Neuropsychological complications of chemotherapy and the involvement of the endocannabinoid system

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Introduction

- Advancements in cancer screening and treatment have led to more people living with or beyond a cancer diagnosis, but with persistent side effects from their treatment
- The neuropsychological symptom cluster, characterised by cognitive deficits, fatigue, anxiety and depression, is increasingly documented as an unmet need among cancer survivors[1]
- The endocannabinoid system (ECS) is a complex communication network with known involvement in cognition and mood[2,3] but has not been explored in cancer therapy

We aimed to explore changes in the ECS following chemotherapy and link with neuropsychological symptoms

Methods

N=36 C57BL/6 mice treated with 450mg/kg 5-Fluorouracil (5-FU) or vehicle control (VC) i.p.

Promethion cage; Habitual behaviour and metabolism

RT-PCR; ECS, neurotrophic, anti-apoptotic, and extracellular matrix remodeling genes in the hippocampus

Treatment-naïve women with breast cancer (stage I-IV)

Questionnaire; FACT-Cog, neuropsychological symptom burden

ELISA analyses; Brain-derived neurotrophic factor (BDNF)

LCMS analyses; Endocannabinoids; anandamide (AEA) & 2-arachidonoyl-glycerol (2-AG)

Preclinical results

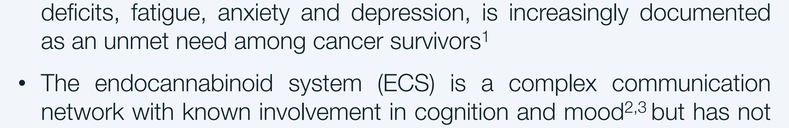

Figure 1. (A, C) Trajectories of food intake and movement over a 4-day period, with Y=0 starting at 12 days after 5-FU/VC treatment. (B, D) Area under the curve (AUC) for food intake and movement in light and dark phases. Data are mean ± SEM. ****p<0.0001.

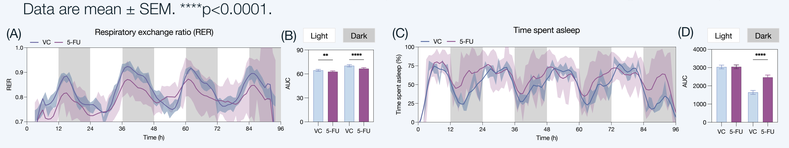

Figure 2. (A, C) Trajectories of respiratory exchange ratio (RER) and time spent asleep over a 4-day period, with Y=0 starting at 12 days after 5-FU/VC treatment. (B, D) Area under the curve (AUC) for RER and time spent asleep in light and dark phases. Data are mean ± SEM. **p<0.01, ****p<0.0001.

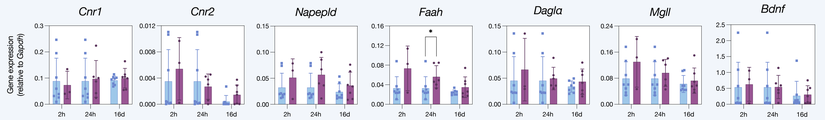

Figure 3. Gene expression levels of ECS (*Cn1*, *Cnr2*, *Napepld*, *Faah*, *Dagla*, *Mgll*) and neurotrophic (*Bdnf*) genes in the hippocampus at 2 hours, 24 hours, and 16 days post-treatment with 5-FU or VC. Data are presented relative to *Gapdh* expression. Data are mean ± SD. *p<0.05.

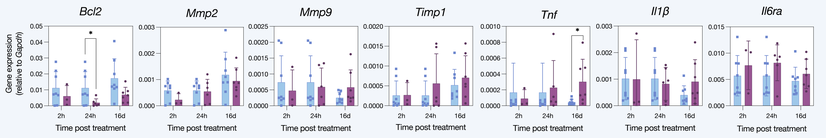

Figure 4. Gene expression levels of anti-apoptotic (*Bcl2*), extracellular matrix remodelling (*Mmp2*, *Mmp9*, *Timp1*) and inflammatory (*Tnf*, *Il1β*, *Il6ra*) genes in the hippocampus at 2 hours, 24 hours, and 16 days post-treatment with 5-FU or VC. Data are presented relative to *Gapdh* expression. Data are mean ± SD. *p<0.05.

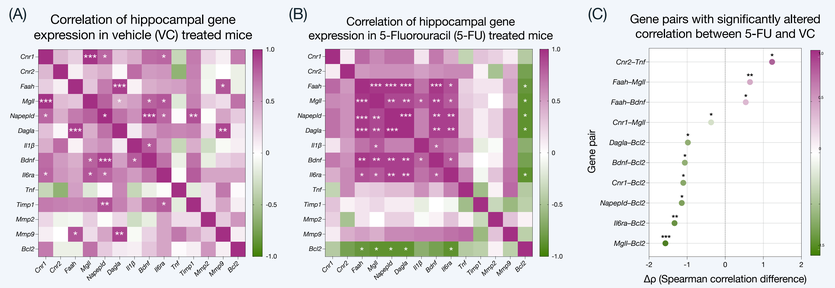

Figure 5. (A-B) Spearman correlation (ρ) matrices of hippocampal gene expression in VC and 5-FU treated groups at 16 days. (C) Gene pairs with significantly altered correlations between groups ranked by correlation difference. *p<0.05, **p<0.01, ***p<0.001.

Clinical results

Table 1. Minimal clinically important difference (MCID) cut-off score derived from baseline FACT-Cog scores (N=45).

MCID cut-off derived from baseline FACT-Cog scores	
Lowest FACT-Cog score	75.25
Highest FACT-Cog score	148
Mean	134.8
Std. Deviation (SD)	17.4
MCID (0.8 SD)	**13.92**

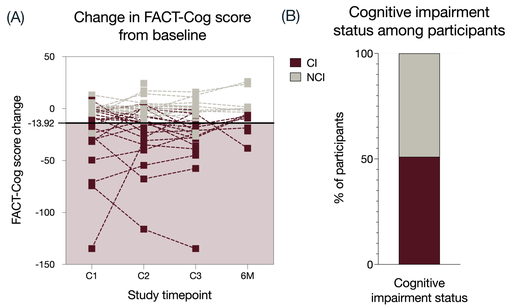

Figure 6. (A) Change in Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) score from baseline to chemotherapy cycle 1 (C1); chemotherapy cycle 2 (C2); chemotherapy cycle 3 (C3); and 6-months (6M) post chemotherapy. (B) Proportion of participants with cognitive impairment (CI) and with no cognitive impairment (NCI) (N=45).

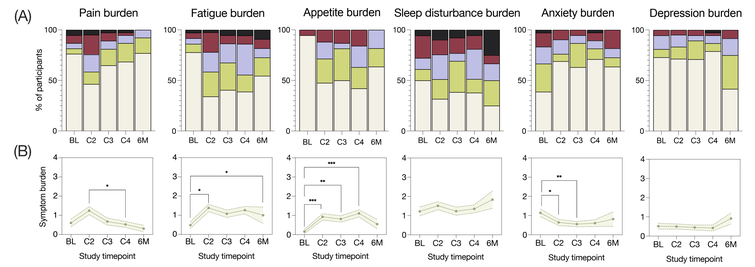

Figure 7. **How much does the symptom bother you at its worse?** (A) Distribution of burden scores (0-4) of pain, fatigue, appetite, sleep disturbance, anxiety and depression among participants from baseline (BL) to 6-months (6M) post chemotherapy (N=45). (B) Mean ± SEM trajectory symptom burden from BL to 6M. *p<0.05, **p<0.01, ***p<0.001.

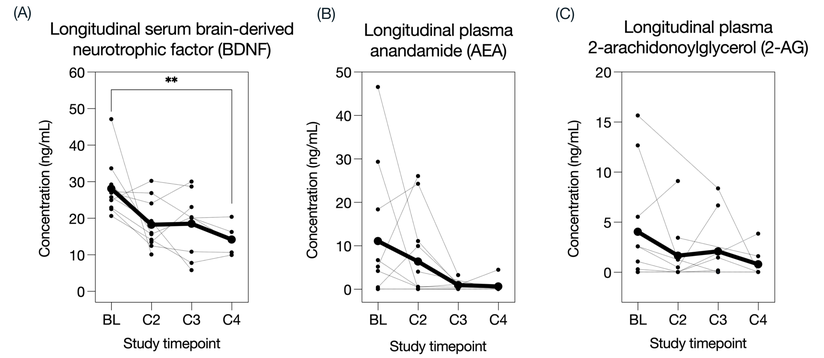

Figure 8. (A) Longitudinal dynamics of BDNF (N=12). Significant reduction in BDNF from baseline (BL) to chemotherapy cycle 4 (C4) (p=0.001). (B) Longitudinal dynamics of AEA (N=13). (C) Longitudinal dynamics of 2-AG (N=13).

Conclusions

- Clinical symptom profile mirrors pre-clinical with persistent fatigue, reduced appetite and cognitive impairment observed across models
- ECS signaling also impacted across models; *Faah* upregulation in the hippocampus aligns with longitudinal reduction in circulating AEA
- These findings highlight ECS dysregulation as a potential contributing mechanism driving chemotherapy-induced neuropsychological complications
- Future directions aim to evaluate neuropsychological changes in the ECS of people receiving chemotherapy for solid tumours and intervention with exogenous cannabinoids (CBD and THC) or placebo (Trial registration: ACTRN12622000419763).

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References: [1]Ramsey et al. 2021, J Cancer Surviv, 15(2). [2]Zanettini et al. 2011, Front Behav Neurosci, 5(57). [3]Stachowicz 2023, Neurosci Biobehav Rev, 155.