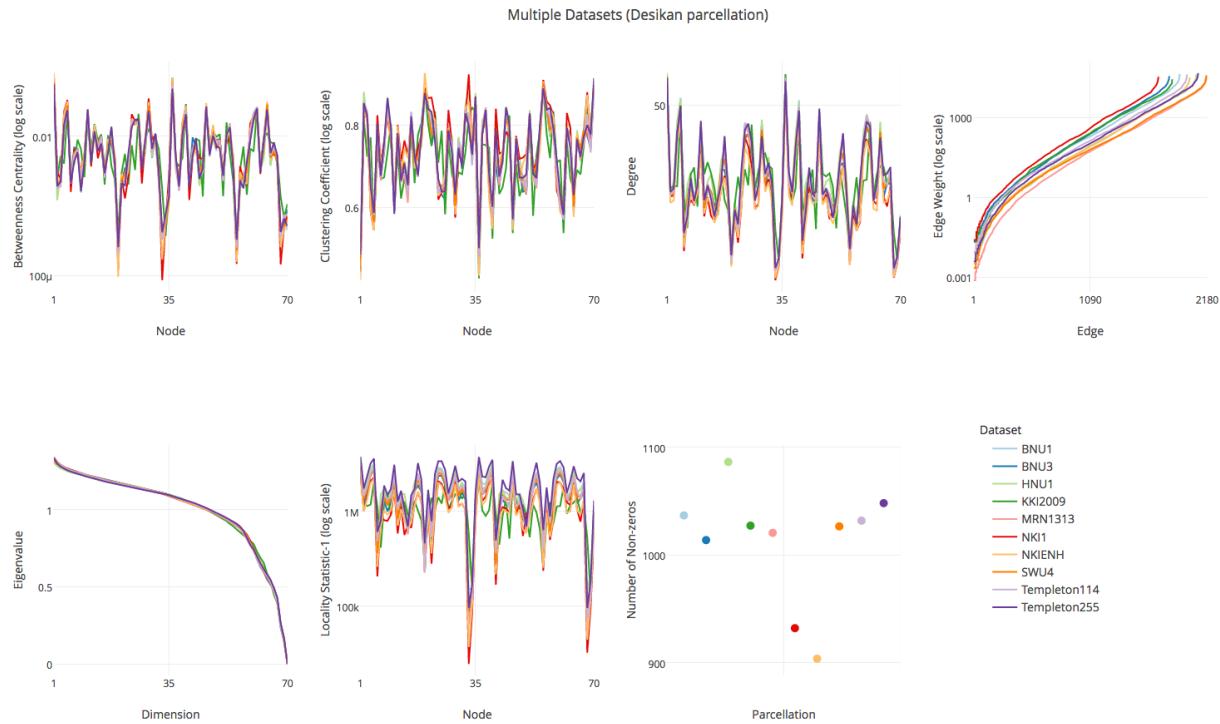
## 2.2 Validation

Results from NDMG have been validated using a metric termed Discriminability [18]. Discriminability as seen in Equation (1) is a statistically generalized version of Test-ReTest (TRT) reliability:

$$\text{Discriminability} = p(||a_{ij} - a_{ij'}|| \leq ||a_{ij} - a_{i'j'}||) \quad (1)$$

Discriminability describes the probability in given a dataset consisting of multiple observations of objects within multiple classes, that the nearest-neighbour for an arbitrary observation,  $a_{ij}$ , is another observation of the same class,  $a_{ij'}$ , and not an observation of another class,  $a_{i'j'}$ . In this case, a class is a subject-id and an observation is a session of scans. A perfect discriminability score is 1, meaning that the nearest-neighbour for any observation is always a different obversation from the same subject, and the worst possible score is 0, meaning the opposite. Optimizing NDMG with respect to discriminability enables us to minimize the upper-bound on error for any general downstream inference task, without overfitting to covariate-specific signal (i.e. optimizing the pipeline for sex classification).

## 3 Results



**Figure 4: Multi-site graph analysis.** NDMG has been used to process 10 publicly available datasets, using an identical version of the pipeline on the same hardware. We can see that though the underlying structure of the connectomes produced is similar by most statistics, there is high variance between data collected as a part of one study to another, even when averaging over the entire cohort.

### 3.1 One-Click Connectomics

NDMG is a reliable, accessible, turn-key solution to human connectome estimation at scale. The NDMG pipeline takes approximately 1 hour to generate connectomes across 24 parcellations for a single session, when provided with 1 CPU and 12 GB of RAM. NDMG has been developed with a low barrier to entry in terms of input data quality, computational resources, and computational expertise. NDMG is installable for Python via the PyPi package repository<sup>1</sup>, or a container image made available through DockerHub<sup>2</sup>. NDMG has been integrated with a variety of platforms and standards including the BIDS data organization standard [1; 19] and the descriptive command-line schema Boutiques<sup>3</sup>. NDMG has been deployed in several large computing infrastructures including OpenfMRI [20] and CBRAIN [21], and has been integrated with the AWS computing cloud, enabling users to launch the pipeline in the cloud with a single command [22; 23]. The NDMG package and pipeline is open-source and available on Github<sup>4</sup>.

### 3.2 Processed Data

The NDMG pipeline has been run on a variety of public datasets, upon which it proves to be highly discriminable. Table 1 summarizes the 2,861 scans that have been processed with NDMG; each scan processed has been parcellated using 24 different atlases, resulting in 68,664 total graphs. All of the derived graphs and intermediate derivatives are publicly available on our S3 bucket, `mrneurodata`. The data can be accessed through our website, <http://m2g.io>.

We can see from Table 1 that NDMG has near-perfect discriminability for many of the TRT datasets evaluated. No outlier removal was done prior to computing discriminability, and eliminating errorful-graphs such as those which could be detected by quality assessment plots (like those in Figure 2) would likely increase the score further.

Figure 4 shows a variety of uni- and multi-variate statistics of the average graphs produced by each of the datasets enumerated in Table 1.

### 3.3 Multi-scale Analysis

As NDMG produces connectomes at a variety of scales, it enables either multi-scale analysis or flexi-

bility in terms of the parcellation a researcher wishes to use for a given task. Figure 3 shows various statistics of graphs generated from the same dataset over a subset of the 24 parcellations used to estimate connectomes. The parcellations used in NDMG range in number of nodes from 48 to 72,783; only those with nodes under 500 nodes are shown in Figure 3. Comparing graphs generated with the same fiber across various parcellations relative to one another may be valuable and can inform the optimal scale upon which to perform specific analyses.

**TODO:** gk: define a narrative

Table 1: **Processed public M3R datasets.** Each dataset has been processed with 24 parcellations, resulting in over 65,000 total publicly available connectomes.

Dataset	Subjs (k)	#	Total	Disc
BNU1 [24]	57	2	114	0.984
BNU3 [24]	48	1	47	-
HNU1 [24]	30	10	300	0.993
KKI2009 [25]	21	2	42	1.0
MRN1313	1313	1	1299	-
NKI1 [24]	24	2	40	0.984
NKI-ENH [26]	198	1	198	-
SWU4 [24]	235	2	454	0.884
Templeton114	114	1	114	-
Templeton255	255	1	253	-
<b>Total</b>	<b>2295</b>	<b>2861</b>	<b>0.994</b>	

A perfect MNR for each TRT dataset is 1 and random-chance is  $1/k$ .

### 3.4 Batch Effects in M3RI

The datasets summarized in Table 1 were all processed using an identical version of NDMG, enabling “mega-analysis” between datasets to be conducted. Here, we investigate the prevalence of batch effects in M3R data. Using discriminability as described as in Equation (1), and substituting subject-id with dataset as the observation class-label, we can compare the similarity between graphs derived within a dataset and across datasets. Shown in Figure 5, we sampled 20 sessions from each dataset, ensuring no subject in the TRT datasets was selected twice, and computed the discriminability between datasets. If there

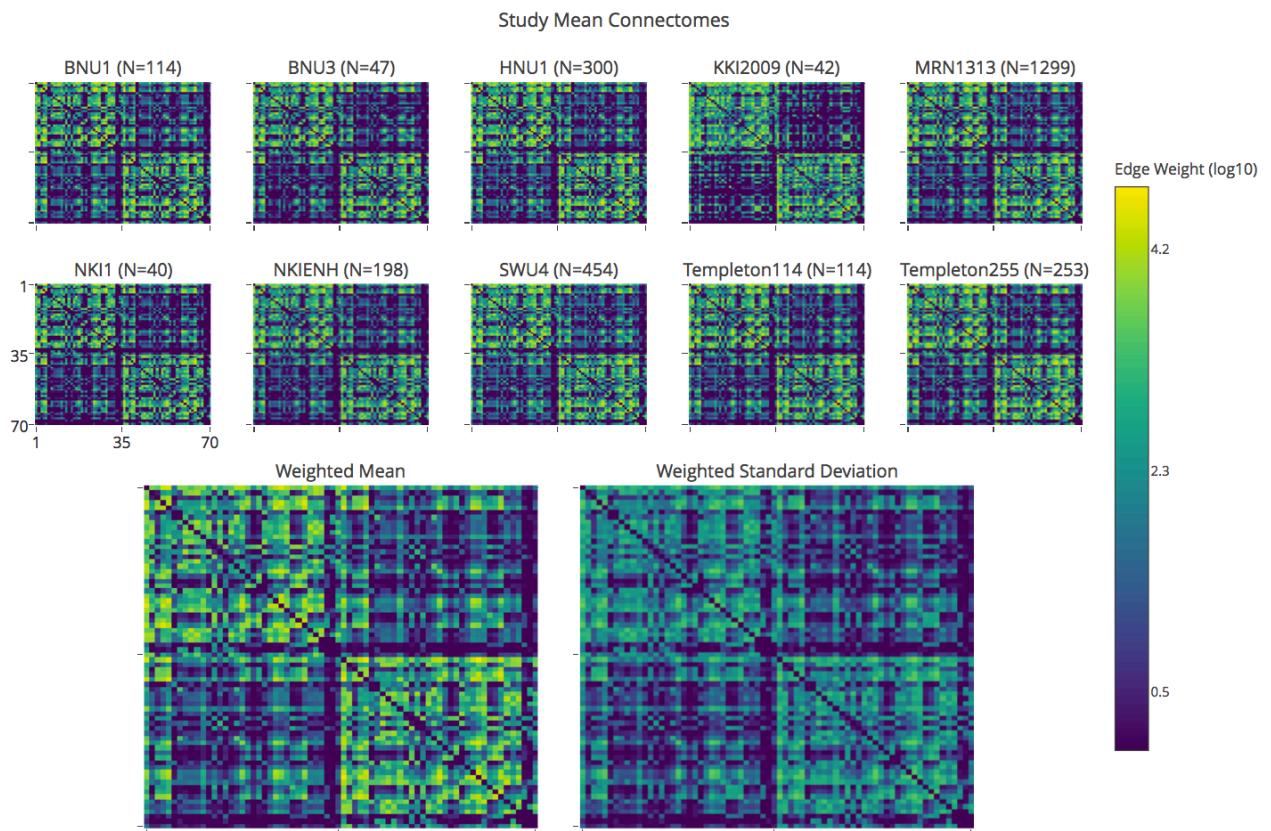
existed no dataset-specific signal, then we would expect a discriminability score of 1/10, as there is an equal probability of selecting each of the 10 datasets. However, we compute a discriminability score of 0.632, suggesting significant dataset-specific signal is present. This analysis was also conducted across all subjects within each dataset, and an interactive figure for both of these analyses is available on our website<sup>5</sup>.

### 3.5 Mean Connectome

We computed a mean connectome using the Desikan parcellation for each dataset processed in Table 1, as well as a mean and standard deviation (SD) connectome across datasets, as shown in Figure 6. With N=2861, we believe this is the largest mean connectome computed to date. Properties of the brain such as high number of ipsi-lateral connections relative to a lower number of contra-lateral connections are present across all datasets. However, the



Figure 5: **Prevalence of batch effects.** Ten datasets have been processed with NDMG, and the discriminability across datasets was computed to quantify the prevalence of batch effects in M3RI data. If no batch effect were present, a discriminability of 0.1 would be expected. A discriminability score of 0.632 as seen here suggests that there is considerable dataset-specific signal in the graphs.



**Figure 6: Multi-Study Mean Connectomes.** Looking at 70-nodes graphs built upon the Desikan parcellation, we have computed the mean connectome from a variety of datasets. The mean-of-mean connectomes and standard deviation-of-mean connectomes were computed, and result in the largest known mean connectome to-date, consisting of 2861 sessions. As expected, ipsi-lateral connectivity is consistently more dense than contra-lateral connectivity. Similarly, the standard deviation connectome, which highlights edges that are more highly variable, shows higher ipsi-lateral variance. This suggests that not only are same-hemisphere connections more likely to occur, but they have a higher variance than across-hemisphere connections, as well.

SD connectome also shows that the ipsi-lateral connectivity is also more highly variable, suggesting that there exists a relationship between connection density and variability. We also notice that the ipsi-lateral connectivity within left (nodes 1-35) and right (nodes 36-70) hemispheres, respectively, are very similar in structure. An interactive version of this figure can be found on our website.

## 4 Discussion

The NDMG pipeline is a highly-reliable tool with a low barrier to entry for neuroscientists. NDMG has shown that it is capable of producing meaningful and consistent graphs across scales and datasets, and to be deployed across a wide range of computing infrastructures with limited dependencies or computational resources. While many existing tools for connectome estimation enable the user to easily select hyper-parameters for their data, NDMG abstracts this selection from users; though this means

that NDMG may not use the optimal parameters for a given dataset, it provides a consistent estimate of connectivity across a wide range of datasets, making it trivial to compare graphs derived from one study to another, and avoids overfitting of the pipeline to a specific dataset.

While NDMG has been verified to be highly reliable, a hyper-parameter sweep over all parameter selections has not yet been conducted. Performing such an optimization over a range of datasets and maximizing their joint discriminability would improve the reliability of NDMG even further. An important contribution of NDMG is that we illustrate that highly sophisticated and computationally burdensome algorithms such as probabilistic tractography are not necessary to create highly reliable estimates of brain connectivity. Evaluating the quality of connectome estimation pipelines using probabilistic tractography with discriminability would enable a decisive answer to the question of whether deterministic or probabilistic tractography is more reliable when estimating connectivity.

The Human Connectome Project (HCP) has recently collected an extraordinary M3R dataset, and developed processing pipelines accordingly. It is our belief that NDMG is explicitly not in competition with the tools and resources produced by HCP. The HCP pipeline when run on the HCP data creates likely the most outstanding map of human brain connectivity to date, however, their pipeline relies on many additional parameters and files (such as scanner bias fields, and multi-shell acquisitions of DWI data), making it unable to be deployed across the majority of existing DWI datasets. NDMG takes the approach of being a generally useful, reliable, and impactful tool, without requiring state-of-the-art acquisitions which are not commonly available outside of next-gen experimental paradigms. NDMG can be deployed on the HCP data, though it would not take advantage of the additional scans and parameters acquired. We believe that the HCP pipelines and NDMG compliment one another, and comparing the two more closely is an exciting avenue to be explored in future work.

As NDMG is highly modular, it can also serve as a reference pipeline for new algorithms when performing connectome estimation. Through the use of discriminability, the NDMG pipeline can be modified with new algorithms and tested against the original.

When algorithms consistently improve the reliability of NDMG, they may be integrated into the pipeline and both i) improve the quality of the NDMG reference pipeline, as well as ii) provide a strong statistical basis for the development and use of new algorithms.

Integration of NDMG to the AWS cloud and with services such as OpenfMRI and CBRAIN makes it an accessible choice for neuroscientists who are limited in their in-house compute infrastructure, and those with limited experience deploying pipelines in high performance computing environments.

The NDMG pipeline takes a step towards democratizing the field of human connectomics, enabling users to produce statistically-validated connectomes at an unprecedented scale with ease, enabling massive-scale analyses of the underlying structure of the human brain.

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## Availability of supporting source code and requirements

**Project name** M3RI to Graphs (m2g)

**Project home page** <http://m2g.io>

**Operating system(s)** Platform independent

**Programming languages** Python, Docker, Bash

**Other requirements** M3RI Data, Python or Docker

**License** Apache 2.0

## Declarations

**Competing Interests** The authors declare no competing interests in this manuscript.



**Abbreviations** Multimodal Magnetic Resonance Imaging (M3RI), NeuroData’s MRI Graph Pipeline (NDMG), M3RI to Graphs (m2g), Brain Imaging Data Structure (BIDS), Amazon Web Services (AWS).

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## Appendix A Processing Pipeline

Here we take a deep-dive into each of the modules of the NDMG pipeline. We will explain algorithm and parameter choices that were implemented at each step, and the justification for why they were used over alternatives.

### Appendix A.1 Registration

- eddy correct to b0 (didn't use eddy because it's too slow and we didn't want to require gpus)
- epi reg from dwi to t1w (obvious, it's the thing to do)
- flirt from t1w to mni152 at 1mm (1mm for higher freedom in fiber tracts which use real coords, flirt because fnirt is unstable for bad data and takes too long at 1mm)
- apply xfm from t1w to mni152 1mm to dwi (obvious, it's the thing to do)
- resample aligned dwi (flirt aligns images in real space (i.e. considering header) and we also want to ensure alignment in voxel space, so that we can just do analysis there)

### Appendix A.2 Tensor Estimation

- selected dipy (all in python)
- selected basic tensor model (reliable for all dwi data and data quality has reduced impact on calculated tensors)

### Appendix A.3 Tractography

- selected dipy (matches I/O expectations with tensors)
- selected eudx deterministic (like fact, which is known to be ok. probs was a) slow and b) little evidence for its performance on low-angular resolution data, which we want our tool to be accessible to)

### Appendix A.4 Graph Estimation

- undirected edge between all nodes on a fiber (direction of connectivity is unknown, so all possible orientations added)
- edge weight is number of fibers (simple, principled, alternatives such as mean FA along tract work for single streamlines, but become unnecessarily complex and reduce dynamic range of data as number of fibers increases)
- parcellations (were selected because people seem to use them, packaged with known tools)

## Notes

<sup>1</sup><https://pypi.python.org/pypi/ndmg>

<sup>2</sup><https://hub.docker.com/r/bids/ndmg/>

<sup>3</sup><http://boutiques.github.io/>

<sup>4</sup><https://github.com/neurodata/ndmg>

<sup>5</sup><https://github.com/neurodata/ndmg-paper>