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Potential Information Processing Differences in Male and Hermaphrodite Neural Networks of *Caenorhabditis elegans*

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Abstract

Connectome generally refers to the macroscale connectivity between anatomical areas of the brain to mesoscale connectivity between neurons to synaptic connectivity at the microscale level. Studies has implicated macroscale connectomes in functional behaviours. Although macroscale connectomes are likely to affect functions via mesoscale connectomes, this has not been demonstrated. Recently, mesoscale connectomes of male and hermaphrodite *Caenorhabditis elegans* have been published. Here, we simulate computationally the mesoscale connectomes of male and hermaphrodite *C. elegans* to examine differences in information processing. Our results show that the number of significantly differently neurons ($n = 28$, p-value < 0.05) is significantly higher than random (p-value = 0.00468), suggesting potential differences in information processing between male and hermaphrodite *C. elegans*. Hence, mesoscale connectome differences may result in information processing differences.

Introduction

Connectome was first defined by Sporns et al. [1] as the connectivity map of neurons in the brain and calls for the assembly of the human connectome. It an important tool for neurobiological research [2] as it is instrumental in the study of neural functions [3]. However, connectomes can also refer to varying resolutions of connectivity - from connectivity between anatomical areas, also known as macro-scale connectome [4]; to connectivity between individual neurons or cellular level, also known as meso-scale connectome [5]; to connectivity at the synapse level, also known as micro-scale connectomes [6]. Since then, connectomes of different organisms have been assembled. These include the roundworm *Caenorhabditis elegans* [7], the fruit fly *Drosophila melanogaster* [8], retina [9] and visual cortex [10] of mouse, and human [11]. There are many clinical applications of connectomes [12]; such as, understanding psychiatric [13] and neurodegenerative [14] disorders.

Recently, Bian et al. [15] examined 79 first-time stroke patients with hemiplegia and found that connectomes obtained from magnetic resonance imaging (MRI) are related to post-injury functional outcomes. Rutherford et al. [16] examined mother-infant bonding and found that changes in MRI-based connectomes across the postpartum period were associated with changes postpartum bonding. Gou et al. [17] examines MRI-based connectomes and found differences between the connectomes of patients with or without migraine. These studies suggest that connectomes are related to information processing in the neural network [18, 19], differences in processing speed [20] and behaviour [21-24]; which can be collectively considered as "connectome basis of information processing".

However, current studies associating connectomes to functions used macroscale connectomes. Although it is plausible to conceive that macroscale connectomes affects functions via mesoscale connectomes and eventually via microscale connectomes, this has not been demonstrated. Recently, mesoscale connectomes of male and hermaphrodite *C. elegans* have been published [7], which is a re-

source to examine biologically relevant neuronal information processing at the mesoscale. In this study, we examine the information processing differences by computer simulation of the mesoscale connectomes of male and hermaphrodite *C. elegans*. Our results show that 28 out of 290 neurons common to male and hermaphrodite are significantly different (p-value < 0.05). The number of significantly differently neurons (n = 28) is significantly higher than random (p-value = 0.00468), suggesting potential differences in information processing between male and hermaphrodite *C. elegans*. This result supports connectome basis of information processing.

Materials and Methods

Connectome. Male and hermaphrodite connectomes of *C. elegans* were obtained from the male chemical adjacency matrix and hermaphrodite chemical adjacency matrix, respectively; which corresponds to Supplementary Information 5 of Cook et al. [7] July 2020 corrected version. The neuronal connectivity was binarize into presence or absence of connections from the weights (accounting for both the number of synapses and the sizes of synapses) of connections. The connectivity matrices were used to generate as simulatable model of male and hermaphrodite connectomes separately in Brainopy [25]. The neurons for each connectome were added using Brainopy.addNamedNeuron function. Pairs of neurons were linked using Brainopy.stapleNeurons function. A hypothetical neurotransmitter X was defined as the only neurotransmitter.

Simulation. To run the simulation, the hypothetical neurotransmitter X was set to a value of 10 for every synapse, which mimic drenching the entire brain in exogenous neurotransmitter. The connectome executed for the number of cycles determined by twice the furthest path between a common sensory neuron and a common head neuron as determined using shortest path function in NetworkX [26]. Default parameter of 1% random variation of neurotransmitter value in Dendrite Modulating Function, Neuron Modulating Function, Axon Modulating Function, and Synaptic Modulating Function of Brainopy [25] was used. After the completion of determined number of cycles, the values of hypothetical neurotransmitter X in each neuron were obtained. 20 replicates were performed.

Data Analysis. The values of hypothetical neurotransmitter X in 290 common neurons (comprising of 18 common head motor neurons, 80 common interneurons, 20 common pharynx neurons, 82 common sensory neurons, 19 common sublateral motor neurons, and 71 common ventral cord motor neurons) across 20 replicates between male and hermaphrodite connectomes are compared using 2-samples t-test assuming unequal variance at 95% confidence. The number of neurons with significantly different hypothetical neurotransmitter X values were tested using randomization procedure [27, 28] as previously described [29, 30].

Results and Discussion

To determine the number of simulation cycles, an analysis of the neuronal connectivity between common sensory neuron and common head neuron was performed. The mean neuronal jumps between common sensory neuron and common head neuron (n = 1422) as determined by NetworkX [26] in male is 4.18 with a standard deviation of 1.103 while that of hermaphrodite is 3.51 with a standard deviation of 0.737 (Table 1, Figure 1); which is indicative of the mean number of interneurons [31]. Both the mean (t-test p-value = 3.66E-74) and variance (Fligner-Killeen test p-value = 0.0133) are statistically significant. The furthest path between a common sensory neuron and a common head neuron in male connectome and hermaphrodite connectome are 8 and 5 respectively. Hence, the number of cycles for simulation in male connectome and hermaphrodite connectome are 16 and 10 respectively.

	Male	***Hermaphrodite***
Average	4.18	3.51
Standard Deviation	1.103	0.737
Minimum	2	2
Q1	3	3
Median	4	4
Q3	5	4
Maximum	8	5

Table 1: Statistics of Male and Hermaphrodite Connectomes. Pairwise number of neuronal jumps between common sensory neuron and common head neuron were tabulated and summarized. The furthest path between a common sensory neuron and a common head neuron in male connectome and hermaphrodite connectome are 8 and 5 respectively.

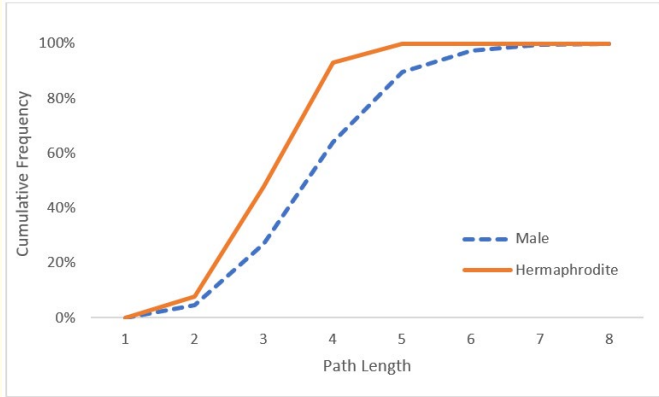


Figure 1: Path Length Between Common Sensory Neurons and Common Head Motor Neurons. Chi-Square p-value = 1.58E-125 using 2-8 path lengths and male distribution as expected distribution.

Our simulation results suggest that the number of common neurons between male and hermaphrodite connectomes showing significant differences (2-samples t-test p-value < 0.05) is 28 out of 290 neurons (9.7%; Figure 2 and 3, Table 2). Using randomization procedure [27-30], the mean number of significantly difference neurons is 26.425 (n = 40 randomized replicates) with standard error of 0.5249. Hence, the number of 28 common neurons between male and hermaphrodite connectomes showing significant differences is statistically significant (t-statistic = 3.001, df = 39, p-value = 0.00468).

While this may be a result of the intraneuronal gap between males and hermaphrodites (average of 4.18 in males versus 3.51 in hermaphrodites), further study is required. However, our results are consistent with experimental studies demonstrating behavioural differences between male and hermaphrodite *C. elegans*. Macoskom et al. [32] found that males and hermaphrodites exhibit different attraction to hermaphrodite pheromones. Loxterkamp et al. [33] found that although males and hermaphrodites exhibit similar spontaneous movement or slow and sustained behaviours such as chemotaxis, they differ in quick response to mechanical and chemosensory stimuli. This is further supported by Tanner et al. [34] demonstrating that males show a delayed food leaving compared to hermaphrodites when exposed to repulsive odours. Collectively, these suggest potential differences between the information processing between male and hermaphrodite *C. elegans* at the level of mesoscale connectome; thereby, supporting the connectome basis of information processing.

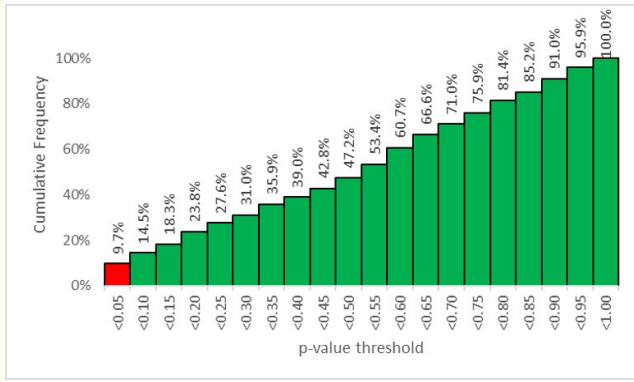
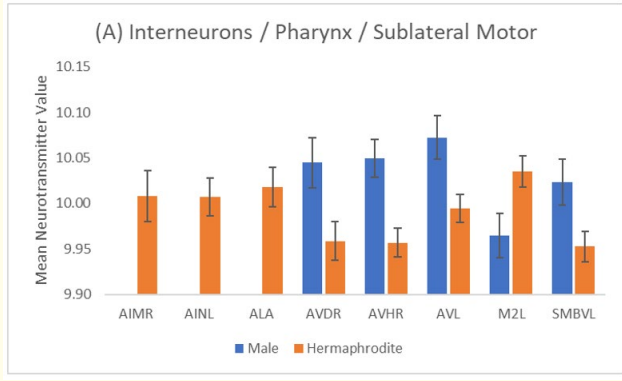


Figure 2: Cumulative Frequency of p-values. 9.7% (n = 28) of the neurons are significantly different between male and hermaphrodite connectomes.

Neuron Group	*Number of Neurons*	*Number of Significantly Different Neurons*	*Name of Significantly Different Neurons*
Common Head Motor	18	0 (0.0%)	(Not Applicable)
Common Interneuron	80	6 (7.5%)	AIMR, AINL, ALA, AVDR, AVHR, AVL
Common Pharynx	20	1 (5.0%)	M2L
Common Sensory	82	13 (15.9%)	ASGR, ASHL, ASIR, ASJL, ASJR, ASKL, AWBR, CEPVL, IL2DR, PLML, PLMR, URYDLT, URYDR
Common Sublateral Motor	19	1 (5.3%)	SMBVL
Common Ventral Cord Motor	71	7 (9.9%)	AS03, VA06, VA09, VA10, VB03, VD08, VD12

Table 2: List of 28 Neurons Significantly Different Between Male and Hermaphrodite Connectomes.



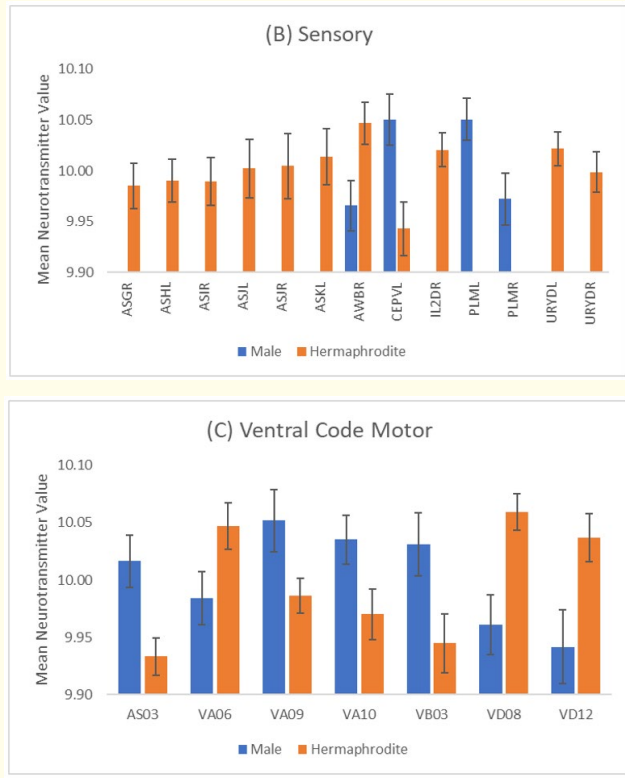


Figure 3: Mean Neurotransmitter Values Between Male and Hermaphrodite Connectomes.

Conclusion

Differences in mesoscale connectomes may result in differences information processing.

Supplementary Materials

Scripts and data files for this project can be downloaded at https://bit.ly/ConnectomeCEL.

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Conflict of Interest

The authors declare no conflict of interest.

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