

## Supplementary tables

**Table 1:** Effects of injected dose, body weight and plasma glucose on measured regional tissue activity, examined by a mixed linear model representing a logarithmic transformation of equation 1.

```
> library(nlme)

> # log transforms
> LX$Logglc = log10(LX$glc)
> LX$Logwgt = log10(LX$wgt)
> LX$Logdose = log10(LX$dose)
> LX$Logvalue = log10(LX$value)

> str(LX)
'data.frame': 2176 obs. of 12 variables:
 $ ID      : Factor w/ 34 levels "h00018","h00020",...: 1 1 1 1 1 1 1 1 1 1 1 ...
 $ ROI     : Factor w/ 64 levels "Amygdala_1_sum",...: 1 2 3 4 5 6 7 8 9 10 ...
 $ Group   : Factor w/ 4 levels "AD amn","AD mixed",...: 4 4 4 4 4 4 4 4 4 4 ...
 $ value   : num  22.1 20.9 25.1 23.7 21.5 ...
 $ Age     : num  60 60 60 60 60 60 60 60 60 60 ...
 $ glc     : num  5.18 5.18 5.18 5.18 5.18 5.18 5.18 5.18 5.18 5.18 ...
 $ wgt     : num  89 89 89 89 89 89 89 89 89 89 ...
 $ dose    : num  352 352 352 352 352 ...
 $ Logglc  : num  0.714 0.714 0.714 0.714 0.714 0.714 ...
 $ Logwgt  : num  1.95 1.95 1.95 1.95 1.95 ...
 $ Logdose : num  2.55 2.55 2.55 2.55 2.55 ...
 $ Logvalue: num  1.34 1.32 1.4 1.38 1.33 ...

> lmewgt = lme(Logvalue ~ ROI + Group + Group:ROI + Logwgt +
Logdose + Logglc, data=LX, random = ~ 1|ID)

> anova(lmewgt, type = "marginal")
      numDF denDF  F-value p-value
(Intercept)      1  1890   0.02547  0.8732
ROI              63  1890  36.93920 <.0001
Group            3    27   4.55200  0.0105
Logwgt           1    27  12.81089  0.0013
Logdose          1    27   2.36434  0.1358
Logglc           1    27   1.88871  0.1806
ROI:Group       189  1890   6.51786 <.0001
```

**Table 2:** Regional metabolic main effects and interactions: data structure, R commands and statistical results. Variable “value” represents measured regional tissue activity; “valnorm” represents regional tissue activity with adjustment by body weight and injected dose (proportional to SUV as defined in eq. 1).

```
> str(LRN)
'data.frame': 2176 obs. of  9 variables:
 $ ID      : Factor w/ 34 levels "h00018","h00020",...: 1 2 3 4 5 6 7 8 9 10 ...
 $ Group   : Factor w/ 4 levels "AD amn","AD mixed",...: 4 4 4 4 4 4 4 4 4 3 ...
 $ ROI     : Factor w/ 64 levels "Amygdala_1_sum",...: 11 11 11 11 11 11 11 11 11 11
 ...
 $ value   : num  33.3 31.6 40.2 44.2 35.5 ...
 $ Age     : num  60 70 72 63 73 70 76 69 62 69 ...
 $ Scale   : num  1.308 1.511 1.278 0.894 1.403 ...
 $ Side    : Factor w/ 2 levels "L","R": 1 1 1 1 1 1 1 1 1 1 ...
 $ RName   : Factor w/ 32 levels "FL_mid_fr_G",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ valnorm: num  43.6 47.7 51.4 39.5 49.9 ...
```

```
> lme4 = lme(valnorm ~ RName + Group + Side + Group:RName +
Side:RName + Side:Group, data=LRN, random = ~ 1|ID)
```

```
> anova(lme4, type="marginal")
```

	numDF	denDF	F-value	p-value
(Intercept)	1	1983	281.38223	<.0001
ROI	31	1983	50.63734	<.0001
Group	3	30	3.02786	0.0447
Side	1	1983	5.12671	0.0237
ROI:Group	93	1983	11.31263	<.0001
ROI:Side	31	1983	0.39525	0.9989
Group:Side	3	1983	11.87365	<.0001

With inclusion of age as covariate:

```
> lme4A = lme(valnorm ~ RName + Group + Side + Group:RName +
Side:RName + Side:Group + Age, data=LRN, random = ~ 1|ID)
```

```
> anova(lme4A, type="marginal")
```

	numDF	denDF	F-value	p-value
(Intercept)	1	1983	17.71253	<.0001
RName	31	1983	50.63734	<.0001
Group	3	29	3.15527	0.0397
Side	1	1983	5.12671	0.0237
Age	1	29	0.53620	0.4699
RName:Group	93	1983	11.31263	<.0001
RName:Side	31	1983	0.39525	0.9989
Group:Side	3	1983	11.87365	<.0001

**Table 3:** Significance of hemispheric asymmetries

```
> library(phia)

> testInteractions(lme4, pairwise= "Side", fixed = "Group",
adjustment="fdr")

Chisq Test:
P-value adjustment method: fdr
      Value Df  Chisq Pr(>Chisq)
L-R :   AD amn -0.99923  1 15.5778  0.0001584 ***
L-R :   AD multi -1.94439  1 66.3585  1.504e-15 ***
L-R :  AD visual -0.36110  1  2.0344  0.2050396
L-R :   Control -0.07568  1  0.1005  0.7511953
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

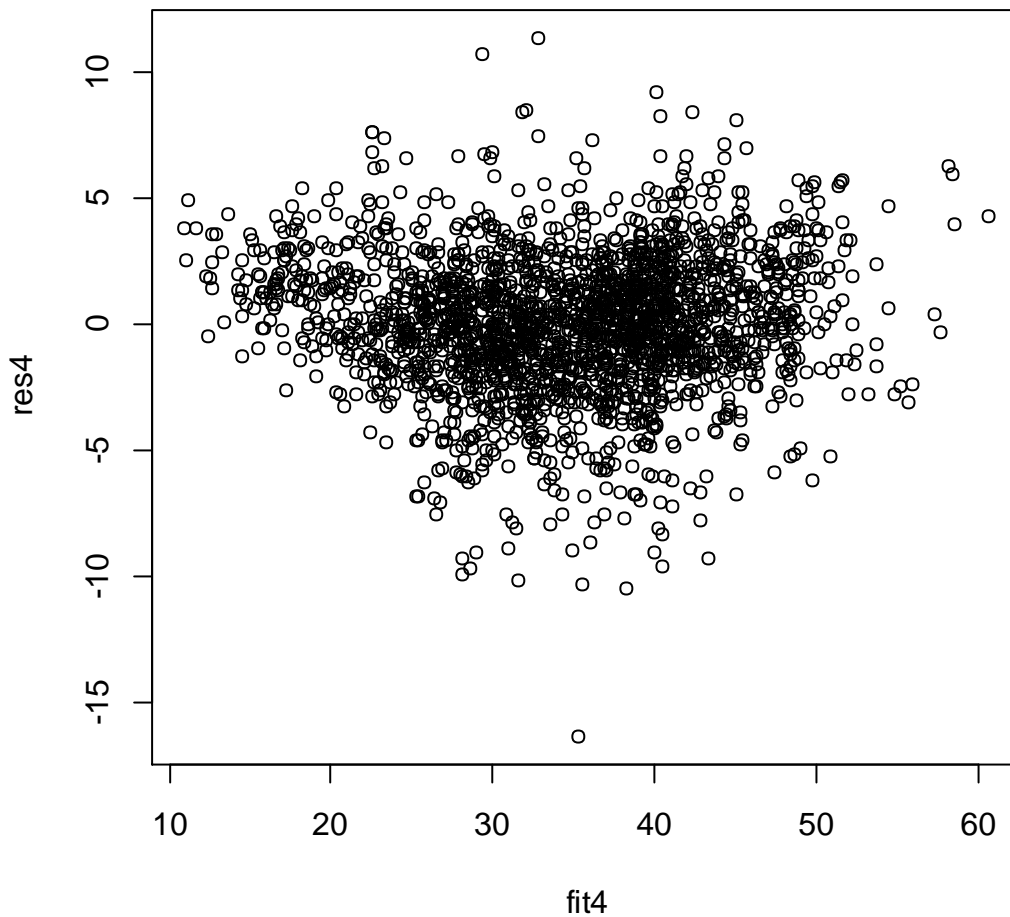
**Table 4:** Regions showing significantly reduced metabolism compared to controls (p values, corrected for multiple comparisons). Right lateral occipital metabolism was also significantly lower compared to amnesic AD, while metabolism in all other regions did not differ significantly between AD subtypes.

ROI	AD amnesic	AD multidomain	AD visual
PCC : L	0.0053	0.0053	0.0053
PCC : R	0.0151	0.0151	0.0186
Inferolateral parietal cortex : L		0.0005	0.0005
Inferolateral parietal cortex: R		0.0032	0.0006
Mid-inferior temporal gyri : L		0.0186	
Lateral occipital cortex : L		0.0245	0.000004
Lateral occipital cortex : R			0.000004
Superior parietal gyrus : L		0.0111	0.0005
Superior parietal gyrus : R			0.0006
Posterior temporal lobe : L		0.0017	0.0011
Posterior temporal lobe : R		0.0151	0.0016
Cuneus : L			0.0260
Cuneus : R			0.0338

**Table 5:** Quality of fit, heteroscedasticity (Breusch-Pagan test)

```
> res4 = residuals(lme4)
> lm3 = lm(res4 ~ LRN$RName + LRN$Group + LRN$Side)
> ncvTest(lm3)
Non-constant Variance Score Test
Variance formula: ~ fitted.values
Chisquare = 4.650134    Df = 1    p = 0.03105112
```

**Figure 1:** Plot of residuals versus fitted values



### *Interpretation*

Diagnostic procedures of the residuals did not show major deviations. The Breusch-Pagan test for heteroscedasticity of the residuals was just significant at  $P=0.03$ . A plot of the residuals versus the fitted values demonstrated that the inhomogeneity was due to slightly higher variance around the mid values rather than at the extremes, indicating that results were not influenced unduly by outliers (see supplementary table 5 and figure 1). Robustness of the significance of interactions was also confirmed by using the modification of Wald F-Tests for small samples by Kenward and Roger [1] (R modules lmer and KRmodcomp).

Kenward MG, Roger JH: **Small sample inference for fixed effects from restricted maximum likelihood**. *Biometrics* 1997, **53**(3):983-997.