Insulin resistance following childhood craniopharyngioma may influence neural response to food cues in food reward-related brain regions: a preliminary investigation.

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1 BACKGROUND

- Craniopharyngioma is a benign tumour arising in the sellar and suprasellar regions, proximal to the hypothalamic area.[1] Incidence is rare (0.5-2 cases per million per year)[2]
- Long term sequalae include endocrine dysfunction, visual impairment and hypothalamic obesity[3], with a negative impact on quality of life[4].
- Although 50% of craniopharyngioma patients experience hypothalamic obesity – predicted by hypothalamic damage on MRI in some instances[5] - there is limited research investigating underlying mechanisms, which are poorly understood.
- Hypothalamic damage following craniopharyngioma may have wide-spread effects, e.g.
  - ➢ differential neural responses to food cues in the brain[6,7]
  - ➢ dysfunctional parasympathetic nervous system activity leading to altered glucose metabolism and hyperinsulinemia.[8]
- Evidence in healthy volunteers suggests a link between insulin resistance (IR), neural responses to food and obesity.[9]

2 AIM & HYPOTHESIS

Aim: To explore a potential link between IR and neural responses to food and obesity in patients with childhood craniopharyngioma.

Hypothesis: IR in craniopharyngioma may alter neural response to food cues, as measured by fMRI, in several brain regions of interest (ROIs), and thereby contribute to obesity.

ROIs: hypothalamus, insula, amygdala, nucleus accumbens, putamen, orbitofrontal cortex, temporal occipital fusiform cortex

This is part of a larger feasibility study which investigated eating behaviours, energy homeostasis and obesity in patients with childhood craniopharyngioma using various techniques (e.g. oral glucose tolerance test, indirect calorimetry, *ad libitum* meal, functional MRI).

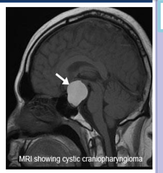
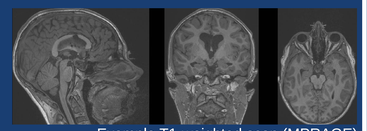


Image credit: UCLA Pituitary Tumor Program

3 METHODS

Overnight fast
↓
Body composition (Tanita)
↓
Baseline fMRI scan
↓
Fixed glucose load/kg (OGTT)
↓
60 mins
↓
Post glucose fMRI scan

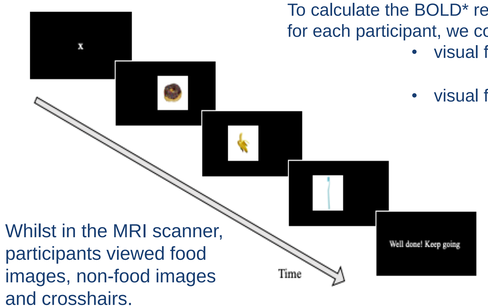
Study took place at Clinical Research & Imaging Centre, Bristol on a Siemens 3T Magnetom Skyra



Example T1-weighted scan (MPRAGE)

As this feasibility study was not powered for null hypothesis significance testing, we focussed on measure of effect size (Kendall's Tau correlation coefficient).

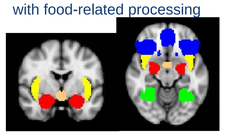
4 fMRI FOOD-CUE REACTIVITY



Whilst in the MRI scanner, participants viewed food images, non-food images and crosshairs.

To calculate the BOLD* response in ROIs (fig. below) for each participant, we contrasted the following:

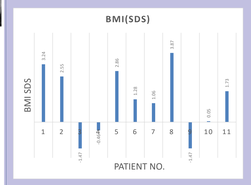
- visual food cues at baseline
  - Food cues > Crosshairs
- visual food cues post-glucose
  - Post-glucose > Baseline
- Non-parametric permutation analysis (RANDOMISE, FSL[10]) in 7 *a priori* ROIs associated with food-related processing



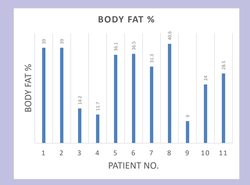
*Blood oxygen level dependent

5 PATIENTS WITH CRANIOPHARYNGIOMA

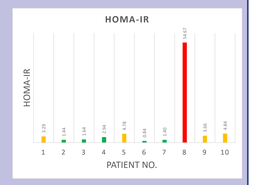
- n = 11; median age = 14y (range = 10-23); 5 female & 6 male
- Normal glucose tolerance (based on WHO criteria) was found (median fasting glucose = 4.45mmol/L; n = 10) in all but one patient with T2DM



median BMISDS = 1.3 [range = -1.5-3.9]



median Body fat % = 31.3 [range = 9.0-40.6]



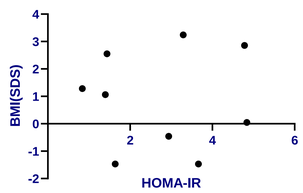
median HOMA-IR = 3.11 [range = 0.8-54.7]

T2DM
Insulin resistant
Normal HOMA-IR

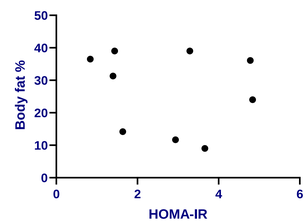
6 INSULIN RESISTANCE AND BODY COMPOSITION

No evidence for a correlation was found between HOMA-IR and body fat % (τ=-.25) or BMISDS (τ=.00) (n = 9).

Relationship between HOMA-IR and BMI(SDS)



Relationship between HOMA-IR and body fat %



Patient with T2DM removed from HOMA-IR correlational analyses as an outlier.

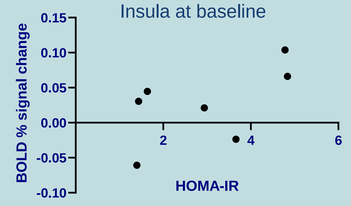
7 INSULIN RESISTANCE AND NEURAL RESPONSES

Relationship between HOMA-IR and neural response to food cues (n = 7; Kendall's tau):

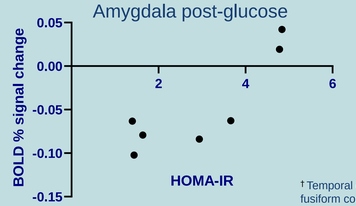
HOMA-IR	TOFC†	Amygdala	Hypothalamus	Insula	Nucleus accumbens (NA)	Putamen	Orbitofrontal cortex (OFC)
Baseline	-0.048	-0.238	0.238	0.429*	-0.143	0.524	0.238
Post-glucose	0.333	0.619*	-0.333	0.048	0.429	-0.333	-0.048

*examples shown in figures

Insula at baseline



Amygdala post-glucose



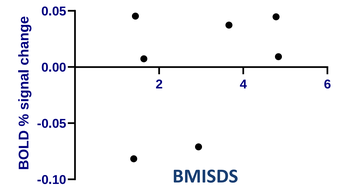
† Temporal occipital fusiform cortex

8 BMISDS & NEURAL RESPONSES

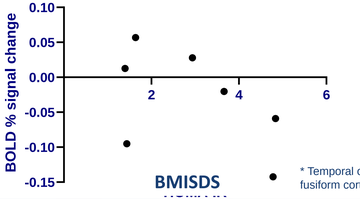
Relationship between BMISDS and neural response to food cues (n = 9; Kendall's tau):

BMISDS	TOFC*	Amygdala	Hypothalamus	Insula	Nucleus accumbens (NA)	Putamen	Orbitofrontal cortex (OFC)
Baseline	0.333	-0.056	0.556	0.444	0.111	0.222	0.444
Post-glucose	0.278	0.111	-0.556	-0.389	-0.389	-0.056	-0.278

Hypothalamus at baseline



Hypothalamus post-glucose



* Temporal occipital fusiform cortex

9 DISCUSSION

- *Preliminary* results showed:
  - The expected relationship between insulin resistance and measures of body composition (BMISDS and body fat) was not found,
  - Evidence for a relationship between IR with the BOLD response was found (akin to [9]), both after fasting and after glucose consumption in different appetitive brain regions.
  - BMISDS was positively related to hypothalamic response to food cues after fasting and negatively post-glucose consumption, similar to the hypothalamic response to food cues in people without craniopharyngioma[11,12]
- Results should be considered in the light of differences in brain volume[13], beyond the immediate tumour area, which was related to hyperphagia.

CONCLUSION

These preliminary findings in this small group of craniopharyngioma patients suggest that insulin resistance may influence the response to food cues in brain regions responsible for appetite control. Further investigation of this intriguing link is warranted in larger, multicentre research.

References: [1]Muller (2014), [2]Garr & Cama (2007), [3]Wijnen et al. (2017), [4]Muller et al (2005), [5]Roth et al. (2015), [6]Roth et al. (2012), [7] Elsworth et al. (2021), [8]van Iersel et al.(2019), [9] Cheke et al., (2017), [10]Winkler et al. (2014), [11]Hinton et al. (2004), [12]Matsuda et al. (1999), [13]Hinton et al. (2021).

Trial registered with ISRCTN (isrctn.com/ISRCTN86005167)

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