A Prospective Study of Visuospatial Memory Dysfunction in Irritable Bowel Syndrome

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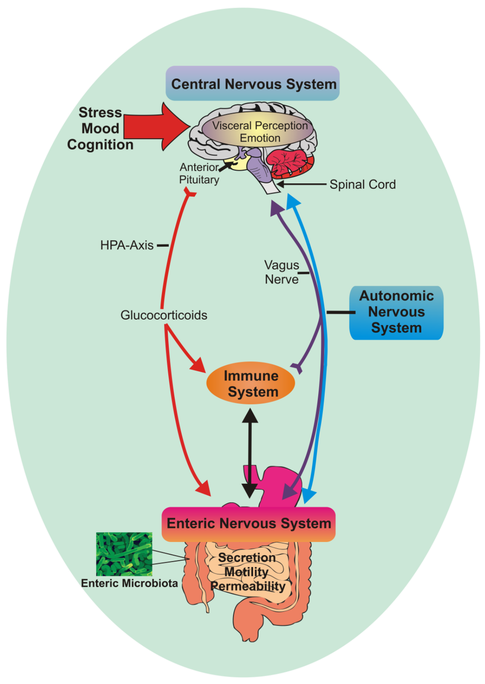


Figure 1: The Brain-Gut Axis (1)

Introduction

- Irritable bowel syndrome (IBS) is a stress-related functional gastrointestinal disorder of the brain-gut axis. (**1,2**; see **Figure 1**).
- The cognitive neurobiological model of IBS (**1**), proposes that some of the key pathophysiological features, including stress-related changes in hypothalamic pituitary adrenal (HPA)-axis functioning and the immune-mediated degradation of tryptophan along the kynurenine pathway, may impact on patients' cognitive performance. (see **Figure 2**).
- Support for this model has been demonstrated by a study showing that patients with IBS exhibit a visuospatial memory deficit associated with alterations in HPA axis activity(**3,4**).
- However, whether visuospatial memory dysfunction is a stable feature of IBS is currently unknown.

Aims

- To assess prospectively, if patients with IBS consistently exhibit visuospatial memory dysfunction in comparison to healthy controls participants, and if this is related to plasma tryptophan, kynurenine, proinflammatory cytokine or salivary cortisol levels .

Figure 2: Representation of the cognitive neurobiological model of IBS. Pathophysiological factors key to IBS such as stress, pain, and heightened immune activity , are also linked to cognitive dysfunction. SNS, sympathetic nervous system; HPA, hypothalamic–pituitary–adrenal; HYP, hypothalamus; HPP, hippocampus; PFC, prefrontal cortex; LPFC, lateral prefrontal cortex; ACC, anterior cingulated cortex; AMG, amygdala; CRF, corticotropin releasing factor; ACTH, adrenocorticotropic hormone; IL, interleukin; TNF, tumour necrosis factor . **Figure from (1)**

Methods

Study Design:

- Thirty two patients with IBS and 30 healthy age and IQ matched controls, male and female, age 18-50 years old (see **Table 1** for demographics), were re-enrolled from a previous investigation and followed prospectively over a 6 month period (Baseline (**Visit 1**), 6 months (**Visit 2**)).

Measures:

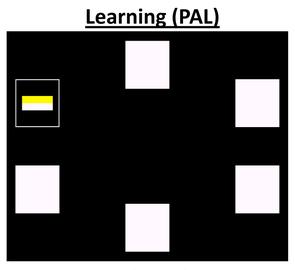
- Salivary cortisol (ELISA)
- Plasma proinflammatory cytokines
- Plasma tryptophan (Trp), kynurenine (Kyn), and the Trp:Kyn ratio
- Hosptial Anxiety Depression Scale (HADS)
- Pittsburgh Sleep Quality Index (PSQI)

Cognitive Function:

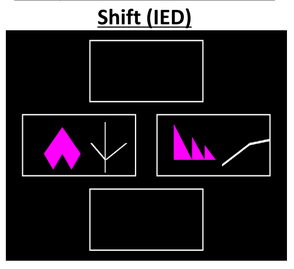
CANTAB

Cambridge Cognition

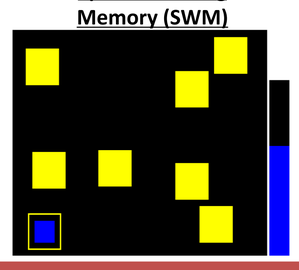
Paired Associates Learning (PAL)



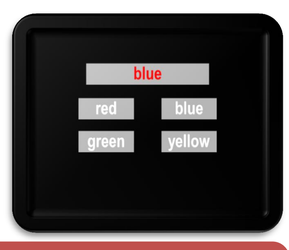
Intra/Extra Dimensional Set Shift (IED)



Spatial Working Memory (SWM)



Stroop test



Results

Baseline Sample Characteristics

	Healthy Controls (n=30)	IBS (n=32)	p- value
Age	28.23 ± 1.71	28.41 ± 1.35	.937
Sex: Male (%)	10 (33.3%)	5 (15·6%)	.104
Female (%)	20 (66.7%)	27 (84·4%)	
BMI	23.27 ± .71	24.15 ± .65	.364
Units of Alcohol Per Week	5.17 ± .79	5.63 ± 1	.723
WAIS-R Full Scale IQ (NART conversion)	109.19 ± 1.19	105.64 ± 1.43	.064
Symptom Duration (years)	-	9.19 ± 1.27	-
HADS-A	3.6 ± .53	7.63 ± .89	.005**
HADS-D	1.43 ± .32	3.12 ± .53	.002
PSQI	3.57 ± .41	5.94 ± .67	.001

Table 1: Comparisons between IBS patients and healthy controls on demographic and clinical characteristics. Study participants were matched on the basis of age, sex , BMI, units of alcohol per week, IQ. Data are expressed as mean± SEM. Independent samples t-tests using IBM SPSS V20.0 were used to determine group differences. *IBS, irritable bowel syndrome; WAIS-R, Wechsler Adult Intelligence Scale- Revised; HADS-A/D, Hospital Anxiety and Depression Scale- Anxiety/ Depression; PSQI, Pittsburgh Sleep Quality Index.*

Results

Impaired Visuospatial Memory in IBS

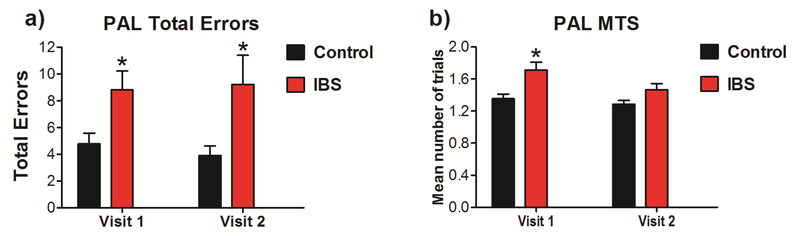


Figure 3. a. Across visits, patients with IBS made significantly more errors on the Paired Associates Learning (PAL) test of visuospatial memory ($F(1, 60)=7.405$; $p= 0.008$, $h_p^2= 0.11$). Post-hoc t-tests with a Bonferroni correction revealed that at both visit 1 ($p= 0.042$) and Visit 2 ($p= 0.034$), patients with IBS made a greater number of total errors on the PAL test. **b.** similarly, across visits, patients with IBS took a greater number of trials to complete the PAL test ($F(1, 60)=9.314$; $p= 0.003$, $h_p^2= 0.134$), which was significant at visit 1 ($p= 0.004$) but not visit 2 ($p=0.08$). Data are expressed as mean± SEM.

No difference in Executive Function(s)

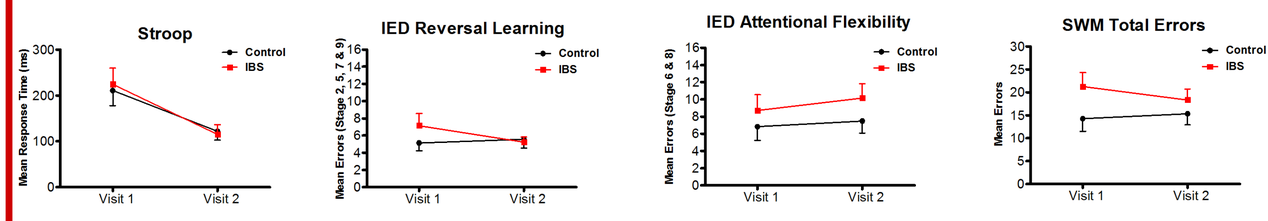


Figure 4. There was no significant difference between patients with IBS and healthy control participants on **a.** response inhibition on the Stroop test ($F(1, 58)=0.011$; $p= 0.918$, $h_p^2< 0.01$) **b.** reversal learning on the Intra/Extradimensional Set Shift Test (IED) ($F(1, 59)=0.19$; $p= 0.664$, $h_p^2= 0.003$); **c.** attentional set shifting on the IED ($F(1, 58)=1.203$; $p= 0.277$, $h_p^2= 0.02$); **d.** or working memory on the Spatial Working Memory (SWM) test ($F(1, 60)=2.844$; $p= 0.097$, $h_p^2= 0.045$). Data are expressed as mean± SEM.

Correlations Between Biological Measures & Cognitive Performance in IBS

	IBS Group	
Measure	PAL Total Errors (Mean Visit 1 & 2)	PAL Mean Trial to Success (Mean Visit 1 & 2)
L Tryptophan	-.346[#]	-.304[##]
L-Kynurenine	-.302 [##]	-.207
Kyn: Trp Ratio	-.136	-.067
IL-6	-.188	-.084
IL-8	.08	.097
TNF-a	-.04	-.027
IFN-Y	.081	.130
CAR (AUCg)	.289	.335

Table 2. a Summary of correlations between averaged Visit 1 and 2 values for visuospatial memory performance in patients with IBS (PAL total errors and PAL mean trials to success), plasma levels of tryptophan, kynurenine, the kynurenine to tryptophan ratio, proinflammatory cytokines (IL-6, IL-8, TNF-a, IFN-Y), and the CAR. *IL- 6/ 8, interlukin- 6/8; TNF-tumor necrosis factor; IFN-Y, Interferon-gamma; Kyn/Trp ratio, Kynurenine: Tryptophan Ratio; CAR, cortisol awakening response.* ([#] p=0.057; [##]p=0.09).

Conclusions

- Impaired visuospatial memory performance is a persistent feature of IBS that appears to be unrelated to biological indices immune activity or HPA axis function.
- However, these results provide a preliminary indication that tryptophan and kynurenine may play a role in this deficit.
- The functional implications of impaired visuospatial memory in IBS are currently unclear and future studies are needed to elucidate the full impact on patients daily living.
- Moreover, interventional strategies are required to understand the neurobiological underpinnings of cognitive dysfunction in IBS.

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