

1 **Longer latency of sensory response to intravenous odor injection predicts olfactory neural**
2 **disorder**

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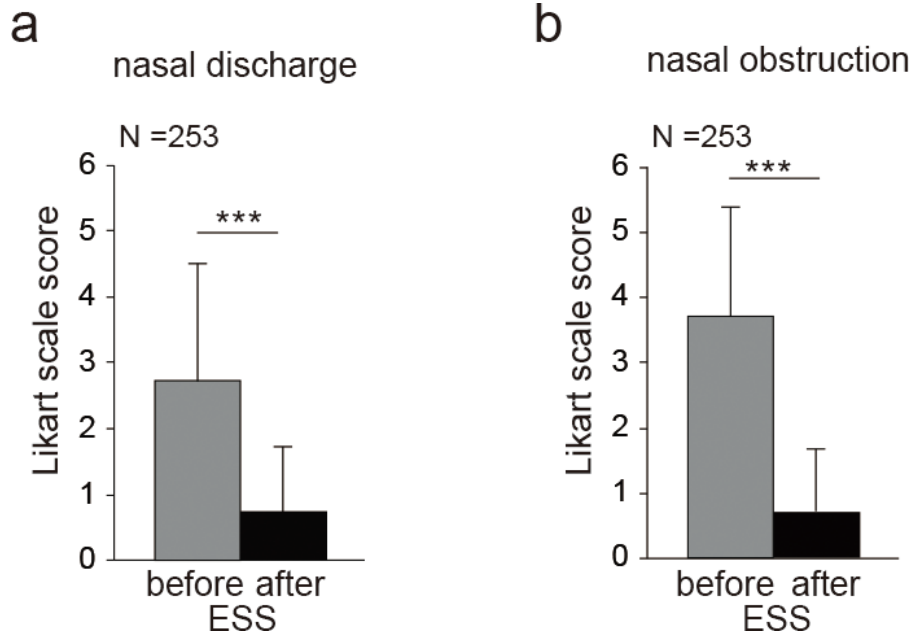
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19 **Supplementary information**



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21 **Supplementary Figure 1. Endoscopic sinus surgery (ESS) improves Likart scale scores for**
22 **nasal discharge and obstruction**

23 **(a, b)** Comparisons of Likart scale scores for nasal discharge **(a)** and nasal obstruction **(b)**
24 before and after ESS. Statistical comparisons using Mann–Whitney *U*-test (a and b). *** $p <$
25 0.001. All values are mean \pm SD.

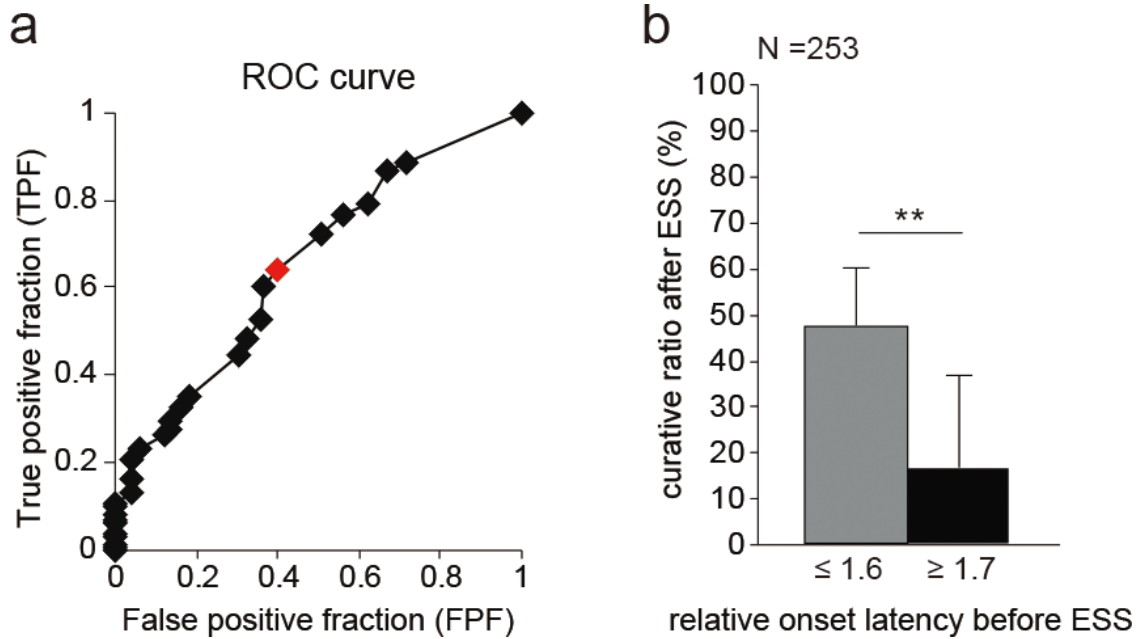
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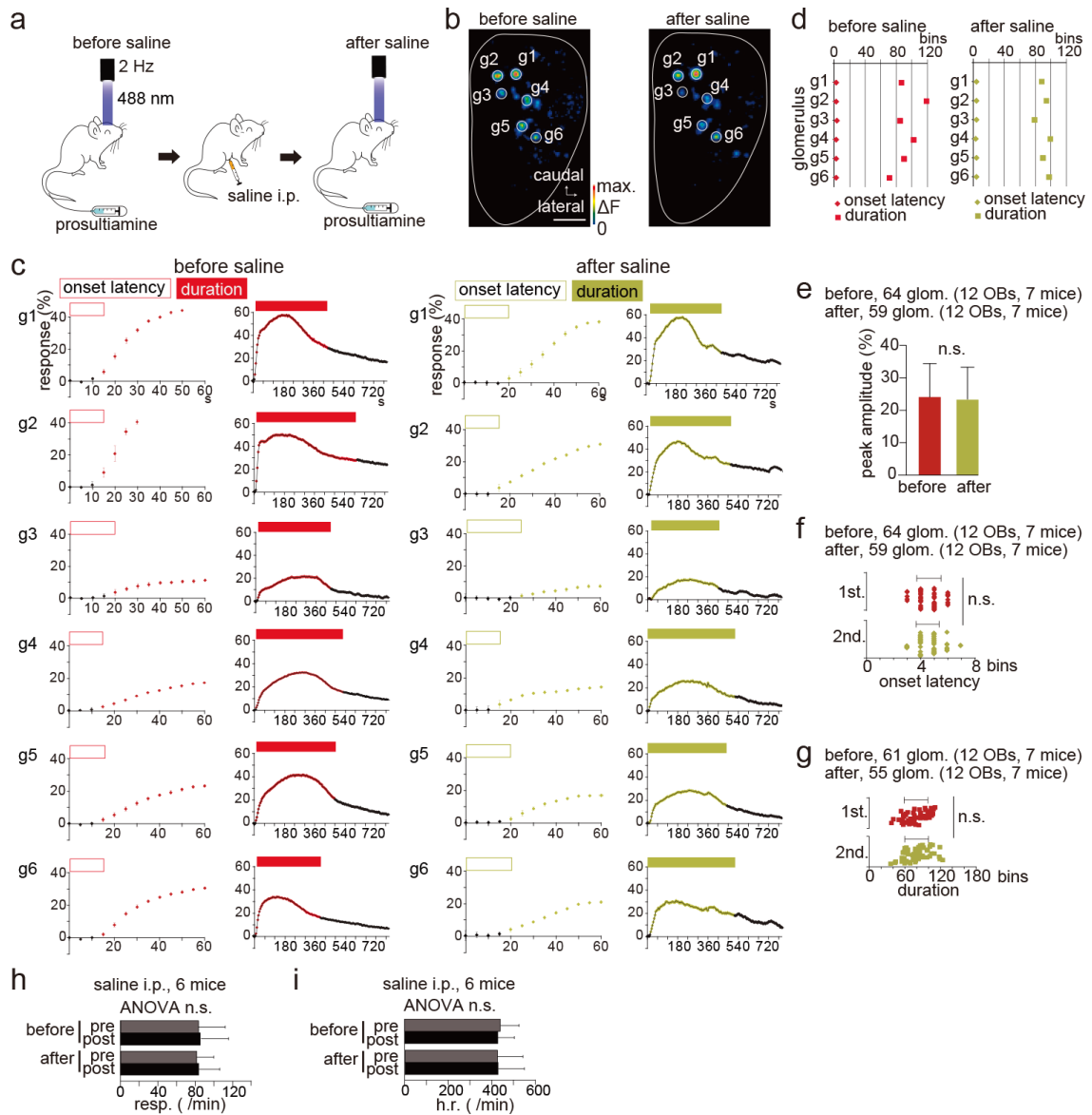
32 **Supplementary Figure 2. Receiver operator characteristic (ROC) curve analysis**

33 (a) ROC curves of the modeling dataset. The curve was created by plotting the true positive
 34 fraction (TPF, y-axis) known as sensitivity against the false positive fraction (FPF, x-axis)
 35 known as 1- specificity at various threshold settings. The red dot indicates the cut off value as
 36 the point on the curve closest to the upper left corner in the ROC (sensitivity;64%,
 37 specificity;60%).

38 (b) Comparison of the curative ratio following ESS in the optimum cut off value of 1.6.

39 Statistical comparisons using Mann–Whitney *U*-test. ** $p < 0.01$. All values are mean \pm SD.

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42 **Supplementary Figure 3. No significant difference in neural response delay and duration**
 43 **between before and after intravenous prosultiamine (PST) injections**

44 **(a) Experimental protocol for consecutive PST injections. PST-induced synaptopHluorin (spH)**

45 **signals were recorded before (left) and after i.p. saline administration (right).**

46 **(b) Images of the olfactory bulb (OB) dorsal surface before (left) and after saline administration**

47 (right) from glomeruli g1–g6. Scale bar, 500 μ m.

48 (c) Two sequential PST-induced spH responses from individual glomeruli (g1–g6). Before saline
49 administration (left) and after saline administration (right). Open rectangle, onset latency; filled
50 rectangle, duration.

51 (d) Summary of onset latency and duration in each glomerulus shown in (b). Red diamond,
52 onset latency; red square, duration.

53 (e) Comparison of peak amplitude between before and after saline administration. There are no
54 significant differences. Red, before saline administration; yellow, after saline administration.
55 glom, glomerulus.

56 (f, g) Comparison of onset latency (f) and duration (g) before and after saline administration. No
57 significant differences in onset latency and duration are detected.

58 (h, i) Comparison of respiration (resp., h) and heart rate (h.r., i) before and after saline
59 administration. Each recording includes the period of pre- (pre) and post-response (post).
60 Statistical comparisons were done using Mann–Whitney *U*-test (e, f, and g) and two-way
61 ANOVA (h and i). n.s., no significant difference. All values are mean \pm SD.

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	nasal discharge	+++	++	+
65	saliva	+++	++	+

66 **Supplementary Figure 4. Pilocarpine increases nasal discharge and saliva**

67 Each photograph shows the frontal view of a mouse after the administration of a different
 68 pilocarpine concentration (0.2, 0.1, and 0.05 mg/kg). +++, prominent increase in nasal discharge
 69 and saliva; +, little increase; ++, intermediate increase.

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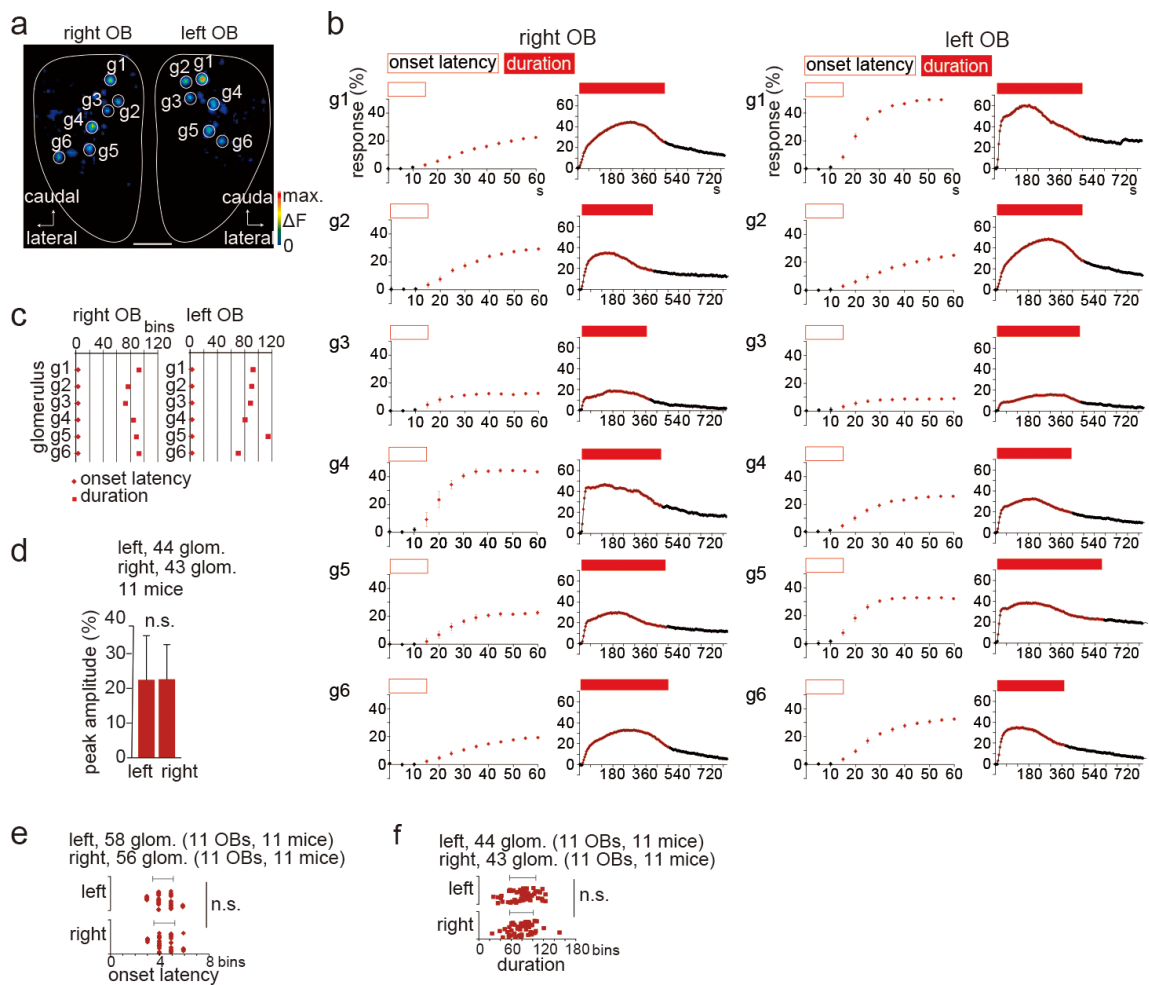
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81 **Supplementary Figure 5. No significant differences in onset time and duration between**
82 **right and left olfactory bulbs following prosultiamine (PST) injection**

83 **(a)** Images of the right and left OE dorsal surfaces during PTS-induced synaptopHluorin (spH)
84 responses. g1–g6 are individual glomeruli on each side. OB, olfactory bulb. Scale bar, 500 μ m.

85 **(b)** PST-induced spH responses of individual glomeruli (g1–g6) in both right and left OBs.

86 **(c)** Summary of onset latency and duration for each glomerulus shown in **(a)**. Red diamond,
87 onset latency; red square, duration.

88 **(d)** Comparison of peak amplitude between right and left OBs. Significant differences are not

89 detected. glom., glomerulus.

90 (e, f) Comparison of onset latency and duration between right and left OBs. Significant

91 differences are not detected. Statistical comparisons by Mann–Whitney *U*-test (d, e, and f). n.s.,

92 no significant difference. All values are mean ± SD.

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Condition	Mice	Side	Response ※1	Histology	Related figure	Note
Normal	#1	rt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
		lt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p, 6e, f, g	
	#2	rt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p, Supplementary Fig. 5a, b, c, d, e, f	
		lt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p, Supplementary Fig. 5a, b, c, d, e, f,	
	#3	rt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
		lt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
	#4	rt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
		lt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
	#5	rt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
		lt	Yes (PST)	Yes	Figs. 2d, e, 3e, 6c, d, o, p	
	#6	rt	Yes (PST)	No	Figs. 2d, e, 3e, 6c, d	
lt		Yes (PST)	No	Figs. 2b, c, d, e, 3e, 6c, d,		
#7	lt	Yes (PST)	No	Fig. 3a, b, c, e		
	rt	Yes (PST)	No	Figs. 2d, e, 3e, 6c, d, Supplementary Fig. 5d, e, f		
#9	rt	No (saline)	No	Figs. 2d, e, 3e, 6c, d, Supplementary Fig. 5d, e, f		
	rt	No (saline)	No	Fig. 2c		
	rt	No (saline)	No			
	lt	No (saline)	No			
Saline administration	#1	rt	Yes (PST)	Yes	Figs. 3e, 4d, Supplementary Fig. 3e, f, g, h, i	※2
		lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3b, c, d, e, f, g, h, i	※2
	#2	rt	Yes (PST)	Yes	Figs. 3e, 4d, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2
		lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2
	#3	rt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2
		lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2
	#4	lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g	※2
		lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i	※2
	#6	rt	Yes (PST)	No	Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2
lt		Yes (PST)	No	Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2	
#7	rt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2	
	lt	Yes (PST)	No	Fig. 3e, Supplementary Fig. 3e, f, g, h, i, Supplementary Fig. 5d, e, f	※2	
#8	rt	n.d.	Yes	Fig. 4d		
	lt	n.d.	Yes	Fig. 4d		
	rt	n.d.	Yes	Fig. 4d		
Tracheotomy	#1	lt	No (PST)	No		
		lt	No (PST)	No	Fig. 2g, h, i, j	
	#3	rt	No (PST)	No	Fig. 2i, j	
		rt	No (PST)	No	Fig. 2i, j	
	#5	rt	No (PST)	No		

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95 **Supplementary Table 1. Number of animals in normal conditions.**

96 n.d., not determined.

97 ※1; response to stimulation with PST or saline

98 ※2; The results in Fig. 3 and Supplementary Fig. 5 were obtained from the first trial before
99 saline administration.

Condition	Mice	Days		Response ※1	Histology	Related figure	Note
		following injury	Side				
Pirocalpine administration	#1		rt	No	No	Fig. 4e	
			lt	No	No		
	#2		rt	No	No	Fig. 4e	
			lt	No	No		
	#3		rt	No	No	Fig. 4e	
			lt	No	No		
	#4		rt	No	No	Fig. 4e	
			lt	No	No		
	#5		rt	Yes	No	Figs. 3e, 4e, l, m, n, o, Supplementary Fig. 5d, e, f	※2
			lt	Yes	No	Figs. 3e, 4e, l, m, n, o, Fig. 4g, h, i, j, k, Supplementary Fig. 5d, e, f	※2
	#6		rt	Yes	Yes	Figs. 3e, 4d, e, l, m, n, o	※2
			lt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
	#7		rt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
			lt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
	#8		rt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
			lt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
	#9		rt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
			lt	Yes	No	Fig. 4e, l, m, Supplementary Fig. 5d, e, f	※2
	#10		rt	Yes	No	Fig. 4e, l, m, n, o, Supplementary Fig. 5d, e, f	※2
			lt	Yes	No	Fig. 4e, l, m, n, o, Supplementary Fig. 5d, e, f	※2
#11		rt	Yes	No	Fig. 4e, l, m, n, o, Supplementary Fig. 5d, e, f	※2	
		lt	Yes	No	Fig. 4e, l, m, n, o, Supplementary Fig. 5d, e, f	※2	
#12		rt	No	No	Fig. 4e	※2	
		lt	No	No	Fig. 4e	※2	
#13		rt	No	No	Fig. 4e		
		lt	No	No	Fig. 4e		
#14		rt	n.d.	Yes	Fig. 4d		
		lt	n.d.	Yes	Fig. 4d		
#15		rt	n.d.	No	Supplementary Fig. 4		
		lt	n.d.	No	Supplementary Fig. 4		
#16		rt	n.d.	No	Supplementary Fig. 4		
		lt	n.d.	No	Supplementary Fig. 4		
#17		rt	n.d.	No	Supplementary Fig. 4		
		lt	n.d.	Yes	Fig. 4d		
#18		rt	n.d.	Yes	Fig. 4d		
		lt	n.d.	Yes	Fig. 4d		
#19		rt	n.d.	Yes	Fig. 4d		
		lt	n.d.	Yes	Fig. 4d		
#20		rt	n.d.	Yes	Fig. 4d		
		lt	n.d.	Yes	Fig. 4d		
Nostril occlusion	#1			Yes	No	Fig. 5b, d, h, i, j, k, l, m	
				Yes	No	Fig. 5d, h, l, m	
	#2			Yes	No	Fig. 5d, h, l, m	
				Yes	Yes	Fig. 5d, g, h, l, m	
	#3			Yes	Yes	Fig. 5d, g, h, l, m	
				Yes	No	Fig. 5d, h, l, m	
	#4			Yes	Yes	Fig. 5d, h, l, m	
				Yes	No	Fig. 5d, h, l, m	
	#5			Yes	Yes	Fig. 5d, h, l, m	
				Yes	No	Fig. 5d, h, l, m	
	#6			Yes	No	Fig. 5d, h, l, m	
				Yes	No	Fig. 5d, h, l, m	
	#7			Yes	No	Fig. 5e	
				Yes	No	Fig. 5e	
#8			Yes	No	Fig. 5e		
			Yes	Yes	Fig. 5g		
#9			Yes	Yes	Fig. 5g		
			Yes	Yes	Fig. 5g		
#10			n.d.	Yes	Fig. 5g		
			n.d.	Yes	Fig. 5g		
Methimazole administration	#1		7 rt	No	No	Fig. 6b	
			7 lt	No	No	Fig. 6b	
	#2		7 rt	No	No	Fig. 6b	
			7 lt	No	No	Fig. 6b	
	#3		7 rt	No	No	Fig. 6b	
			7 lt	No	No	Fig. 6b	
	#4		7 rt	No	No	Fig. 6b	
			7 lt	No	No	Fig. 6b	
	#5		7 rt	No	No	Fig. 6b	
			7 lt	No	No	Fig. 6b	
	#6		9 rt	No	No	Fig. 6b	
			9 lt	No	No	Fig. 6b	
	#7		9 rt	No	No	Fig. 6b	
			9 lt	No	No	Fig. 6b	
	#8		9 rt	No	No	Fig. 6b	
			9 lt	No	No	Fig. 6b	
	#9		9 rt	No	No	Fig. 6b	
			9 lt	No	No	Fig. 6b	
	#10		9 rt	No	No	Fig. 6b	
			9 lt	No	No	Fig. 6b	
	#11		13 rt	Yes	Yes	Fig. 6b, o, p	
			13 lt	Yes	Yes	Fig. 6b, o, p	
#12		13 rt	No	No	Fig. 6b		
		13 lt	No	No	Fig. 6b		
#13		13 rt	Yes	Yes	Fig. 6b, c, d, o, p		
		13 lt	Yes	Yes	Fig. 6b, c, d, o, p		
#14		14 rt	Yes	Yes	Fig. 6b, c, d, o, p		
		14 lt	Yes	Yes	Fig. 6b, c, d, k, l, m, o, p		
#15		14 rt	Yes	Yes	Fig. 6b, c, d, o, p		
		14 lt	Yes	Yes	Fig. 6b, c, d, o, p		
#16		14 rt	No	No	Fig. 6b		
		14 lt	No	No	Fig. 6b		
#17		14 rt	Yes	Yes	Fig. 6b, c, d, o	※3	
		14 lt	Yes	Yes	Fig. 6b, c, d, o	※3	
#18		14 rt	No	No	Fig. 6b		
		14 lt	No	No	Fig. 6b		
#19		14 rt	Yes	Yes	Fig. 6b, c, d, o, p		
		14 lt	Yes	Yes	Fig. 6b, c, d, o, p		
#20		19 rt	No	No	Fig. 6b		
		19 lt	No	No	Fig. 6b		
#21		19 rt	Yes	Yes	Fig. 6b, c, d, o, p		
		19 lt	Yes	Yes	Fig. 6b, o, p		
#22		21 rt	Yes	Yes	Fig. 6b, o, p		
		21 lt	Yes	Yes	Fig. 6b, h, i, j, o, p		

101 **Supplementary Table 2. Number of animals in pathological conditions.**

102 n.d., not determined.

103 ※1; response to stimulation with PST

104 ※2; The results in Fig. 3 and Supplementary Fig. 5 were obtained from the first trial before
105 pilocarpine administration.

106 ※3; In this mouse, response duration was not determined.

107

108 **Supplementary movie legends**

109 **Supplementary movie 1: SynaptopHluorin responses of individual glomeruli to**
110 **stimulation with prosultiamine**

111 The dorsal surface of the olfactory bulb was exposed, and the activity of individual glomeruli
112 was recorded using confocal microscopy. Arrowheads show representative responsive glomeruli.

113 Individual glomeruli exhibit neural responses almost simultaneously. Acq. Time, acquisition
114 time.

115

116 **Supplementary movie 2: SynaptopHluorin responses of individual glomeruli to**
117 **prosultiamine in both open and occluded olfactory bulbs (OBs)**
118 Arrowheads show representative responsive glomeruli. Individual glomeruli in both open (right
119 side) and occluded OBs (left side) exhibit neural responses almost simultaneously. Acq. Time,
120 acquisition time.