

# Hippocampal volume mediates the association between depression and cognitive function differently by sex

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**Take Home Message:** Depression symptom severity influences cognition via hippocampal and amygdalar volumes only in women. These findings suggest sex-specific neural pathways for the relationship between depression and cognition.

## Introduction

Sex differences are prominent features of both depression and Alzheimer's disease, with women showing an increased lifetime risk relative to men. However, the neural mechanisms that explain sex differences in the relationship between depression and cognition are poorly understood. **The goal of this study was to evaluate whether smaller brain volumes mediate the relationship between higher depression symptom severity and poorer cognition, and whether this association differed by sex.**

## Methods

### UK Biobank Cohort



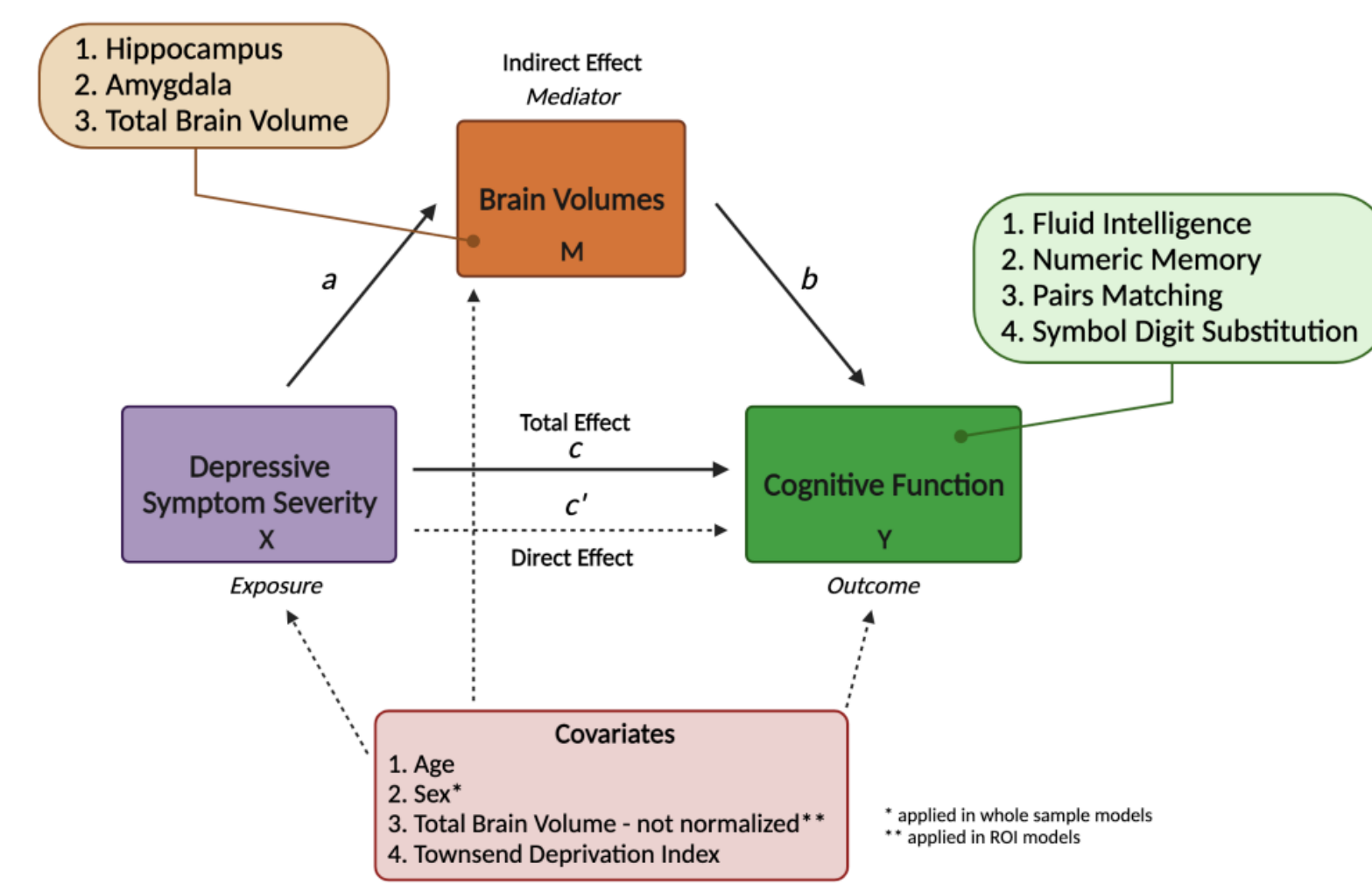
- Age at recruitment 40 to 69 years
- Inclusion criteria:** underwent a brain MRI scan, completed the online Patient Health Questionnaire (PHQ), and completed one of the online cognitive measures
  - Fluid Intelligence: verbal and numeric reasoning
  - Numeric Memory: working memory
  - Pairs Matching: visual declarative memory
  - Symbol Digit Substitution: processing speed
- Exclusion criteria:** any dementia diagnosis

**Table 1** Subject demographics. Sex differences were evaluated by Student's t-test for continuous variables and with Chi-Square test for categorical variables.

	Women (N=14,953)	Men (N=12,532)	Total (N=27,485)	P-value
<b>Demographics</b>				
Age at MRI scan [Mean ± SD]	63.4 ± 7.36	65.0 ± 7.59	64.1 ± 7.51	<0.001
Ethnicity [% White]	97.3%	97.1%	97.2%	0.78
Townsend Deprivation Index [Mean ± SD]	-1.88 ± 2.72	-1.97 ± 2.68	-1.92 ± 2.71	0.01
Depression Severity Score [Mean ± SD]	2.91 ± 3.70	2.23 ± 3.28	2.60 ± 3.53	<0.001
<b>Depression Diagnosis</b>				
Minimal depression	78.6%	84.0%	81.0%	<0.001
Mild depression	15.2%	12.0%	13.7%	
Moderate depression	4.2%	2.7%	3.5%	
Moderately severe depression	1.4%	1.0%	1.2%	
Severe	0.6%	0.4%	0.5%	
<b>Brain Measures</b>				
Total Brain Volume – not normalized (mm <sup>3</sup> ) [Mean ± SD]	1,110,000 ± 89,700	1,230,000 ± 98,500	1,160,000 ± 110,000	<0.001
Total Brain Volume – normalized (mm <sup>3</sup> ) [Mean ± SD]	1,510,000 ± 72,600	1,480,000 ± 70,600	1,490,000 ± 72,900	<0.001
Hippocampal volume (mm <sup>3</sup> ) [Mean ± SD]	4,150 ± 375	4,440 ± 411	4,280 ± 417	<0.001
Amygdalar volume (mm <sup>3</sup> ) [Mean ± SD]	1,900 ± 220	2,040 ± 241	1,960 ± 240	<0.001
<b>Cognitive Measures</b>				
Fluid Intelligence (n = 17,677) [Mean ± SD]	6.58 ± 1.98	6.82 ± 2.08	6.69 ± 2.03	<0.001
Numeric Memory (n = 16,784) [Mean ± SD]	6.94 ± 1.45	7.13 ± 1.40	7.03 ± 1.43	<0.001
Pairs Matching (n = 17,192) [Mean ± SD]	0.666 ± 1.19	0.618 ± 1.21	0.644 ± 1.20	0.009
Symbol Digit Substitution (n = 17,499) [Mean ± SD]	20.5 ± 5.09	20.2 ± 4.74	20.4 ± 4.94	<0.001

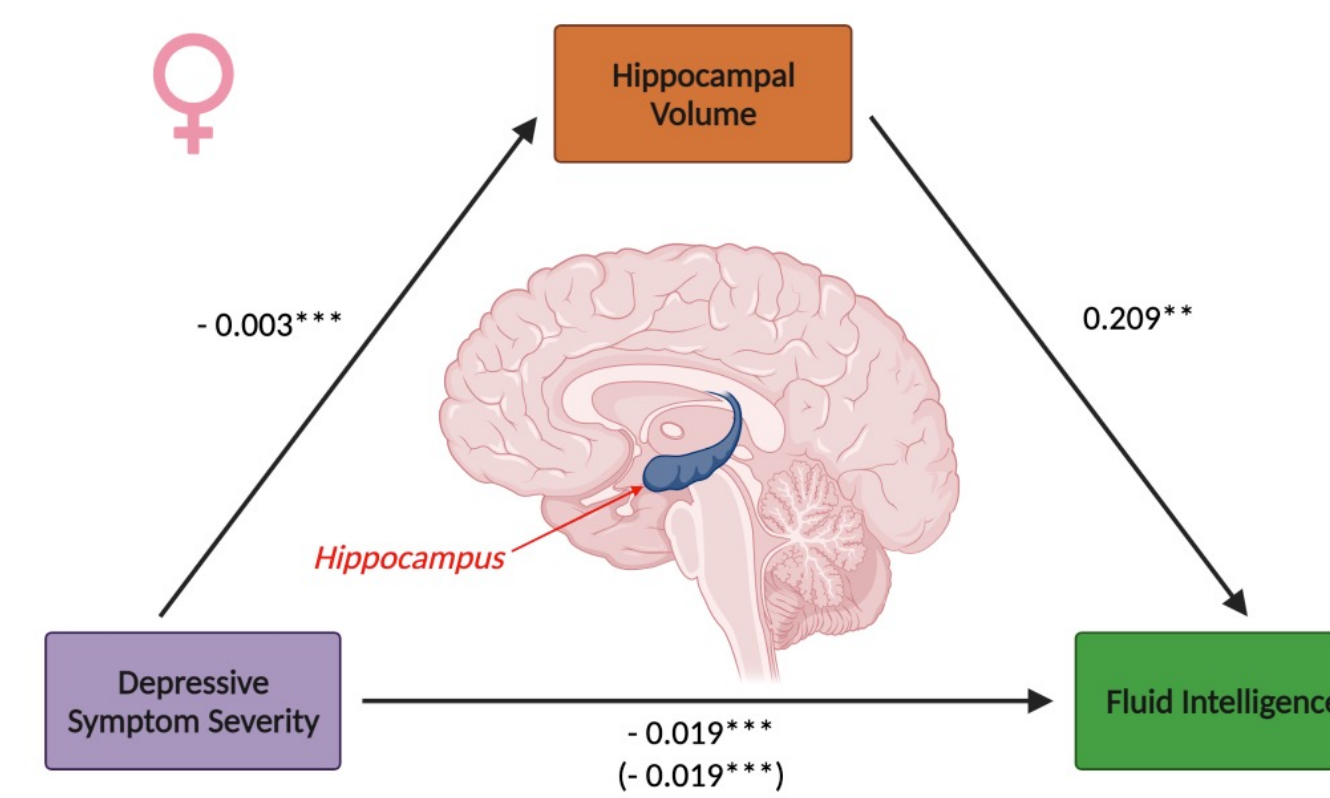
## Statistical Analyses

- Causal Mediation Models (Figure 1) were analyzed using the *mediation* package in R.
- Analyses on the aggregated sample (both men and women) were conducted first. Mediation models that were significant were then run on the sex-stratified samples.
- The significance of indirect effects was evaluated using bootstrapping procedures.

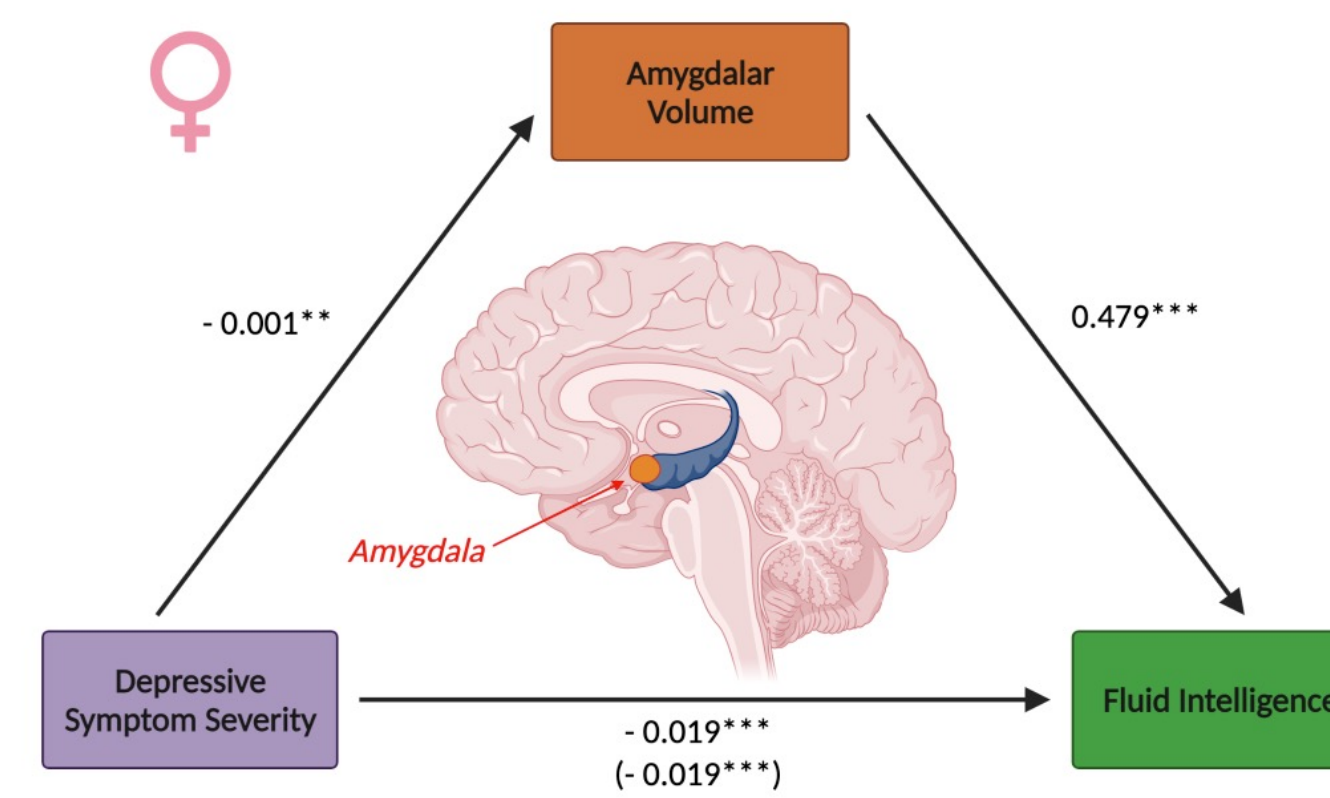


**Figure 1** Causal Mediation Models

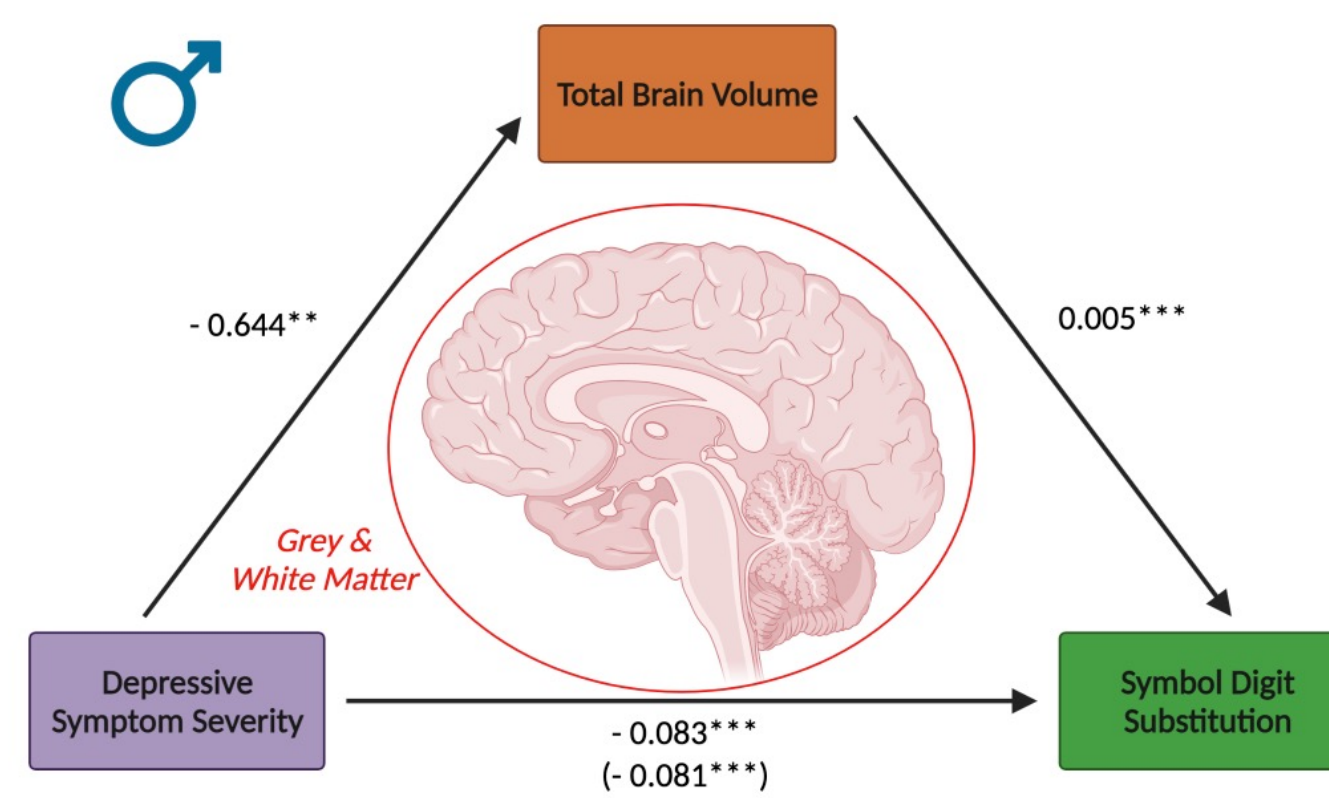
## Results



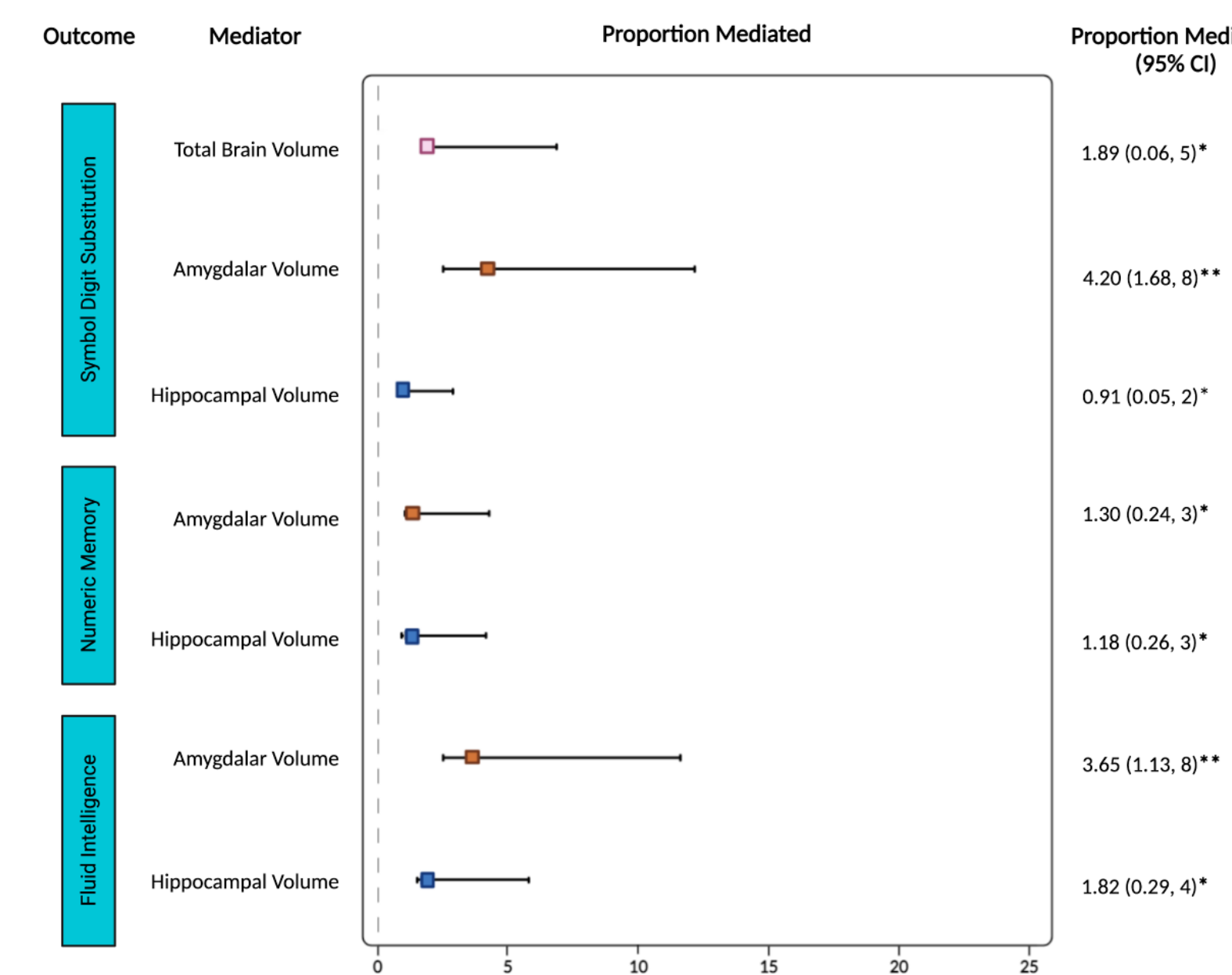
**Figure 2** Hippocampal volumes mediate the relationship between depressive symptom severity and fluid intelligence scores in women.  $p\text{-value} > 0.05$  (\*);  $p\text{-value} > 0.01$  (\*\*);  $p\text{-value} > 0.001$  (\*\*\*)



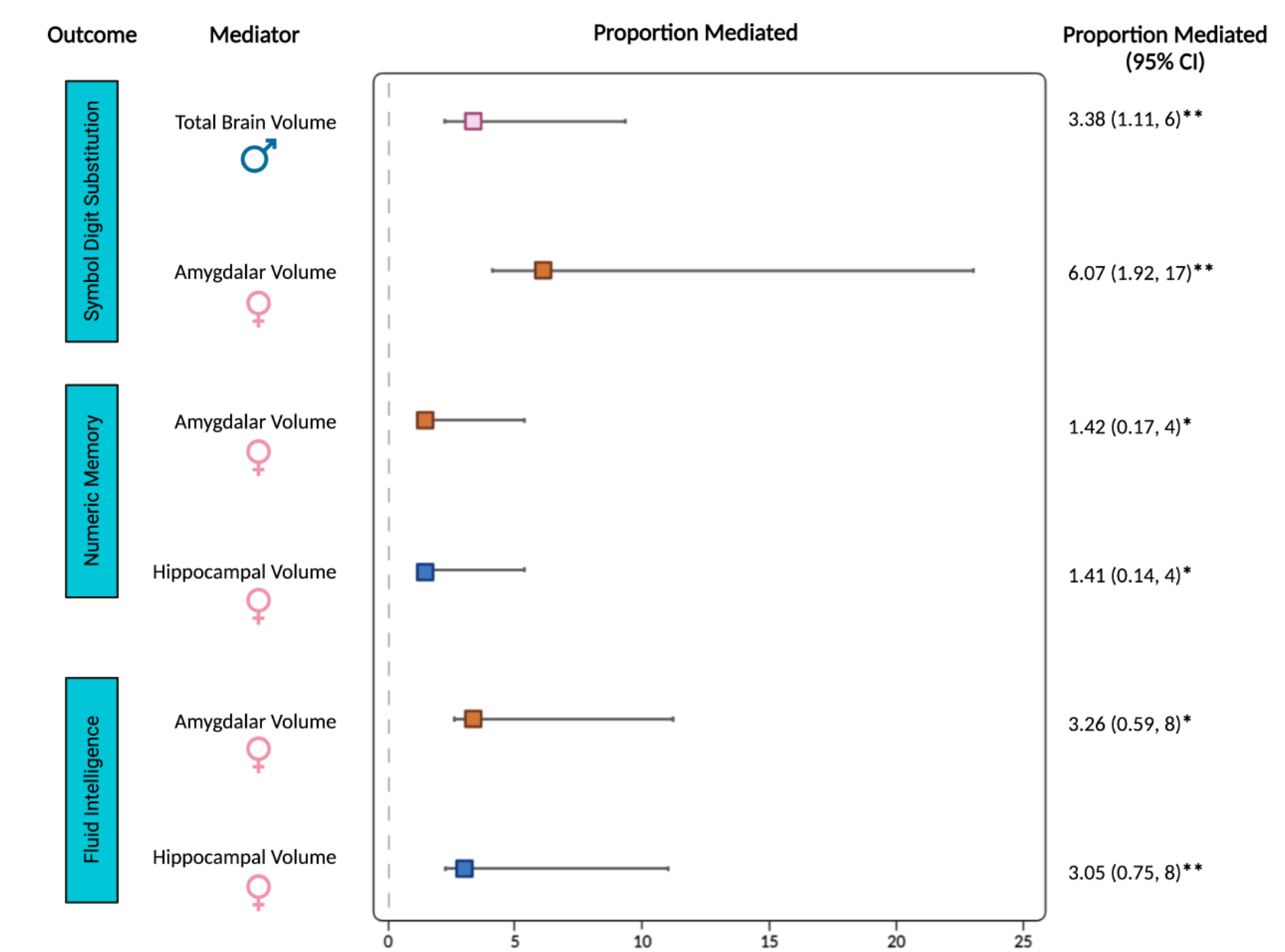
**Figure 3** Amygdalar volumes mediate the relationship between depressive symptom severity and fluid intelligence scores in women.  $p\text{-value} > 0.05$  (\*);  $p\text{-value} > 0.01$  (\*\*);  $p\text{-value} > 0.001$  (\*\*\*)



**Figure 4** Total brain volumes mediate the relationship between depressive symptom severity and number of correct matches on the symbol digit substitution test in men.  $p\text{-value} > 0.05$  (\*);  $p\text{-value} > 0.01$  (\*\*);  $p\text{-value} > 0.001$  (\*\*\*)



**Figure 5** Proportion mediated with 95% confidence intervals reported for all significant causal mediation models conducted on the aggregated samples (both men and women).  $p\text{-value} > 0.05$  (\*);  $p\text{-value} > 0.01$  (\*\*)



**Figure 6** Proportion mediated with 95% confidence intervals reported for all significant causal mediation models conducted on the sex-stratified samples (men only; women only).  $p\text{-value} > 0.05$  (\*);  $p\text{-value} > 0.01$  (\*\*)

## Conclusions

### Sex-stratified sample (Fig. 2, 3, 4, 6):

- In women, the effect of depression symptom severity on Fluid Intelligence, Numeric Function, and Symbol Digit Substitution was mediated by hippocampal and amygdalar volumes. In men, the effect of depression symptom severity on Symbol Digit Substitution was mediated by total brain volume.

### Aggregated sample (Fig. 5):

- Hippocampal & amygdalar volumes mediated the relationship between depression symptom severity and cognition for Fluid Intelligence, Numeric Memory, and Symbol Digit Substitution. Total brain volume mediated this relationship for Symbol Digit Substitution.

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