TABLE S1. Equations Used in CWave Software to Calculate Metabolic Rates

Mass Balance Equations

$dGlu_N/dt=V_{cycle} + V_{pdhN} + V_{dilN} - (V_{tcaN} + V_{cycle})=0$

$dGlu_A/dt=V_{cycle} + V_{pdhA} + V_{dilA} - (V_{gln} + V_{tcaANet})=0$

$dGln/dt=V_{gln} - (V_{cycle\_GABA} + V_{cycle} + V_{efflux})=0$

$dGlu_{GABA}/dt=V_{cycle\_GABA} + V_{pdhGABA} + V_{dilGluGABA} - (V_{gad} + V_{tcaGABAnet})=0$

$dGABA/dt=V_{gad} - (V_{shunt} + V_{cycle\_GABA})=0$

$dTCANIntmd_N/dt=0$

$dTCAIntmd_{gaba}/dt=0$

$dTCAIntmd_A/dt=0$

$dLactate/dt=2 \times CMR_{gl} - (V_{ana} + V_{pdhA} + V_{pdhN} + V_{pdhGABA})=0$

$dGlucose/dt=V_{max\_Glc\_in}\,(Plasma\_Glucose) / (K_{m\_Glc\_in} + Plasma\_Glucose) - [CMR_{gl} + (V_{max\_Glc\_out})\,(Glucose) / (K_{m\_Glc\_out} + Glucose)]=0$

Isotope Balance Equations

$dGlu_{N4}/dt=V_{cycle}\,(Gln_4/Gln) + V_{pdhN}\,(Lactate_3/Lactate) + V_{dilN}\,(0) - [V_{tcaN} + V_{cycle}]\,(Glu_{N4}/Glu_N)$

$dGlu_{A4}/dt=V_{cycle}(Glu_{N4}/Glu_N) + V_{pdhA}\,(Lactate_3/Lactate) + V_{dilA}\,(NA_0/NA) - [V_{gln} + V_{tcaANet}]\,(Glu_{A4}/Glu_A)$

$dGln_4/dt=V_{gln}\,(Glu_{A4}/Glu_A) - [V_{cycle\_GABA} + V_{cycle} + V_{efflux}]\,(Gln_4/Gln)$

$dGlu_{N3}/dt=V_{tcaN}\,(TCANIntmd_{N2}/TCANIntmd_N) + V_{cycle}\,(Gln_3/Gln) - [V_{tcaN} + V_{cycle}]\,(Glu_{N3}/Glu_N)$

$dGln_3/dt=V_{gln}\,(Glu_{A3}/Glu_A) - [V_{cycle\_GABA} + V_{cycle} + V_{efflux}]\,(Gln_3/Gln)$

$dGlu_{A3}/dt=V_{cycle}\,(Glu_{N3}/Glu_N) + V_{tcaANet2}\,(TCAIntmd_{A2}/TCAIntmd_A) - [V_{gln} + V_{tcaANet}]\,(Glu_{A3}/Glu_A)$

$dGlu_{GABA4}/dt=V_{cycle\_GABA}\,(Gln_4/Gln) + V_{pdhGABA}\,(Lactate_3/Lactate) + V_{dilGluGABA}\,(NA_0/NA) - [V_{gad} + V_{tcaGABAnet}]\,(Glu_{GABA4}/Glu_{GABA})$

$dGlu_{GABA3}/dt=V_{cycle\_GABA}\,(Gln_3/Gln) + V_{tcaGABA}\,(TCAIntmd_{gaba2}/TCAIntmd_{gaba}) - [V_{gad} + V_{tcaGABAnet}]\,(Glu_{GABA3}/Glu_{GABA})$

$dGABA_2/dt=V_{gad}\,(Glu_{GABA4}/Glu_{GABA}) - [V_{shunt} + V_{cycle\_GABA}]\,(GABA_2/GABA)$

$dGABA_3/dt=V_{gad}\,(Glu_{GABA3}/Glu_{GABA}) - [V_{shunt} + V_{cycle\_GABA}]\,(GABA_3/GABA)$

$dTCANIntmd_{N2}/dt=1/2\ V_{tcaN}\,(Glu_{N4}/Glu_N) + 1/2\ V_{tcaN}\,(Glu_{N3}/Glu_N) + V_{dilC3}\,(NA_0/NA) - [V_{tcaN} + V_{dilC3}]\,(TCANIntmd_{N2}/TCANIntmd_N)$

$dTCAIntmd_{gaba2}/dt=1/2\ V_{tcaGABAnet}\,(Glu_{GABA4}/Glu_{GABA}) + 1/2\ V_{tcaGABAnet}\,(Glu_{GABA3}/Glu_{GABA}) + 1/2\ V_{shunt}\,(GABA_2/GABA) + 1/2\ V_{shunt}\,(GABA_3/GABA) - V_{tcaGABA}\,(TCAIntmd_{gaba2}/TCAIntmd_{gaba})$

$dTCAIntmd_{A2}/dt = 1/2\ V_{cycle\_GABA}\ (GABA_2/GABA) + 1/2\ V_{cycle\_GABA}\ (GABA_3/GABA) + 1/2\ V_{tcaANet}\ (Glu_{A4}/Glu_A) + 1/2\ V_{tcaANet}\ (Glu_{A3}/Glu_A) + V_{ana}\ (Lactate_3/Lactate) - V_{tcaANet2}\ (TCAIntmd_{A2}/TCAIntmd_A)$

$dLactate_3/dt = CMR_{gl}\ (Glucose_1/Glucose) - [V_{ana} + V_{pdhA} + V_{pdhN} + V_{pdhGABA}]\ (Lactate_3/Lactate)$

$dGlucose_1/dt = V_{max\_Glc\_in}\ (Plasma\_Glucose_1)\ /\ (K_{m\_Glc\_in} + Plasma\_Glucose) - [CMR_{gl} + V_{max\_Glc\_out}\ (Glucose)\ /\ (K_{m\_Glc\_out} + Glucose)]\ (Glucose_1/Glucose)$

Variables

$Glu_{Total4} = Glu_{A4} + Glu_{N4} + Glu_{GABA4}$; $Glu_{Total3} = Glu_{A3} + Glu_{N3} + Glu_{GABA3}$; $Glx_3 = Gln_3 + Glu_{A3} + Glu_{GABA3} + Glu_{N3}$; $CMR_{gl} = (V_{pdhA} + V_{pdhN} + V_{pdhGABA} + V_{ana}) / 2$=cerebral metabolic rate of glucose; V_{cycle}=glutamate/glutamine neuron transmitter cycle, iterated; V_{pdhN}=neuronal pyruvate dehydrogenase rate, iterated; $V_{tcaN} = V_{pdhN} + V_{dilN}$=neuronal TCA cycle rate; V_{shunt}=GABA shunt rate, iterated; V_{cycle_GABA}=rate of GABA/glutamine cycling; $V_{gad} = V_{shunt} + V_{cycle\_GABA}$=GABA synthesis rate; V_{ana}=anaplerotic flux; $V_{efflux} = V_{ana}$=glutamine efflux, balanced by Vana; $V_{gln} = V_{cycle} + V_{cycle\_GABA} + V_{efflux}$=glutamine synthesis rate; V_{pdhA}=astrocytic pyruvate dehydrogenase rate; $V_{tcaA} = V_{pdhA} + V_{dilA}$=astrocytic TCA cycle rate; $V_{pdhGABA} = V_{tcaGABA} - V_{dilGluGABA}$=GABAergic pyruvate dehydrogenase rate; $V_{tcaANet} = V_{tcaA} - V_{gln} + V_{cycle}$=astrocytic TCA cycle rate from alpha-KG to succinate; $V_{tcaANet2} = V_{tcaANet} + V_{cycle\_GABA} + V_{ana}$=astrocytic TCA cycle rate from succinate to oxaloacetate; $V_{tcaGABAnet}$=GABAergic neuronal TCA cycle rate from a-KG to succinate; $V_{tcaGABA} = V_{tcaGABAnet} + V_{shunt}$=GABAergic TCA cycle rate; $FracGlu_A$=fraction of total glutamate that resides in astroglial; $FracGlu_{GABA}$=fraction of total glutamate that resides in GABAergic neuron; $K_{m\_Glc\_in}$=Michaelis-Menten half-saturation constant for blood-brain glucose transport; $K_{m\_Glc\_out} = V_d \times K_{m\_Glc\_in}$=Michaelis-Menten half saturation constant for brain-blood glucose transport; V_d=distribution space of brain water; V_{dilA}=astrocytic dilution of acetyl CoA, iterated; V_{dilC3}=neuronal dilution of glutamate C3 relative to C4, iterated; $V_{dilGluGABA}$=GABAergic neuronal dilution of acetyl CoA, iterated; V_{dilN}=glutamatergic neuronal silution of acetyl CoA, iterated; $V_{max\_Glc\_in}$=maximum rate of blood-brain glucose transport; $V_{max\_Glc\_out} = V_{max\_Glc\_in}$=maximum rate if brain-blood glucose transport; GABA=total brain GABA concentration**;** Gln=total brain glutamine concentration**;** Glu=total brain glutamate concentration**;** $Glu_A = FracGlu_A \times Glu_{Total}$=astrocytic glutamate concentration**;** $Glu_N = Glu_{Total} - Glu_A - Glu_{GABA}$=neuronal glutamate concentration**;** $Glu_{GABA} = FracGlu_{GABA} \times Glu_{Total}$=GABAergic glutamate concentration**;** $TCAIntmd_A$=astrocytic TCA cycle intermediates**;** $TCAIntmd_{gaba}$=GABAergic neuronal TCA cycle intermediates**;** $TCANIntmd_N$=glutamatergic neuronal TCA cycle intermediates

TABLE S2. Comparison of Occipital Metabolites

Metabolite	Depression Group (N=23) Mean ± SD	Healthy Group (N=17) Mean ± SD	*t*	*df*	p
GABA (mmol/kg)	1.12 ± 0.10	1.12 ± 0.12	0.04	38	0.97
Glutamine (mmol/kg)	2.32 ± 0.72	2.51 ± 0.70	0.54	38	0.41
Glutamate (mmol/kg)	7.42 ± 1.44	7.47 ± 1.57	0.36	38	0.92

FIGURE S1. Scatter of Occipital GABA Levels

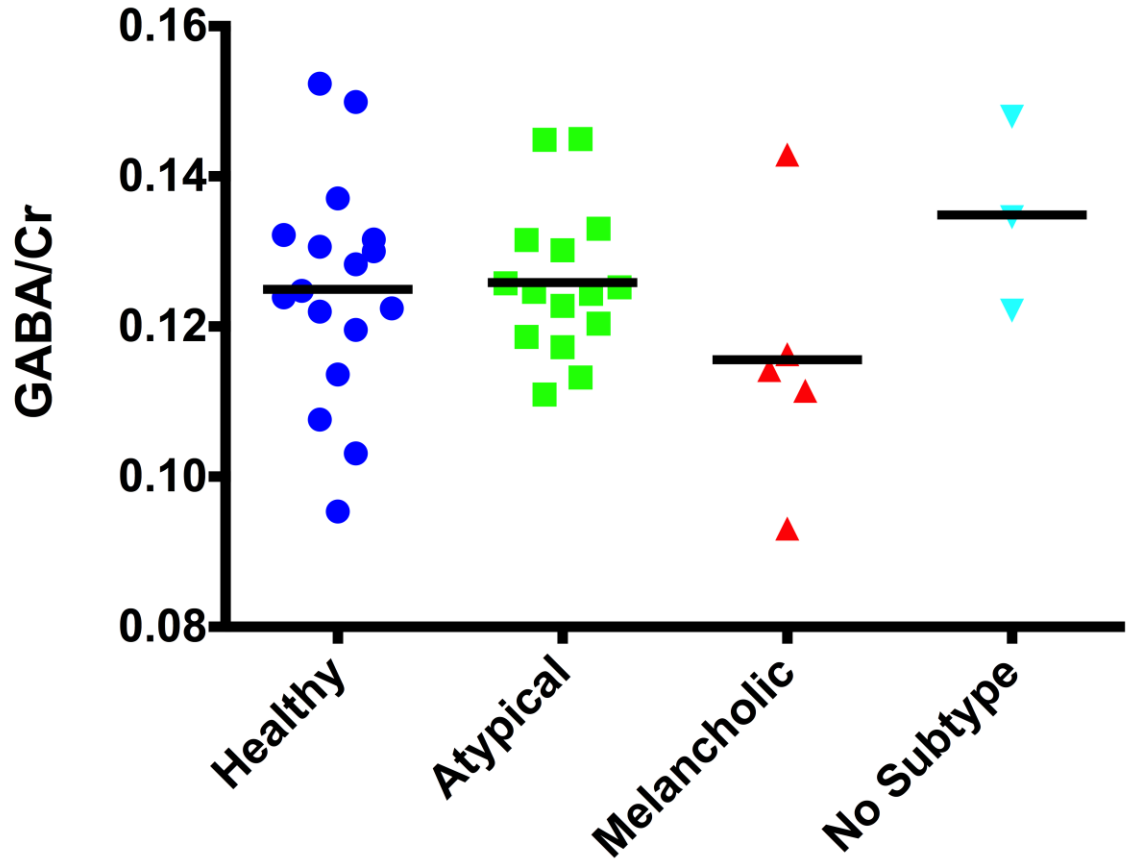

TABLE S3. Correlations (Spearman's Correlation Coefficient) Between Clinical And Spectroscopy Measures in the Depression Group

	HAM-D	HAM-A	BDI	Number of Episodes (Lifetime)
V_{TCAN}	0.19	–0.37‡	0.09	0.19
V_{cycle}	0.15	0.10	0.29	–0.26
V_{GAD}[a]	0.14	–0.17	0.07	–0.21
GABA	0.03	–0.14	–0.09	–0.10
Glutamine	–0.03	**–0.47 ***	–0.23	0.23
Glutamate[b]	0.39‡	0.19	0.36	**–0.59 ***

[a] V_{GAD} was excluded for three participants with noise level higher than 0.05 μmol/g/min.
[b] One subject had poor spectral fitting for Glu and Glx.
Abbreviations: HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; BDI: Beck Depression Inventory.
*p<0.05. ‡p<0.1

TABLE S4. Correlations Between V_{TCAN} and V_{cycle}

		Healthy	MDD
		V_{TCAN}	V_{TCAN}
Healthy	V_{cycle}	r_s=0.44, N=17, p=0.08	
Depression	V_{cycle}		r_s=0.25, N=23, p=0.25