

Fig. S1 Altered cortico-hypothalamic projection pattern in mSOD1 mice at P95, absolute ipsilateral counts. **a** Sum of neurons projecting from selected 28 areas. Projections to the LHA from the ipsilateral hemisphere are significantly increased in mSOD mice ($P = 0.02$; $N = 3$). **b** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ACA ($P < 0.0001$), ILA ($P = 0.009$), ORBI/vl+AI ($P < 0.0001$), Tenia Tecta (TT; $P = 0.0365$), secondary Motor Cortex (MOs, $P < 0.0001$) and Piriform cortex (PIR; $P = 0.0005$). **c** LHA atrophy compensated projections to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ORBI/vl+AI ($P < 0.0001$), MOs ($P < 0.0001$) and PIR ($P = 0.0231$) is detected. **d** Representative *WholeBrain* ipsilateral side view reconstructions of neurons projecting to LHA in WT and mSOD1 mice. Expansion of projections from MOs are visible (arrows). **e** Representative *WholeBrain* cortical top view reconstructions of neurons projecting to LHA in WT and mSOD1 mice. Increased projections from MOs are visible (arrows). Bars show mean \pm SD. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

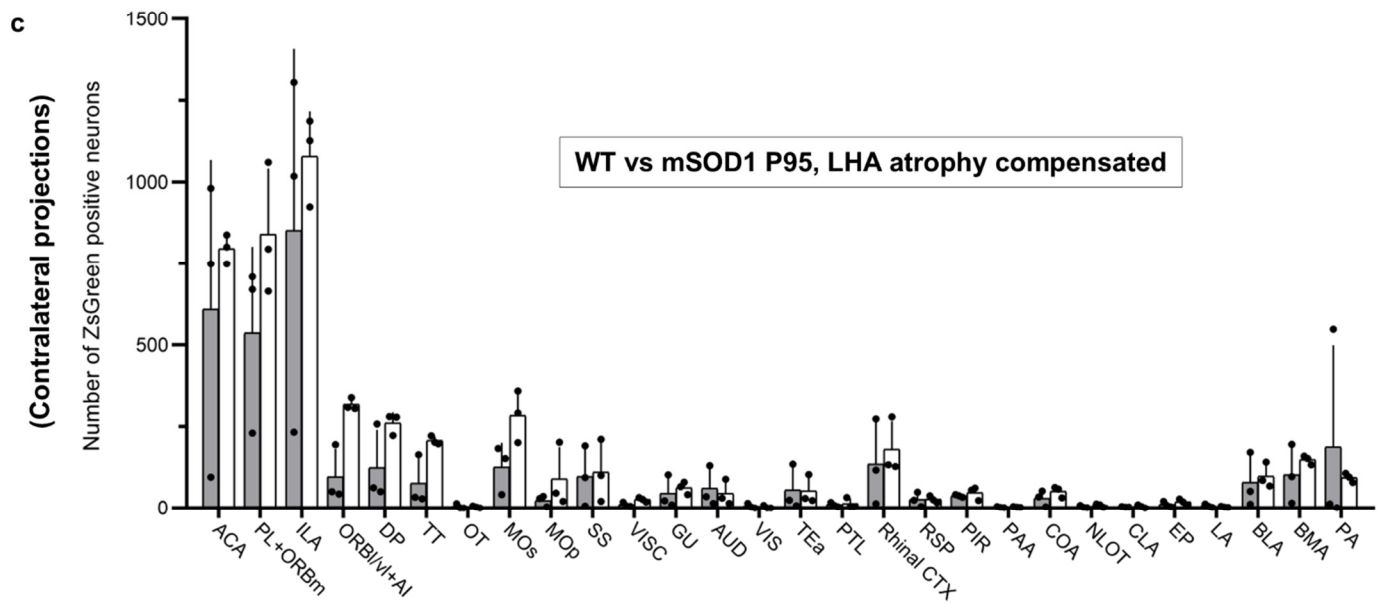
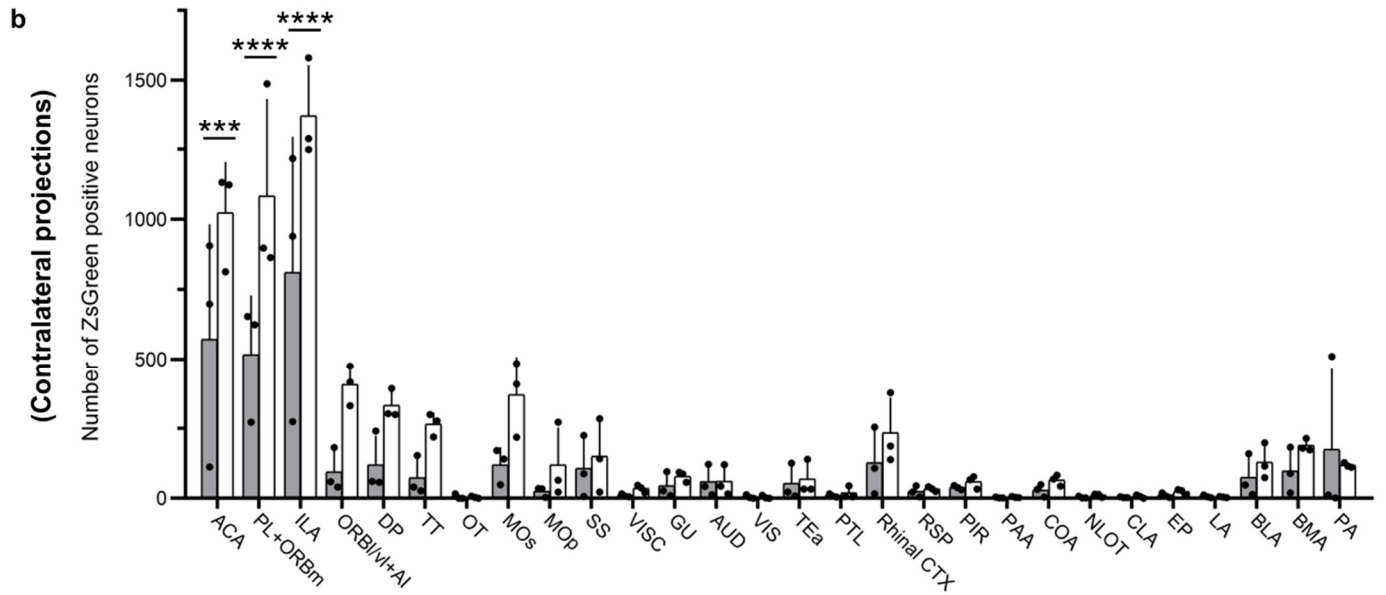


Fig. S2 Altered cortico-hypothalamic projection pattern in mSOD1 mice at P95, contralateral hemisphere. **a** Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and mSOD1 from the contralateral hemisphere ($n=3$). **b** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ACA ($P=0.0008$), PL+ORBm and ILA (both $P<0.0001$) is detected. **c** LHA atrophy compensated projections to LHA from 28 brain structures in WT and mSOD1. No difference is detected in the number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. Bars show mean \pm SD. *** $P < 0.001$, **** $P < 0.0001$.

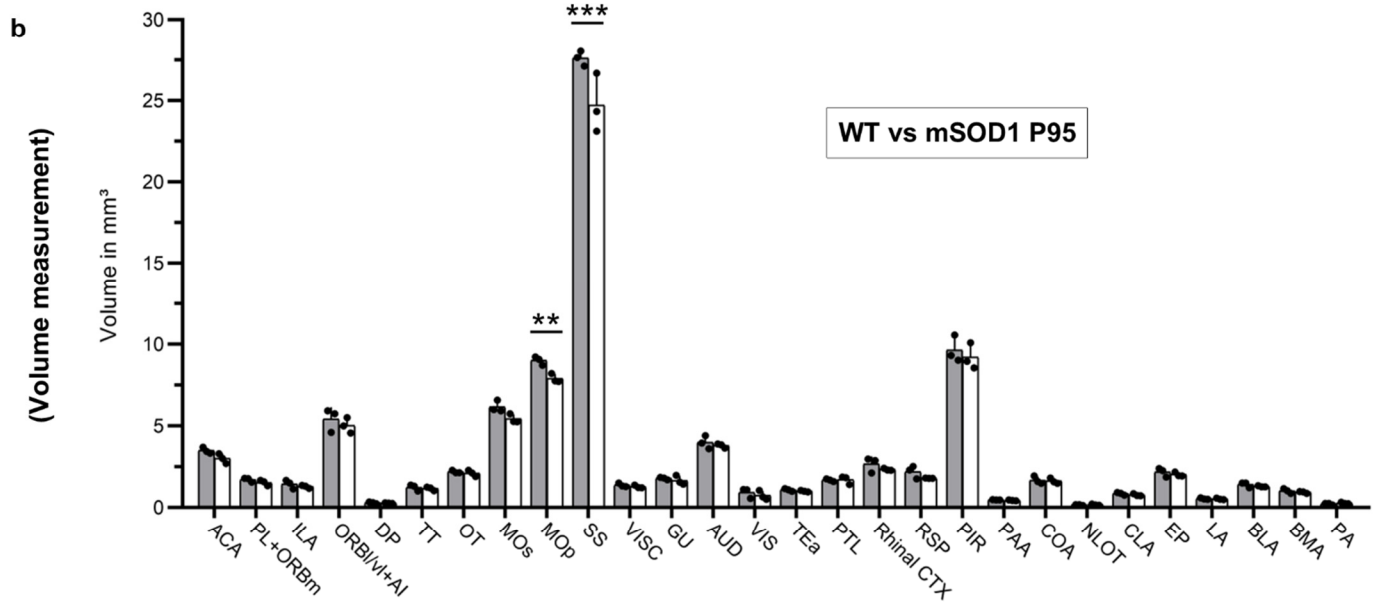
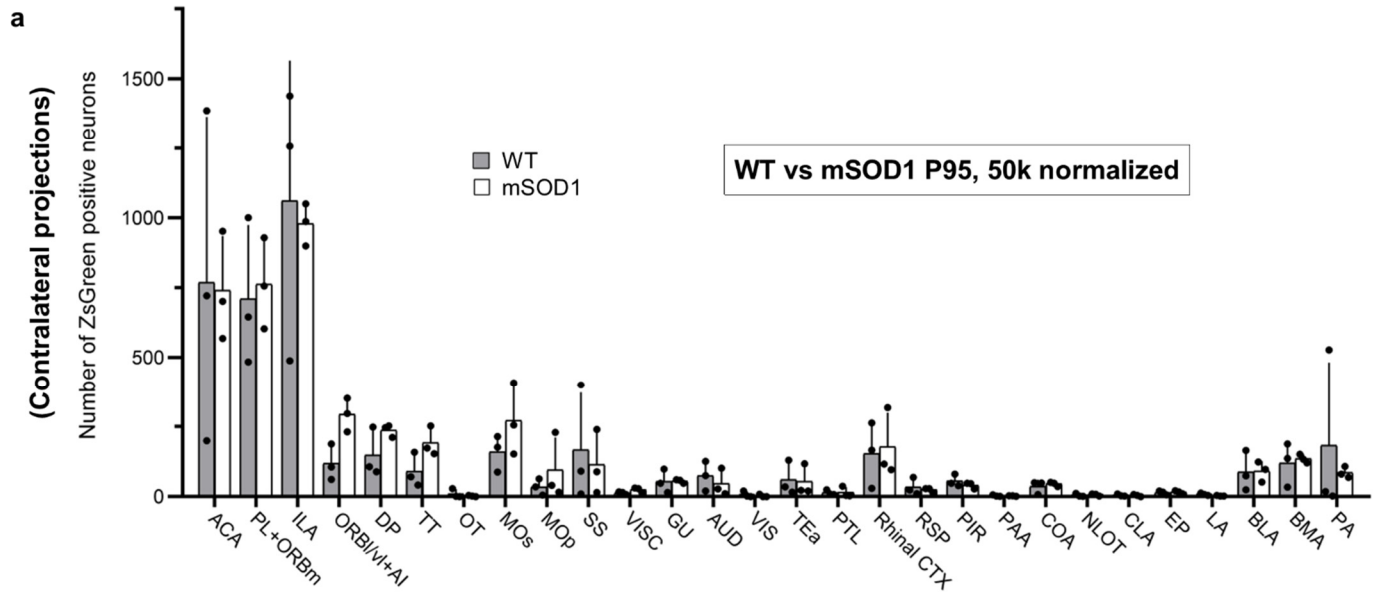
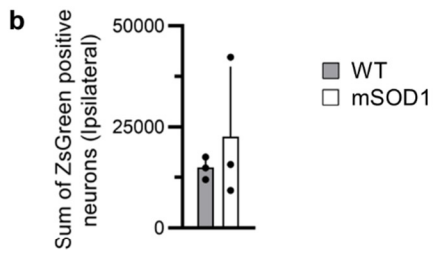
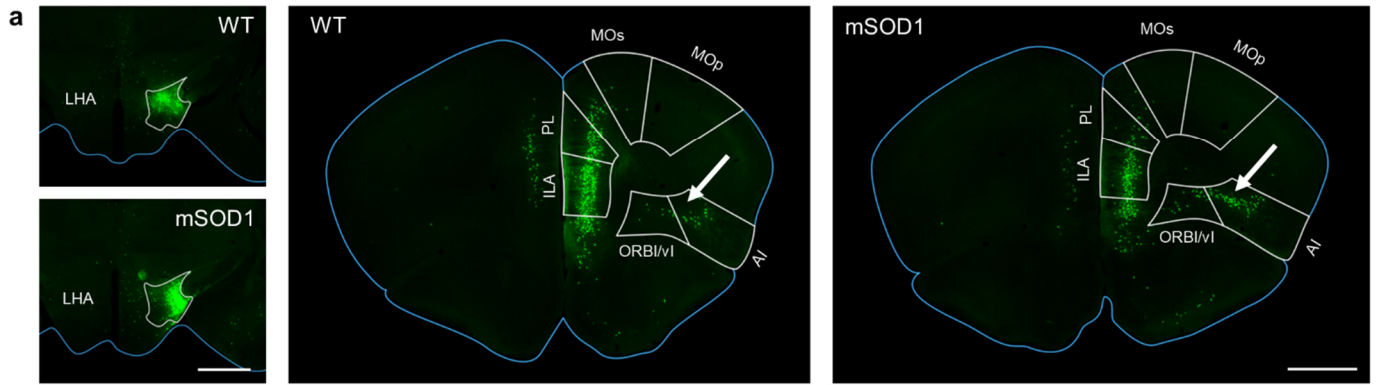
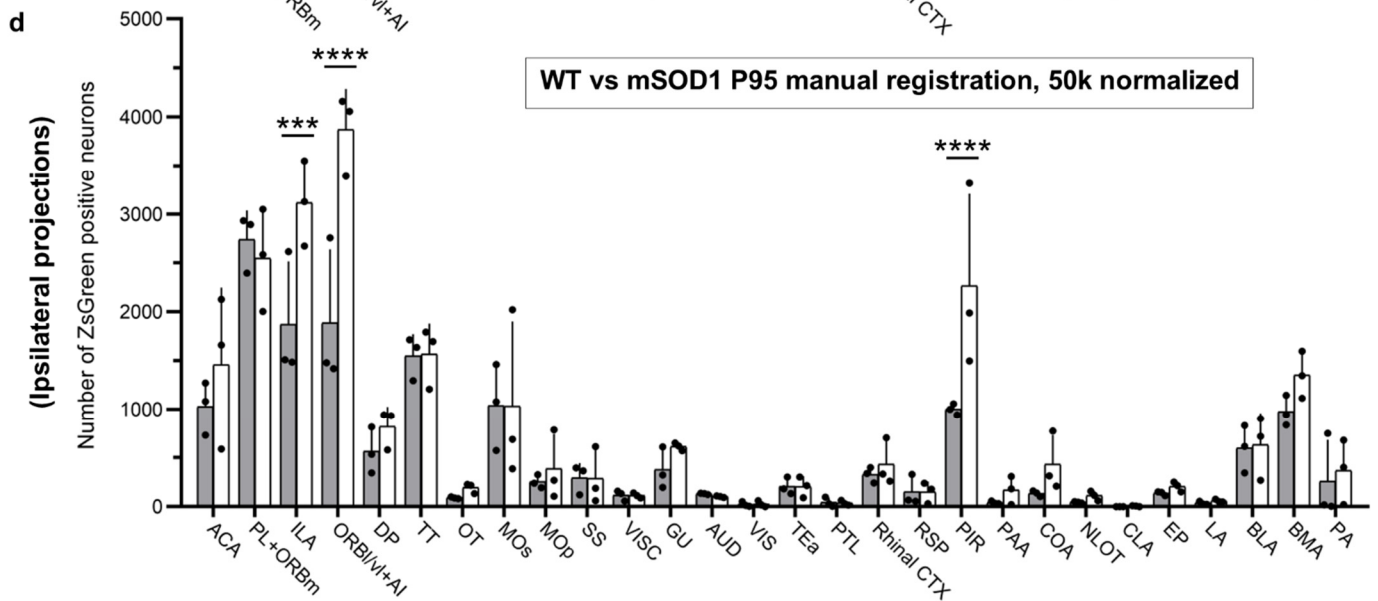
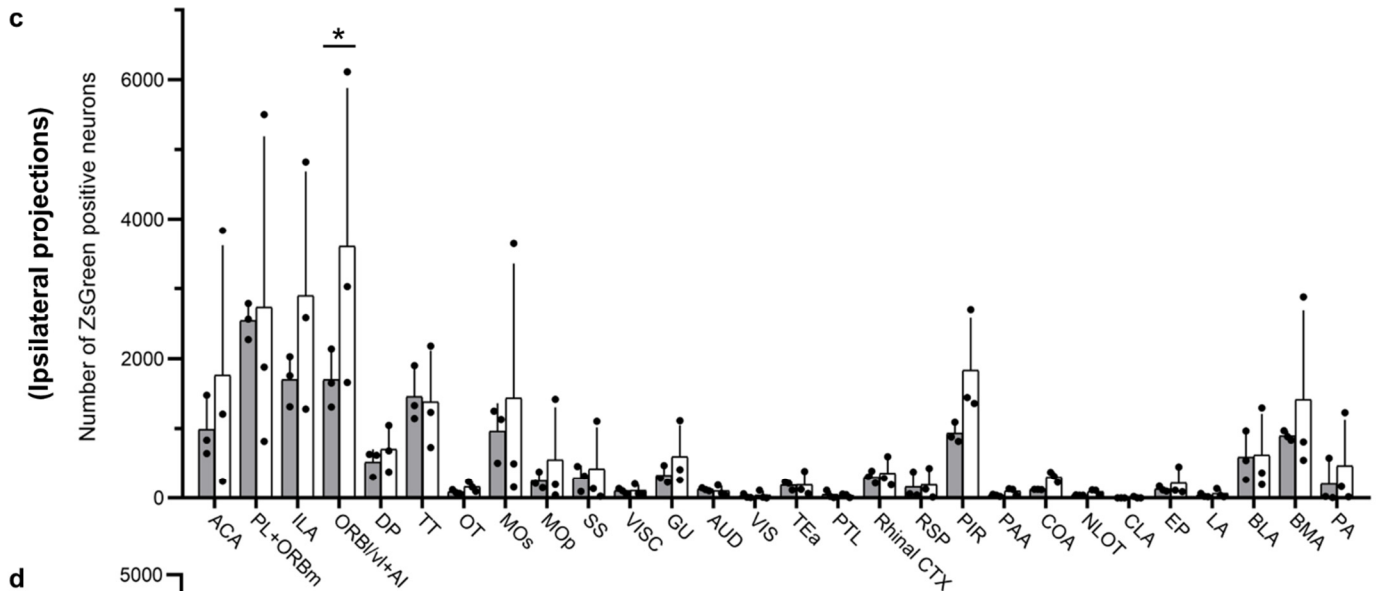


Fig. S3 50k normalized contralateral projection in P95 mSOD1 animals and MOp/SS atrophy in P95 mSOD mice. **a** No difference is detected in the 50k normalized number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. **b** Volumetric comparison of 28 areas in WT and mSOD. Significant atrophy was detected in MOp ($P=0.0080$) and SS ($P<0.0001$). Bars show mean \pm SD. $**P < 0.01$, $***P < 0.001$.



WT vs mSOD1 P95 manual registration, absolute counts



WT vs mSOD1 P95 manual registration, 50k normalized

Fig. S4 Altered cortico-hypothalamic projection pattern in manual registered mSOD1 mice at P95, ipsilateral. **a** Left: representative injection sites in LHA for WT and mSOD1 mice. White outlines represent LHA boundaries. Middle and right: Representative frontal brain sections of WT and mSOD1 mice depicting projections from ORBl/vl+AI (significantly increased, arrow), PL+ORBm, ILA, ACA, MOs and MOp to LHA. **b** Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and mSOD1 from the ipsilateral hemisphere ($n=3$). **c** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ORBl/vl+AI ($P=0.0352$) is detected. **d** 50k normalized number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ILA ($P=0.0001$), ORBl/vl+AI ($P<0.0001$) and PIR ($P<0.0001$) is detected. Bars show mean \pm SD. Scale bars 1 mm. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

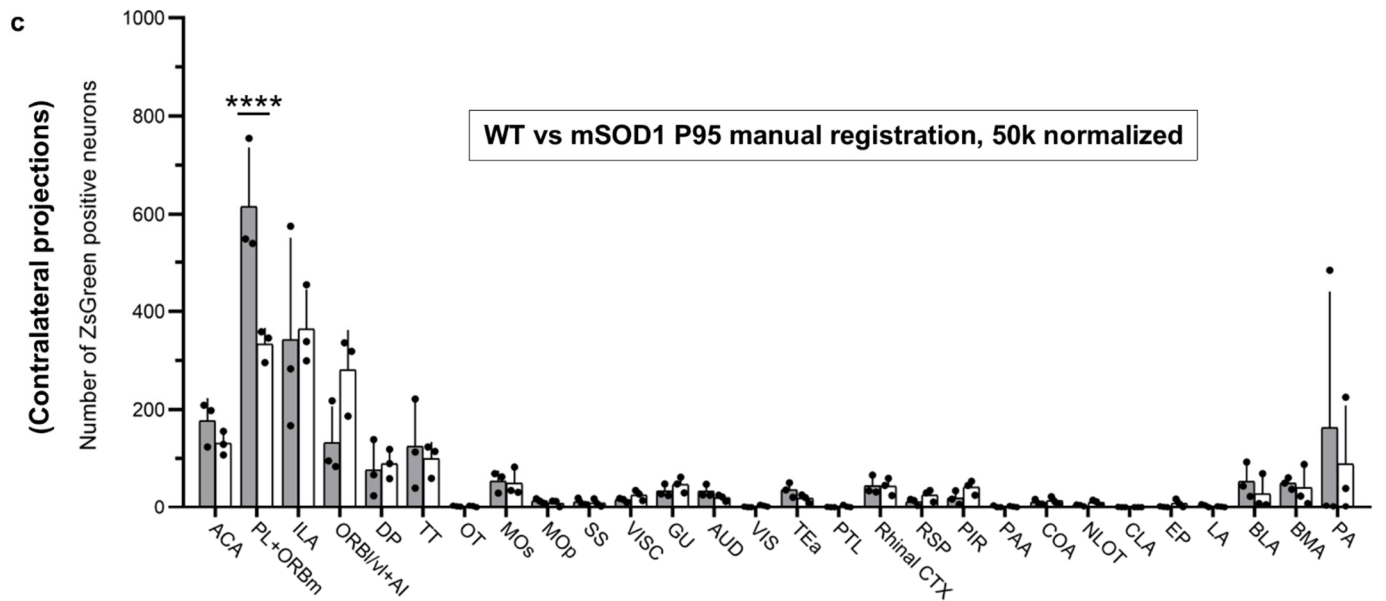
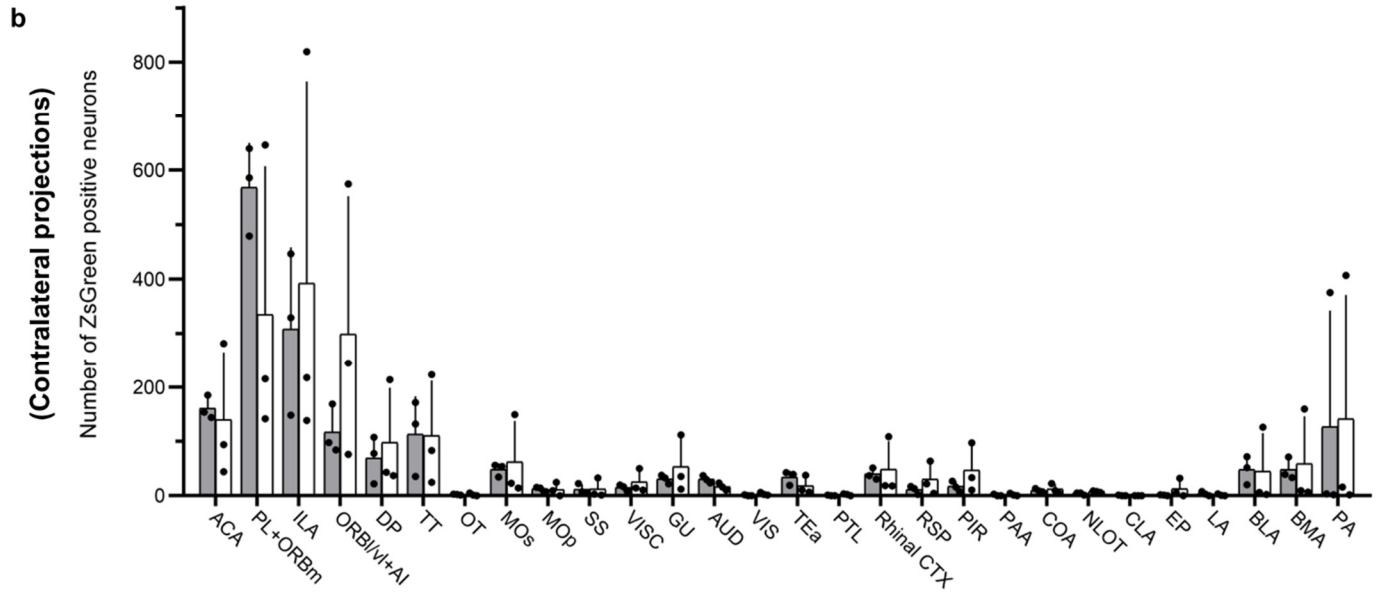
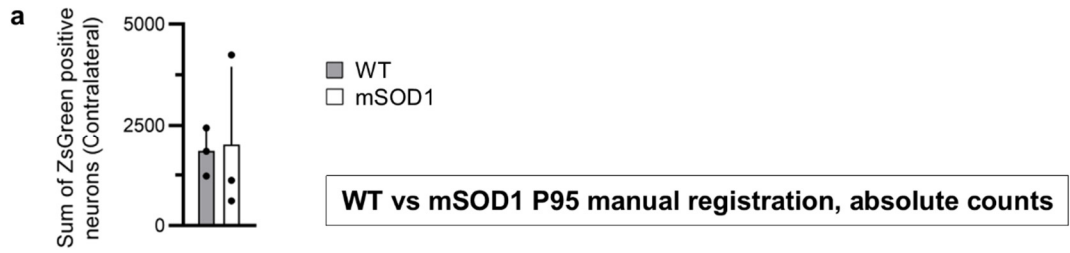


Fig. S5 Altered projection pattern in manually annotated mSOD1 mice at P95, contralateral.

a Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and mSOD1 from the contralateral hemisphere ($n=3$). **b** No difference is detected in the absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. **c** 50k normalized number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from PL+ORBm ($P<0.0001$) is detected. Bars show mean \pm SD. **** $P<0.0001$.

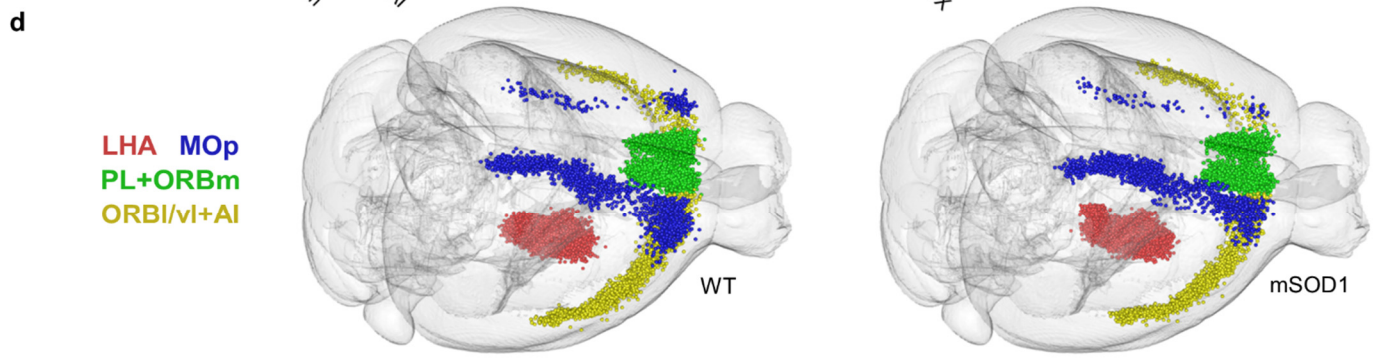
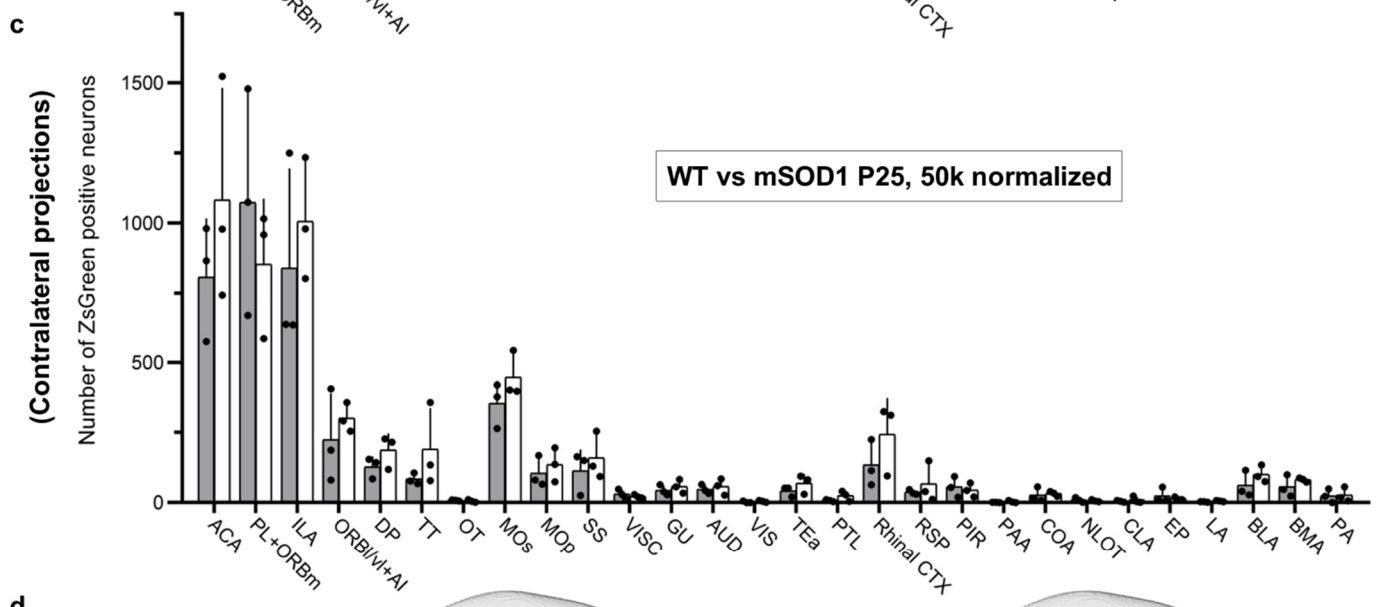
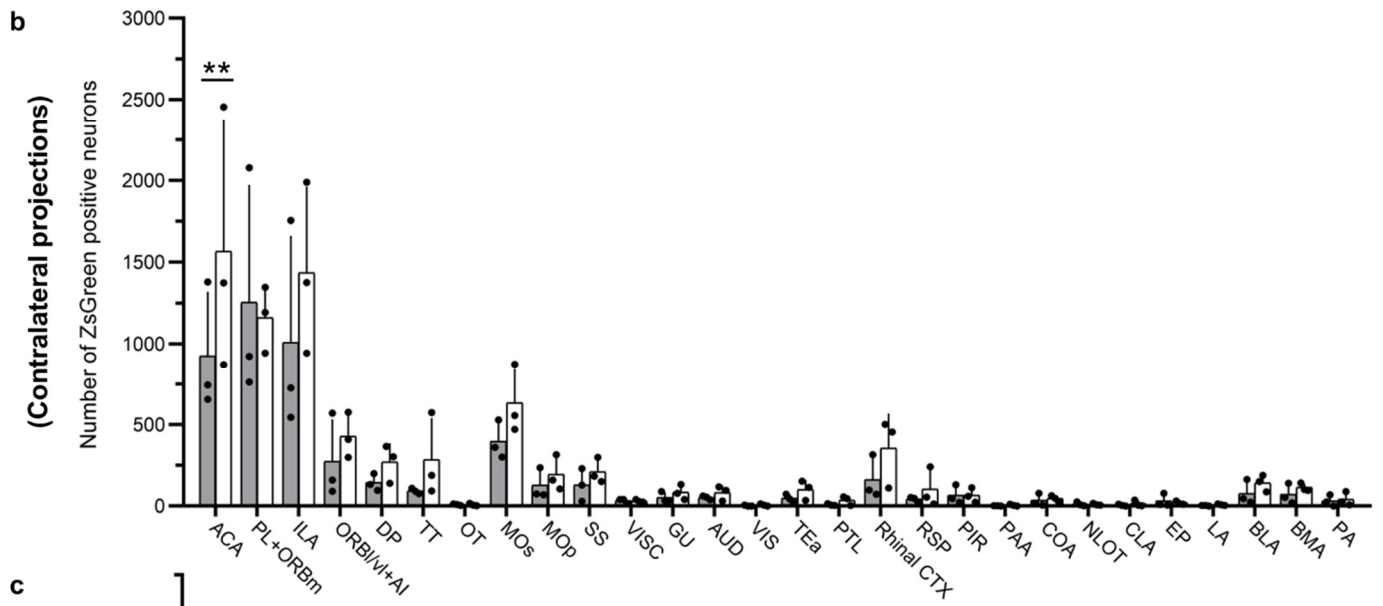
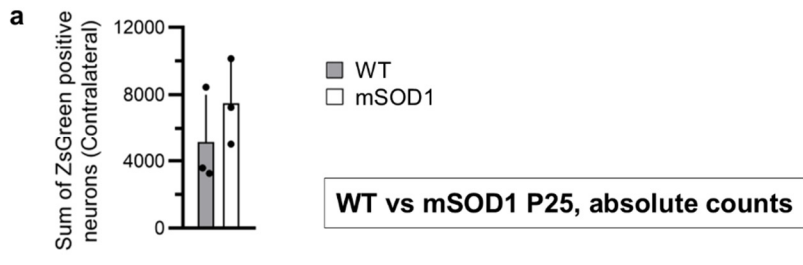


Fig. S6 Unaltered cortico-hypothalamic projection pattern in mSOD1 mice at P25, contralateral hemisphere. **a** Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and mSOD1 from the contralateral hemisphere ($n=3$). **b** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ACA ($P=0.0078$) is detected. **c** 50k normalized number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. No difference is detected in the number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. **d** Representative *WholeBrain* mesoscale reconstructions of neurons projecting to LHA in WT and mSOD1 mice show a similar pattern of projections in MOs (blue), ORBl/vl+AI (yellow) and PL+AI (green). Bars show mean \pm SD. $**P < 0.01$.

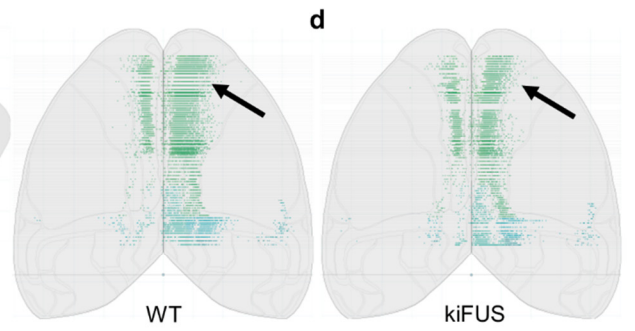
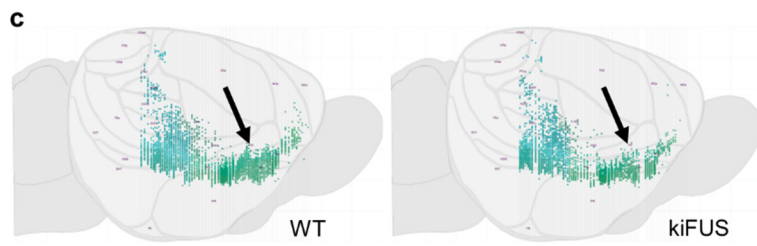
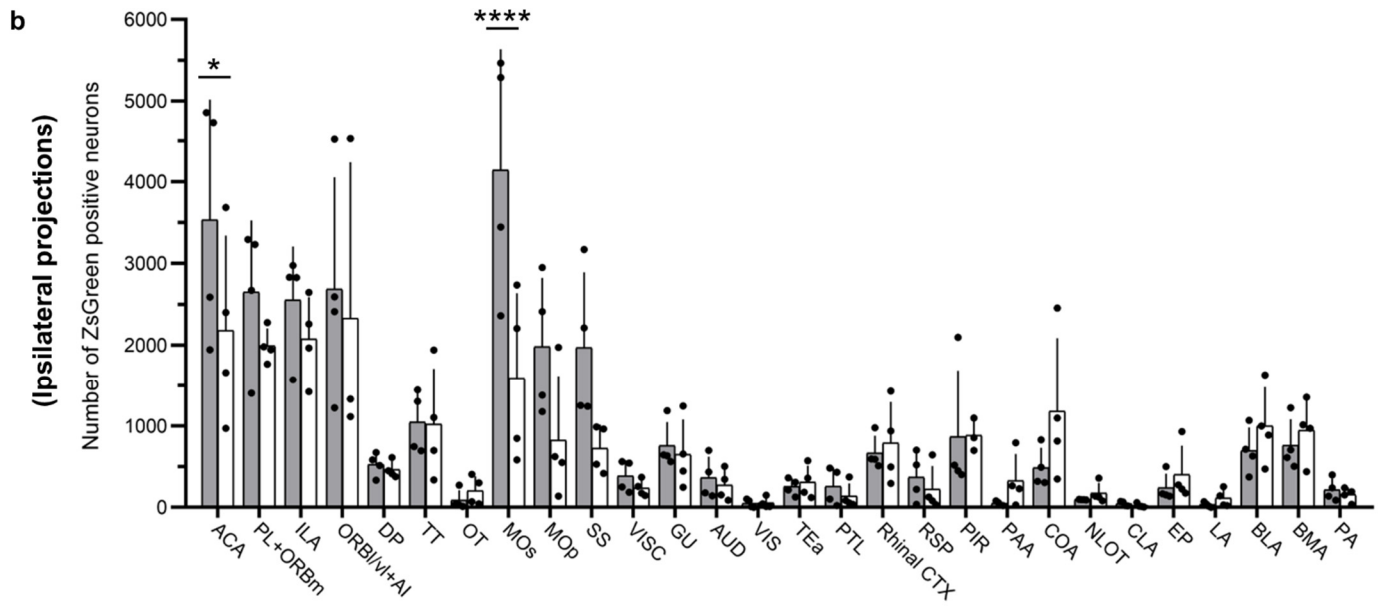
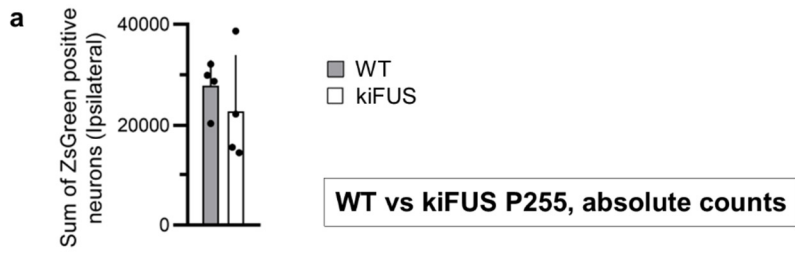


Fig. S7 Altered cortico-hypothalamic projection pattern in kiFUS mice at P255, absolute counts ipsilateral. **a** Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and kiFUS from the ipsilateral hemisphere ($n=4$). **b** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ACA ($P=0.0385$) and MOs ($P<0.0001$) is detected. **c** Representative *WholeBrain* ipsilateral side view reconstructions of neurons projecting to LHA in WT and mSOD1 mice. Decrease of projections from MOs are visible (arrows). **d** Representative *WholeBrain* cortical top view reconstructions of neurons projecting to LHA in WT and mSOD1 mice. Decrease of projections from MOs are visible (arrows). Bars show mean \pm SD. * $P < 0.05$, **** $P < 0.0001$.

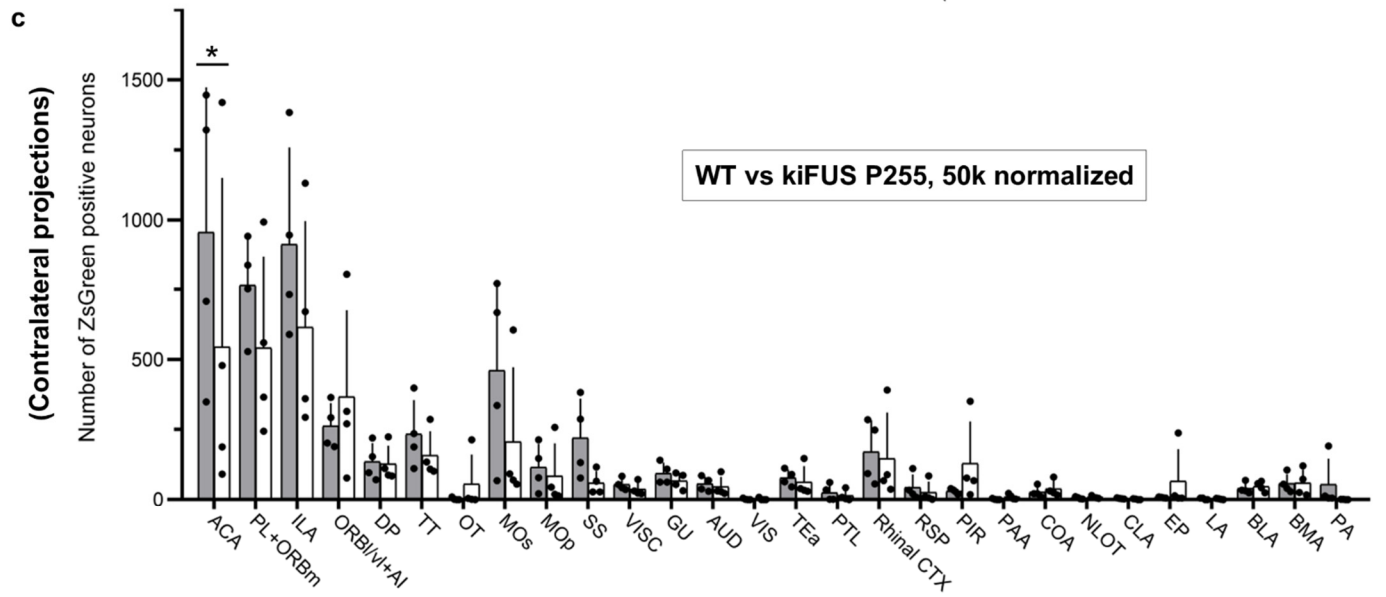
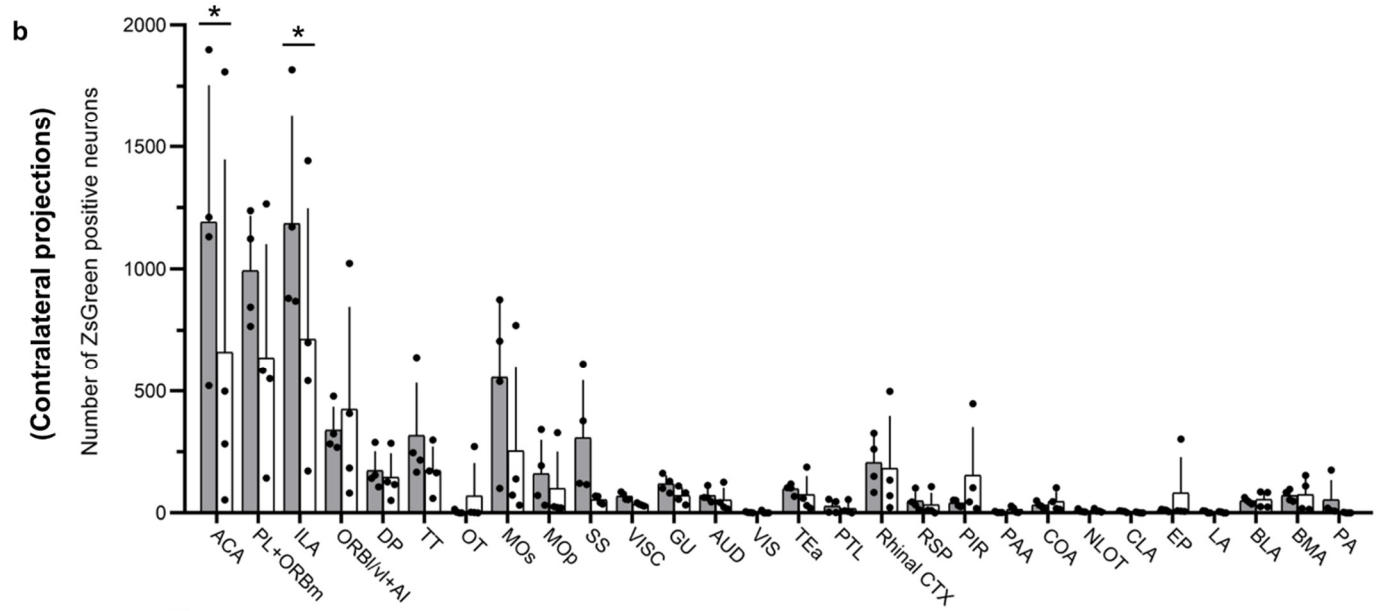
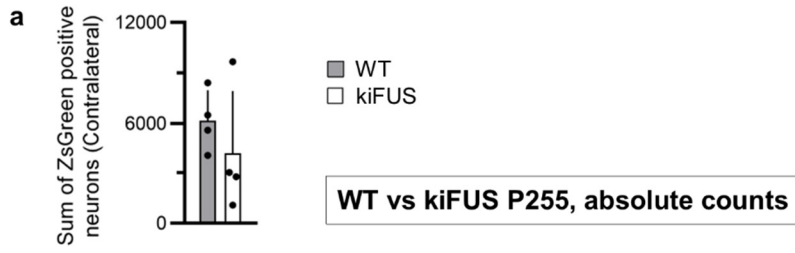


Fig. S8 Altered cortico-hypothalamic projection pattern in kiFUS mice at P255, contralateral hemisphere. **a** Sum of neurons projecting from selected 28 areas. No difference is detected in the number of neurons projecting to LHA in WT and kiFUS from the contralateral hemisphere ($n=3$). **b** Absolute number of neurons projecting to LHA from 28 brain structures in WT and mSOD1. A significant increase in projections from ACA ($P=0.0121$) and ILA ($P=0.0474$) is detected. **c** 50k normalized number of neurons projecting to LHA from 28 brain structures in WT and kiFUS. A significant decrease in projections from ACA ($P=0.0137$) is detected. Bars show mean \pm SD. $*P < 0.05$.