Supplementary materials

Variant *brain-derived neurotrophic factor* val66met polymorphism engages memory-associated systems to augment olfaction

Yun-Ting Chao¹,²,³, Tzu-Yi Hong¹,³, Ching-Ju Yang¹,³, Jen-Chuen Hsieh¹,³,⁴,⁵,⁶

¹Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan
²Division of Rhinology, Department of Otorhinolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
³Integrated Brain Research Unit, Division of Clinical Research, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
⁴Department of Biological Science and Technology, College of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan
⁵Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan
⁶Center for Intelligent Drug Systems and Smart Bio-devices, National Yang Ming Chiao Tung University, Hsinchu Taiwan.
Supplementary table 1: original data on olfactory subtests of each subject

| No. | Genotype   | T  | D  | I  | TDI |
|-----|------------|----|----|----|-----|
| 1   | Met/Met    | 9.25 | 14 | 14 | 37.25 |
| 2   | Val/Met    | 6.75 | 15 | 14 | 35.75 |
| 3   | Val/Met    | 6.5  | 11 | 15 | 32.5  |
| 4   | Val/Met    | 8.25 | 12 | 15 | 35.25 |
| 5   | Val/Met    | 5.25 | 11 | 14 | 30.25 |
| 6   | Val/Met    | 7.5  | 15 | 14 | 36.5  |
| 7   | Val/Met    | 4.75 | 12 | 14 | 30.75 |
| 8   | Val/Met    | 10.5 | 14 | 14 | 38.5  |
| 9   | Met/Met    | 9.25 | 15 | 15 | 39.25 |
| 10  | Val/Met    | 8    | 13 | 16 | 37    |
| 11  | Val/Met    | 6.5  | 14 | 14 | 34.5  |
| 12  | Val/Val    | 7.5  | 16 | 15 | 38.5  |
| 13  | Val/Met    | 7    | 12 | 15 | 34    |
| 14  | Val/Met    | 6.75 | 14 | 14 | 34.75 |
| 15  | Val/Val    | 7.5  | 13 | 12 | 32.5  |
| 16  | Val/Met    | 6    | 15 | 15 | 36    |
| 17  | Met/Met    | 4.75 | 14 | 15 | 33.75 |
| 18  | Val/Met    | 6.25 | 13 | 15 | 34.25 |
| 19  | Val/Val    | 9    | 12 | 14 | 35    |
| 20  | Val/Val    | 7.5  | 13 | 14 | 34.5  |
| 21  | Met/Met    | 7.75 | 12 | 16 | 35.75 |
| 22  | Met/Met    | 6.5  | 15 | 15 | 36.5  |
| 23  | Met/Met    | 9.5  | 15 | 14 | 38.5  |
| 24  | Val/Met    | 5.75 | 14 | 14 | 33.75 |
| 25  | Val/Val    | 8.5  | 11 | 12 | 31.5  |
| 26  | Met/Met    | 6.5  | 12 | 16 | 34.5  |
| 27  | Met/Met    | 6.25 | 12 | 16 | 34.25 |
| 28  | Met/Met    | 6.75 | 15 | 15 | 36.75 |
| 29  | Val/Met    | 6.5  | 12 | 14 | 32.5  |
| 30  | Met/Met    | 9.25 | 14 | 13 | 36.25 |
| 31  | Met/Met    | 7.25 | 13 | 14 | 34.25 |
| 32  | Met/Met    | 6.5  | 5  | 14 | 25.5  |
| 33  | Val/Val    | 5    | 15 | 13 | 33    |
| 34  | Val/Met    | 5.75 | 12 | 14 | 31.75 |
| 35  | Val/Met    | 6.5  | 13 | 13 | 32.5  |
| 36  | Val/Met    | 4.75 | 9  | 13 | 26.75 |
| 37  | Val/Met    | 6.25 | 13 | 14 | 33.25 |
| 38  | Val/Met    | 7.5  | 12 | 14 | 33.5  |
| 39  | Val/Val    | 7.5  | 14 | 16 | 37.5  |
| 40  | Val/Met    | 7.5  | 13 | 15 | 35.5  |
| 41  | Val/Val    | 8.75 | 14 | 14 | 36.75 |
| 42  | Val/Val    | 5    | 12 | 15 | 32    |
| 43  | Val/Val    | 3.5  | 11 | 12 | 26.5  |
| 44  | Val/Val    | 3.75 | 13 | 15 | 31.75 |
| 45  | Val/Val    | 5.5  | 16 | 14 | 35.5  |
| 46  | Val/Val    | 6    | 12 | 13 | 31    |
| 47  | Met/Met    | 7    | 14 | 16 | 37    |

T: threshold; D: discrimination; I: identification; TDI: T + D + I
**Supplementary Table 2** behavioral factors in the olfaction cohort (n = 47)

| Behavioral measurement | Genotype | ANOVA | Linear regression for Met-allele dosage effect |
|------------------------|----------|-------|-----------------------------------------------|
|                        |          |       | Cohen's $\text{f}^2$ | $r$ | beta | $t$ | $P$ |
| (mean ±SD )            | Met/Met  | Val/Met | Val/Val | $F$ | $P$ |       |       |
| (n=13)                 | (n=21)   | (n=13) |         |     |     |       |       |
| Detection threshold    | 7.42 ±1.48 | 6.69 ±1.29 | 6.53 ±1.86 | 1.323 | 0.277 | 0.08 | 0.26 | 0.45 | 1.40 | 0.170 |
| Odor discrimination    | 13.08 ±2.69 | 12.81 ±1.50 | 13.23 ±1.69 | 0.267 | 0.818 | 0.02 | 0.14 | 0.03 | 0.08 | 0.939 |
| Odor identification    | 14.84 ±0.99 | 14.29 ±0.72 | 13.77 ±1.30 | 3.967 | 0.027 | 0.25 | 0.45 | 0.61 | 3.02 | 0.004 |
| Composite TDI score    | 35.35 ±3.40 | 33.79 ±2.61 | 33.54 ±3.22 | 2.419 | 0.246 | 0.08 | 0.27 | 1.09 | 1.71 | 0.095 |
| Sino-nasal Outcome test| 7.62 ±10.25 | 8.62 ±9.45 | 10.62 ±8.78 | 0.339 | 0.714 | 0.06 | 0.24 | -1.87 | -0.94 | 0.353 |
| Beck depression Inventory | 3.15 ±4.91 | 4.33 ±4.98 | 3.15 ±2.48 | 0.413 | 0.664 | 0.03 | 0.18 | 0.00 | 0.00 | 0.999 |
| Beck anxiety inventory  | 3.08 ±4.61 | 2.57 ±5.33 | 2.00 ±2.08 | 0.19  | 0.828 | 0.08 | 0.27 | 0.71 | 0.77 | 0.446 |

SD, standard deviation; TDI, threshold + discrimination + identification
### Supplementary Table 3 Peak coordinates in comparison of olfactory networks among various genotypes in the PDM cohort (n = 145)

| Genotype contrast | Seeds | MNI x | MNI y | MNI z | Peak level | Cluster level | BA | Anatomic label                      | linear regression for Met-allele dosage effect |
|-------------------|-------|-------|-------|-------|------------|---------------|----|-------------------------------------|-----------------------------------------------|
|                   |       |       |       |       | $P_{\text{uncorr.}}$ | $P_{\text{FWE-corr.}}$ |     |                                     | $f^2$ | $r$ | beta | $t$ | $P$ |
| Met/Met > Val/Val | PC (left) (-22, 0, -14) | -15 | -45 | 3 | 4.08 | $< 0.001$ | 711* | 29 | Retrospenial cortex (L) | 0.19 | 0.40 | 0.07 | 3.75 | $< 0.001$ |
|                   |       | -6   | -54 | 12  | 3.98 | $< 0.001$ | 30 | Retrospenial cortex (L) | 0.21 | 0.41 | 0.07 | 3.75 | $< 0.001$ |
|                   |       | 9    | -63 | 24  | 3.90 | $< 0.001$ | 7  | Precuneus (R)                | 0.19 | 0.40 | 0.07 | 3.91 | $< 0.001$ |
|                   | PC (right) (22, 2, -12) | -15 | -54 | 3 | 4.04 | $< 0.001$ | 576* | 30 | Retrospenial cortex (L) | 0.22 | 0.42 | 0.07 | 3.87 | $< 0.001$ |
|                   |       | -6   | -87 | 27  | 3.73 | $< 0.001$ | 18 | Cuneus (L)                  | 0.20 | 0.41 | 0.07 | 3.83 | $< 0.001$ |
|                   |       | -3   | -69 | 21  | 3.64 | $< 0.001$ | 18 | Cuneus (L)                  | 0.26 | 0.45 | 0.07 | 3.81 | $< 0.001$ |
| Met carrier > Val/Val | PC (left) (-22, 0, -14) | 0   | -90 | 18  | 3.93 | $< 0.001$ | 403* | 18 | Cuneus | 0.13 | 0.34 | 0.06 | 3.10 | 0.002 |
|                   |       | -9   | -96 | 27  | 3.54 | $< 0.001$ | 19 | Cuneus (L)                  | 0.10 | 0.30 | 0.04 | 3.15 | 0.002 |
|                   |       | 9    | -63 | 24  | 3.43 | $< 0.001$ | 7  | Precuneus (R)                | 0.19 | 0.40 | 0.07 | 3.91 | $< 0.001$ |
|                   | PC (right) (22, 2, -12) | -6  | -90 | 27  | 4.30 | $< 0.001$ | 404* | 19 | Cuneus (L) | 0.12 | 0.32 | 0.06 | 3.26 | 0.001 |
|                   |       | -15 | -54 | 3   | 3.51 | $< 0.001$ | 30 | Retrospenial cortex (L) | 0.22 | 0.42 | 0.07 | 3.87 | $< 0.001$ |
|                   |       | 12  | -78 | 24  | 3.47 | $< 0.001$ | 18 | Cuneus (R)                  | 0.19 | 0.40 | 0.05 | 3.21 | 0.001 |
| Val/Met > Val/Val | PC (left) (-22, 0, -14) | 0   | -90 | 18  | 3.67 | $< 0.001$ | 72  | 18 | Cuneus | 0.13 | 0.34 | 0.06 | 3.10 | 0.002 |
|                   |       | -9   | -96 | 24  | 3.28 | $< 0.001$ | 19 | Cuneus (L)                  | 0.08 | 0.27 | 0.05 | 2.63 | 0.010 |
|                   | PC (right) (22, 2, -12) | -6  | -90 | 27  | 3.84 | $< 0.001$ | 71  | 19 | Cuneus (L) | 0.12 | 0.32 | 0.06 | 3.26 | 0.001 |
|                   |       | 0   | -90 | 21  | 3.39 | $< 0.001$ | 18 | Cuneus | 0.14 | 0.35 | 0.05 | 2.577 | 0.01 |
|                   |       | -18 | -93 | 27  | 2.89 | $< 0.001$ | 19 | Cuneus (L)                  | 0.07 | 0.25 | 0.04 | 2.397 | 0.02 |

PC, piriform cortex; BA, Brodmann area; L, left; R, right. Significance in linear regression was defined as $P = 0.003$. (0.05/17, the number of brain areas examined=17)

*The asterisks indicate the clusters that can also survive, but to a lesser spatial extent, the more stringent threshold criteria: uncorrected $P < 0.001$. 