A nested case-control cohort of post-operative delirium finds levels of higher levels of ornithine pre-operatively, and higher levels of spermine post-operatively in plasma, indicating disturbed polyamine metabolism

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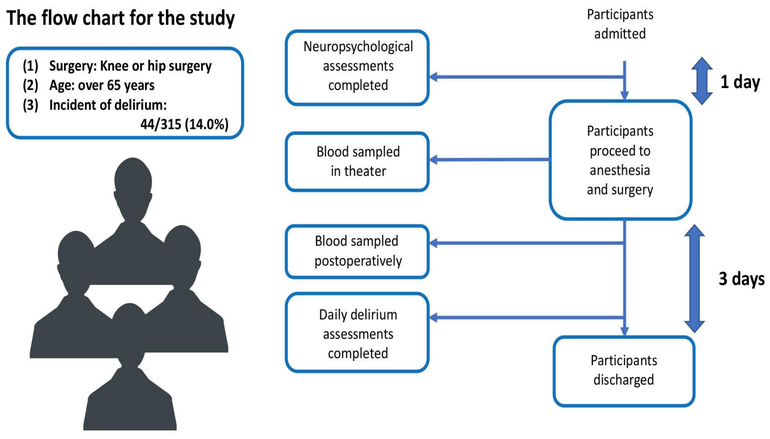
INTRODUCTION

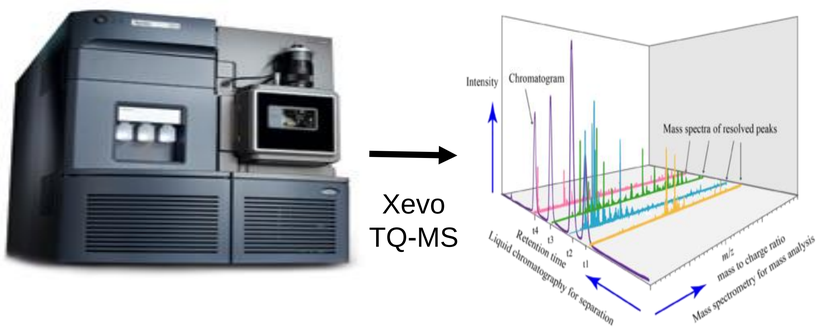
Delirium after surgery is common in older people. The mechanisms underlying delirium development are unclear. We investigated the plasma metabolites significantly affected by orthopaedic surgery to better understand the causes of post-operative delirium.

MATERIALS & METHODS

1. The chart of process of sample collection

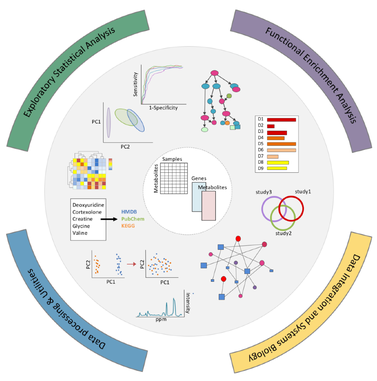


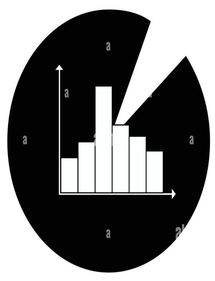
2. Targeted metabolomics



3. Data analysis

MetaboAnalyst software
PLS-DA, VIP scores





Statistics
Paired Student's t-test
the Wilcoxon Mann-Whitney test
False discovery rates (FDR, q-value)
Binary logistic regression

Participants (n = 54) matched for age and gender were sampled from an observational cohort study investigating post-operative delirium. Participants were ≥65 years without a diagnosis of dementia presenting for primary elective hip or knee arthroplasty. Plasma samples collected pre- and post-operatively were grouped as either control (n = 26, aged: 75.8 ± 5.2) or delirium (n = 28, aged: 76.2 ± 5.7). Metabolite profiling of plasma was undertaken using a triple-quadrupole mass spectrometer.

RESULTS

Clinical characteristics

	Control (n=26)	Delirium (n=28)	Statistical test	P value
Age, mean (SD)	75.8 (5.2)	76.2 (5.7)	T= -0.224	0.82
Sex, female (%)	14/26	15/28	X2= 0	1.00
Type of surgery (hip vs knee), hip (%)	15 out of 26	9 out of 28	X2=2.604	0.11
Years in Education, mean (SD)	11.4 (2.3)	11.3 (1.8)	MWU= 363	0.985
BADL Score (Range:0-9), median (IQR)	3 (1-3)	3 (1-3)	MWU=356	0.884
Vertical Visual Analogue Pain Scale pain at rest, mean (SD)	26.5 (22.7)	19.7 (24.9)	MWU=260.5	0.107
Vertical Visual Analogue Pain Scale pain on movement, mean (SD)	75.7 (14.7)	65.0 (24.0)	T= 1.969	0.055
Estimated IQ, mean (SD)	111.7 (7.5)	106.8 (9.3)	T=2.093	**0.041***
CLOX 1 score, (Range:6-15), median (IQR)	13 (11-14)	12 (11-13)	MWU=303.5	0.286
Letter fluency mean, mean (SD)	11.5 (3.9)	10.4 (4.2)	T= 1.077	0.286
Category fluency mean, mean (SD)	16.3 (3.8)	15.2 (3.7)	T= 1.106	0.274
Stroop colour-word score, mean (SD)	22.3 (6.1)	20.1 (6.8)	T= 1.247	0.218
Time taken to complete Colour Trails 2 (seconds), mean (SD)	146.4 (50.2)	205.2 (115.1)	MWU=235.5	**0.041***
New York university paragraph recall test (immediate recall score), (Range:1-9), median (IQR)	5.44 (3.83-6.89)	4.00 (3.00-5.27)	MWU=237.5	**0.026***
New York university paragraph recall test (delayed recall score), (Range:0-12), median (IQR),	5 (3-8)	4 (2-5.75)	MWU=251.5	0.050
American Society Anesthesiologists (ASA) physical status (I/II/III)	0/22/3	1/21/6	MWU=328	0.564
Charlson Comorbidity Index (CCI) 0/1/2/3	15/8/3/0	11/11/4/1	MWU=286.5	0.209
Mini Mental State Examination Score (MMSE), mean (SD)	27.7 (1.9)	26.0 (2.8)	MWU= 203	**0.012***
AB42 in CSF, mean (SD)	613.88 (190.34)	453.01 (175.77)	T=3.198	**0.002****
T-tau in CSF, mean (SD)	291.32 (181.73)	401.01 (233.02)	MWU=204	**0.009****
p-tau in CSF, mean (SD)	51.55 (21.98)	63.88 (23.45)	MWU=201	**0.008****
p-tau/AB42 in CSF, man (SD)	0.10 (0.08)	0.17 (0.09)	MWU=122	**4.60E-05*****

Table 1. Groups were matched for age and sex. Cognitive scores and Alzheimer's disease biomarkers (AB42, T-tau, and p-tau) differed between the groups. Significant p-values are shown in bold. *p < 0.05, **p < 0.01, *** p < 0.001 control vs delirium.

Changes related to delirium and surgery

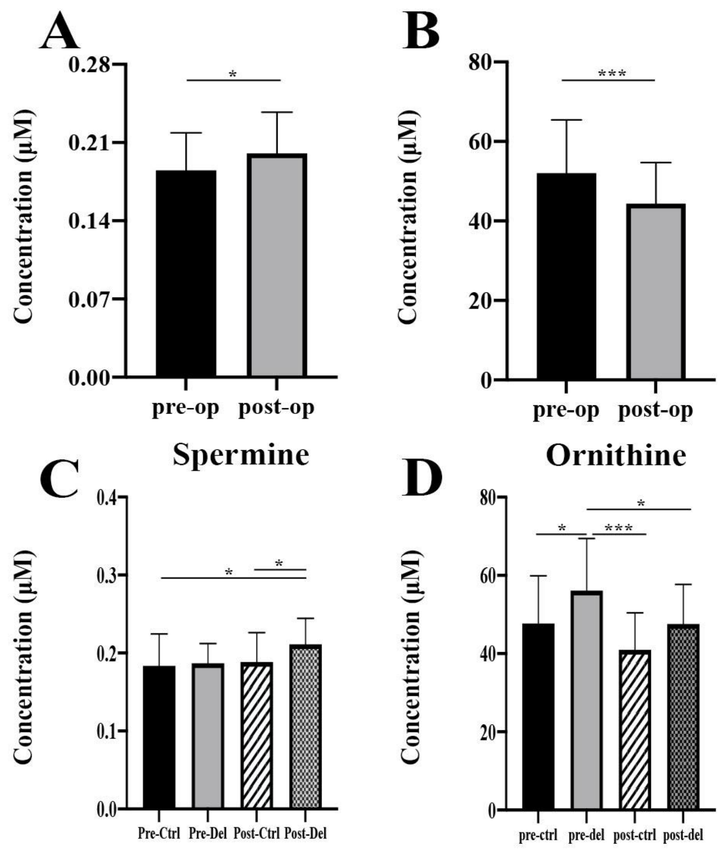


Fig 1. Perioperative changes in spermine and ornithine differed significantly between delirium and no delirium groups. Spermine (A) and ornithine (B) concentrations (μM) in pre- and post-op samples. Spermine (C) and ornithine (D) concentrations (μM) in pre- and post-op samples with control and delirium. *p < 0.05, **p < 0.01, and ***p < 0.01 for both pre- and post-op and pre- and post-op with control and delirium for each group.

Multivariate modelling

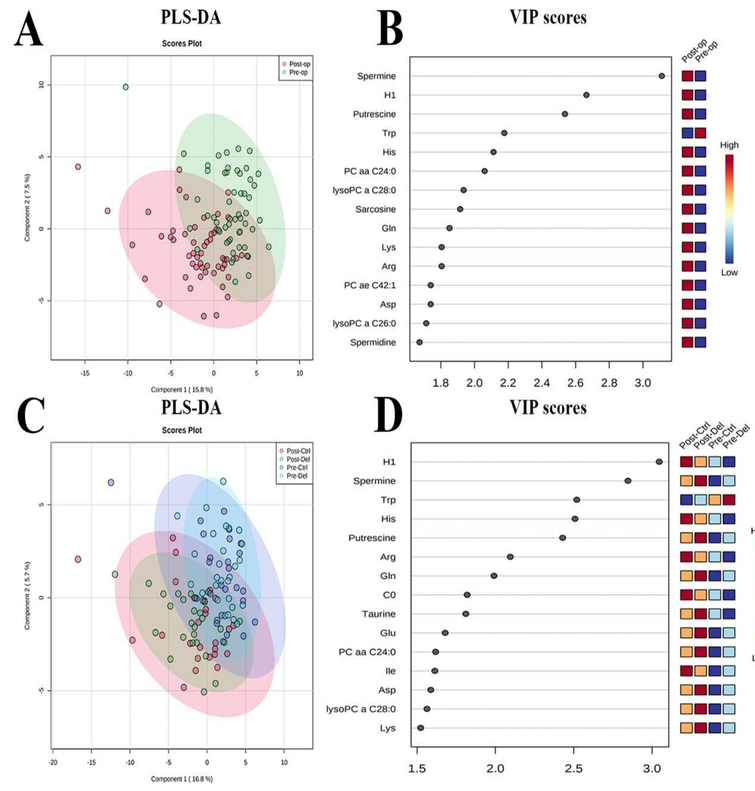


Fig 2. Multivariate modelling of metabolite data. (A) Partial least squares discriminant analysis (PLS-DA) of pre-operative and post-operative samples and (B) the resulting variable importance in projection (VIP) plot showing the 15 most influential metabolites responsible. (C) PLS-DA of control and delirium cases pre-operatively and post-operatively and (D) resulting VIP showing the 15 most influential metabolites responsible**.**

Predictor variables for delirium

Variables	Unadjusted			Adjusted		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Spermine (% change)	1.019	0.995 – 1.043	.126	1.036	0.997 – 1.076	.071
Ornithine (% change)	1.023	0.983 – 1.064	.263	1.037	0.964 – 1.116	.327
Age	1.012	0.916 – 1.118	.820	0.969	0.842 – 1.114	.658
Sex (F/M)	1.000	0.336 – 2.976	1.000	0.709	0.132 – 3.815	.689
Surgery Type (hip vs knee)	2.879	0.948 – 8.744	.062	1.741	0.295 – 10.281	.540
CCI	1.618	0.776 – 3.372	.199	1.431	0.425 – 4.816	.563
Estimated IQ	0.934	0.872 – 0.999	**.047***	0.946	0.852 – 1.051	.302
MMSE	0.711	0.528 – 0.958	**.025***	0.871	0.578 – 1.311	.507
Aβ42	0.995	0.992 – 0.999	**.005****	0.994	0.989 – 0.999	**.027***

Table 2. Perioperative changes in metabolites did not independently predict prostoperative delirium. Significant p-values are shown in bold. *p < .05, **p < .01 variables vs delirium.

CONCLUSION

Pre- and post-operative changes in plasma ornithine and spermine, respectively, are associated with postoperative delirium. These findings support the hypothesis that disturbed polyamine metabolism is an underlying factor in delirium which must be further investigated.

REFERENCES

1. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet (London, England). 2014; 383(9920):911-922.
2. Cunningham EL, McGuinness B, McAuley DF, Toombs J, Mawhinney T, O'Brien S, et al. CSF Beta-amyloid 1-42 Concentration Predicts Delirium Following Elective Arthroplasty Surgery in an Observational Cohort Study. Ann. Surg. 2019;269(6):1200-1205.
3. Pan X, Cunningham EL, Passmore AP, McGuinness B, McAuley DF, Beverland D, et al. Cerebrospinal Fluid Spermidine, Glutamine and Putrescine Predict Postoperative Delirium Following Elective Orthopaedic Surgery. Sci. Rep. 2019; 9(1): 4191.

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