

Title:

Alzheimer's disease pathogenesis is dependent on neuronal receptor PTP σ

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Alzheimer's disease pathogenesis is dependent on neuronal receptor PTP σ

Abstract:

β -amyloid accumulation and Tau aggregation are hallmarks of Alzheimer's disease, yet their underlying molecular mechanisms remain obscure, hindering therapeutic advances. Here we report that neuronal receptor PTP σ mediates both β -amyloid and Tau pathogenesis in two mouse models. In the brain, PTP σ binds to β -amyloid precursor protein (APP). Depletion of PTP σ reduces the affinity between APP and β -secretase, diminishing APP proteolytic products by β - and γ -cleavage without affecting other major substrates of the secretases, suggesting a specificity of β -amyloidogenic regulation. In human APP transgenic mice during aging, the progression of β -amyloidosis, Tau aggregation, neuroinflammation, synaptic loss, as well as behavioral deficits, all show unambiguous dependency on the expression of PTP σ . Additionally, the aggregates of endogenous Tau are found in a distribution pattern similar to that of early stage neurofibrillary tangles in Alzheimer brains. Together, these findings unveil a gatekeeping role of PTP σ upstream of the degenerative pathogenesis, indicating a potential for this neuronal receptor as a drug target for Alzheimer's disease.

1 **Main Text:**

2 A definitive pathological hallmark of Alzheimer's disease (AD) is the progressive
3 aggregation of β -amyloid ($A\beta$) peptides in the brain, a process also known as β -
4 amyloidosis, which is often accompanied by neuroinflammation and formation of
5 neurofibrillary tangles containing Tau, a microtubule binding protein.

6 Although the etiological mechanisms of AD have been an ongoing debate,
7 concrete evidence from human genetic studies showed that overproduction of $A\beta$ due to
8 gene mutations inevitably inflicts cascades of cytotoxic events, ultimately leading to
9 neurodegeneration and decay of brain functions. Accumulation of $A\beta$ peptides, especially
10 in their soluble forms, is therefore recognized as a key culprit in the development of AD
11 ¹. In the brain, $A\beta$ peptides mainly derive from sequential cleavage of neuronal amyloid
12 precursor protein (APP) by the β - and γ -secretases. However, despite decades of research,
13 molecular regulation of the amyloidogenic secretase activities remains poorly understood,
14 hindering the design of therapeutics to specifically target the APP amyloidogenic
15 pathway.

16 Pharmacological inhibition of the β - and γ -secretase activities, although effective
17 in suppressing $A\beta$ production, interferes with physiological function of the secretases on
18 their other substrates. Such intervention strategies therefore are often innately associated
19 with untoward side effects, which have led to several failed clinical trials in the past ²⁻⁴.
20 To date, no therapeutic regimen is available to prevent the onset of AD or curtail its
21 progression.

22 Here we report our findings that identify neuronal receptor PTP σ (protein tyrosine
23 phosphatase sigma) as a potential molecular target to curb $A\beta$ pathogenesis. Genetic

1 depletion of PTP σ lowers β -secretase affinity to APP and suppresses A β accumulation in
2 a specific manner that does not generically inhibit β - and γ -secretase activities.

3 Besides A β , Tau is another biomarker that has been intensively studied in AD.
4 Cognitive decline in patients often correlates better with Tau pathology than with A β
5 burden ^{5,6}. Overwhelming evidence also substantiated that malfunction of Tau contributes
6 to synaptic loss and neuronal deterioration ⁷. However, what triggers the pathological
7 changes of Tau in AD remains a mystery. Whether neurotoxic A β can lead to Tau
8 pathology *in vivo* has been a debate since quintessential neurofibrillary Tau tangles have
9 not been reported in any of the APP transgenic mouse models, even in those with severe
10 cerebral β -amyloidosis. Here we show that during the process of aging, Tau aggregates
11 form in the brains of two APP transgenic mouse models with a similar distribution
12 pattern as seen in postmortem AD brains, suggesting that Tau misfolding can develop as
13 an event downstream from the expression of amyloidogenic APP transgenes. Genetic
14 depletion of PTP σ , which suppresses A β accumulation, also inhibits the aggregation of
15 Tau.

16 In the two mouse models we studied, a spectrum of AD neuropathologies and
17 behavioral deficits all demonstrate a clear dependency on PTP σ , indicating that this
18 neuronal receptor is a pivotal upstream player in AD pathogenesis.

19

20 **PTP σ is an APP binding partner in the brain.**

21 Previously identified as a neuronal receptor of extracellular proteoglycans ⁸⁻¹⁰,
22 PTP σ is expressed throughout the adult nervous system, most predominantly in the
23 hippocampus ^{11,12}, one of earliest affected brain regions in AD. Using

1 immunohistochemistry and confocal imaging, we found that PTP σ and APP (the
2 precursor of A β) colocalize in hippocampal pyramidal neurons of adult rat brains, most
3 intensively in the initial segments of apical dendrites, and in the perinuclear and axonal
4 regions with a punctate pattern (Fig. 1a-f). To assess whether this colocalization reflects a
5 binding interaction between these two molecules, we tested their co-immunoprecipitation
6 from brain homogenates. In brains of rats and mice with different genetic background,
7 using various antibodies of APP and PTP σ , we consistently detected a fraction of PTP σ
8 that co-immunoprecipitates with APP, providing evidence of a molecular complex
9 between these two transmembrane proteins (Fig. 1h, i; Extended Data Fig. 1).

10

11 **Genetic depletion of PTP σ reduces β -amyloidogenic products of APP.**

12 The molecular interaction between PTP σ and APP prompted us to investigate
13 whether PTP σ plays a role in amyloidogenic processing of APP. In neurons, APP is
14 mainly processed through alternative cleavage by either α - or β -secretase. These
15 secretases release the N-terminal portion of APP from its membrane-tethering C-terminal
16 fragment (CTF α or CTF β , respectively), which can be further processed by the γ -
17 secretase^{13,14}. Sequential cleavage of APP by the β - and γ -secretases is regarded as
18 amyloidogenic processing since it produces A β peptides¹⁵. When overproduced, the A β
19 peptides can form soluble oligomers that trigger ramification of cytotoxic cascades,
20 whereas progressive aggregation of A β eventually results in the formation of senile
21 plaques in the brains of AD patients (Fig. 2a). To test the effect of PTP σ in this
22 amyloidogenic processing, we analyzed the levels of APP β - and γ -cleavage products in
23 mouse brains with or without PTP σ .

1 Western blot analysis with protein extracts from mouse brains showed that
2 genetic depletion of PTP σ does not affect the expression level of full length APP (Fig.
3 2b; Extended Data Fig 2a). However, an antibody against the C-terminus of APP detects
4 a band at a molecular weight consistent with CTF β , which is reduced in PTP σ -deficient
5 mice as compared to their age- sex-matched wild type littermates (Fig. 2b). Additionally,
6 in two AD mouse models expressing human APP genes with amyloidogenic mutations
7 ^{16,17}, we observed a similar decrease of an APP CTF upon PTP σ depletion (Fig. 2b;
8 Extended Data Fig. 2b). The TgAPP-SwDI and TgAPP-SwInd mice, each expressing a
9 human APP transgene harboring the Swedish mutation near the β -cleavage site, were
10 crossed with the PTP σ line to generate offsprings that are heterozygous for their
11 respective APP transgene, with or without PTP σ . Because the Swedish mutation carried
12 by these APP transgenes is prone to β -cleavage, the predominant form of APP CTF in
13 these transgenic mice is predicted to be CTF β . Thus, the reduction of APP CTF in PTP σ -
14 deficient APP transgenic mice may indicate a regulatory role of PTP σ on CTF β level.
15 However, since the APP C-terminal antibody used in these experiments can recognize
16 both CTF α and CTF β , as well as the phosphorylated species of these CTFs (longer
17 exposure of western blots showed multiple CTF bands), judging the identity of the
18 reduced CTF simply by its molecular weight may be inadequate. We therefore performed
19 CTF β immunopurification with subsequent western blot detection, using an antibody that
20 recognizes CTF β but not CTF α (Fig. 2c, d; Extended Data Fig. 2c, d). With this
21 definitive method, we confirmed that PTP σ depletion decreases the level of CTF β
22 originated from both mouse endogenous and human transgenic APP.

1 Because CTF β is an intermediate proteolytic product between β - and γ -cleavage,
2 its decreased steady state level could result from either reduced production by β -cleavage
3 or increased degradation by subsequent γ -secretase cleavage (Fig. 2a). To distinguish
4 between these two possibilities, we measured the level of A β peptides, which are
5 downstream products from CTF β degradation by γ -cleavage. Using ELISA assays with
6 brain homogenates from the TgAPP-SwDI mice, we found that PTP σ depletion decreases
7 the levels of A β peptides to a similar degree as that of CTF β (Fig. 2e, f). Consistently, as
8 A β peptides gradually aggregate into plaques during aging of the transgenic mice, we
9 observed a substantial decrease of cerebral A β deposition in APP transgenic PTP σ -
10 deficient mice as compared to the age-matched APP transgenic littermates expressing
11 wild type PTP σ (Fig. 2g, h; Extended Data Fig. 2e, f). Thus, the concurrent decrease of β -
12 and γ -cleavage products argues against an increased γ -secretase activity, but instead
13 suggests a reduced β -secretase cleavage of APP, which suppresses not only the level of
14 CTF β but also downstream A β production in PTP σ -deficient brains.

15

16 **Curtailed progression of β -amyloidosis in the absence of PTP σ .**

17 Progressive cerebral A β aggregation (β -amyloidosis) is regarded as a benchmark
18 of AD progression. To investigate the effects of PTP σ on this pathological development,
19 we monitored A β deposits in the brains of 9-month old (mid-aged) and 16-month old
20 (aged) TgAPP-SwDI mice. At 9 months of age, A β deposits are found predominantly in
21 the hippocampus, especially in the hilus of the dentate gyrus (DG) (Fig. 2g, h). By 16
22 months, the pathology spreads massively throughout the entire brain. The propagation of

1 A β deposition, however, is curbed by genetic depletion of PTP σ , as quantified using the
2 DG hilus as a representative area (Fig. 2i). Between the ages of 9 and 16 months, the A β
3 burden is more than doubled in TgAPP-SwDI mice expressing wild type PTP σ [APP-
4 SwDI(+) $PTP\sigma$ (+/+)], but only shows marginal increase in the transgenic mice lacking
5 functional PTP σ [APP-SwDI(+) $PTP\sigma$ (-/-)]. Meanwhile, the A β loads measured in 9-
6 month old APP-SwDI(+) $PTP\sigma$ (+/+) mice are similar to those of 16-month old APP-
7 SwDI(+) $PTP\sigma$ (-/-) mice ($p=0.95$), indicating a restraint of disease progression by PTP σ
8 depletion (Fig. 2i).

9

10 **Decreased BACE1-APP affinity in PTP σ -deficient brains.**

11 Consistent with these observations that suggest a facilitating role of PTP σ in APP
12 β -cleavage, our data further reveal that PTP σ depletion weakens the interaction of APP
13 with BACE1, the β -secretase in the brain. To test the *in vivo* affinity between BACE1
14 and APP, we performed co-immunoprecipitation of the enzyme and substrate from mouse
15 brain homogenates in buffers with serially increased detergent stringency. Whereas
16 BACE1-APP association is nearly equal in wild type and PTP σ -deficient brains under
17 mild buffer conditions, increasing detergent stringency in the buffer unveils that the
18 molecular complex is more vulnerable to dissociation in brains without PTP σ (Fig. 3).
19 Thus a lower BACE1-APP affinity in PTP σ -deficient brains may likely be an underlying
20 mechanism for the decreased levels of CTF β and its derivative A β .

21 Although it cannot be ruled out that some alternative uncharacterized pathway
22 may contribute to the parallel decrease of CTF β and A β in PTP σ -deficient brains, these

1 data consistently support the notion that PTP σ regulates APP amyloidogenic processing,
2 likely via facilitation of BACE1 activity on APP, the initial process of A β production.

3

4 **The specificity of β -amyloidogenic regulation by PTP σ .**

5 The constraining effect of PTP σ on APP amyloidogenic products led us to further
6 question whether this observation reflects a specific regulation of APP metabolism, or
7 alternatively, a general modulation on the β - and γ -secretases. We first assessed the
8 expression level of these secretases in mouse brains with or without PTP σ , and found no
9 change for BACE1 or the essential subunits of γ -secretase (Fig. 4a, b). Additionally, we
10 tested whether PTP σ broadly modulates β - and γ -secretase activities, by examining the
11 proteolytic processing of their other substrates. Besides APP, Neuregulin1 (NRG1)¹⁸⁻²⁰
12 and Notch²¹⁻²³ are the major *in vivo* substrates of BACE1 and γ -secretase, respectively.
13 Neither BACE1 cleavage of NRG1 nor γ -secretase cleavage of Notch is affected by
14 PTP σ deficiency (Fig. 4c, d). Taken together, these data rule out a generic modulation of
15 β - and γ -secretases, but rather suggest a specificity of APP amyloidogenic regulation by
16 PTP σ .

17

18 **PTP σ depletion relieves neuroinflammation and synaptic impairment in APP** 19 **transgenic mice.**

20 Substantial evidence from earlier studies has established that overproduction of
21 A β in the brain elicits multiplex downstream pathological events, including chronic
22 inflammatory responses of the glia, such as persistent astrogliosis. The reactive

1 (inflammatory) glia would then crosstalk with neurons, evoking a vicious feedback loop
2 that amplifies neurodegeneration during disease progression²⁴⁻²⁶.

3 The TgAPP-SwDI model is one of the earliest to develop neurodegenerative
4 pathologies and behavioral deficits among many existing AD mouse models¹⁶. We
5 therefore chose these mice to further examine the role of PTP σ in AD pathologies
6 downstream of neurotoxic A β .

7 The APP-SwDI(+) $PTP\sigma$ (+/+) mice, which express the TgAPP-SwDI transgene
8 and wild type PTP σ , have developed severe neuroinflammation in the brain by the age of
9 9 months, as measured by the level of GFAP (glial fibrillary acidic protein), a marker of
10 astrogliosis (Extended Data Fig. 3). In the DG hilus, for example, GFAP expression level
11 in the APP-SwDI(+) $PTP\sigma$ (+/+) mice is more than tenfold compared to that in age-
12 matched non-transgenic littermates [APP-SwDI(-) $PTP\sigma$ (+/+)] (Extended Data Fig. 3b).
13 PTP σ deficiency, however, effectively attenuates astrogliosis induced by the
14 amyloidogenic transgene. In the APP-SwDI(+) $PTP\sigma$ (-/-) brains, depletion of PTP σ
15 restores GFAP expression back to a level close to that of non-transgenic wild type
16 littermates (Extended Data Fig. 3b).

17 Among all brain regions, the most affected by the expression of TgAPP-SwDI
18 transgene appears to be the hilus of the DG, where A β deposition and astrogliosis are
19 both found to be the most severe (Fig. 2g, h; Extended Data Fig. 3). We therefore
20 questioned whether the pathologies in this area have an impact on the mossy fiber axons
21 of DG pyramidal neurons, which project through the hilus into the CA3 region, where
22 they synapse with the CA3 dendrites. Upon examining the presynaptic markers in CA3
23 mossy fiber terminal zone, we found decreased levels of Synaptophysin and Synapsin-1

1 in the APP-SwDI(+) $PTP\sigma$ (+/+) mice, comparing to their age-matched non-transgenic
2 littermates (Extended Data Fig. 4, data not shown for Synapsin-1). Such synaptic
3 impairment, evidently resulting from the expression of the APP transgene and possibly
4 the overproduction of $A\beta$, is reversed by genetic depletion of $PTP\sigma$ in the APP-
5 SwDI(+) $PTP\sigma$ (-/-) mice (Extended Data Fig. 4).

6 Interestingly, we noticed that the APP-SwDI(+) $PTP\sigma$ (-/-) mice sometimes express
7 higher levels of presynaptic markers in the CA3 terminal zone than their age-matched
8 non-transgenic wild type littermates (Extended Data Fig. 4g). This observation, although
9 not statistically significant in our quantification analysis, may suggest an additional
10 synaptic effect of $PTP\sigma$ that is independent of the APP transgene, as observed in previous
11 studies²⁷.

13 **Tau pathology in aging AD mouse brains is dependent on $PTP\sigma$.**

14 Neurofibrillary tangles composed of hyperphosphorylated and aggregated Tau are
15 commonly found in AD brains. These tangles tend to develop in a hierarchical pattern,
16 appearing first in the entorhinal cortex before spreading to other brain regions^{5,6}. The
17 precise mechanism of tangle formation, however, is poorly understood. The fact that Tau
18 tangles and $A\beta$ deposits can be found in separate locations in postmortem brains has led
19 to the question of whether Tau pathology in AD is independent of $A\beta$ accumulation^{5,6}.
20 Additionally, despite severe cerebral β -amyloidosis in many APP transgenic mouse
21 models, Tau tangles have not been reported, further questioning the relationship between
22 $A\beta$ and Tau pathologies *in vivo*.

1 Nonetheless, a few studies did show non-tangle like assemblies of Tau in
2 dystrophic neurites surrounding A β plaques in APP transgenic mouse lines²⁸⁻³⁰, arguing
3 that A β can be a causal factor for Tau dysregulation, despite that the precise nature of
4 Tau pathologies may be different between human and mouse. In our histological analysis
5 using an antibody against the proline-rich domain of Tau, we observed Tau aggregation
6 in the brains of both TgAPP-SwDI and TgAPP-SwInd mice during the course of aging
7 (around 9 months for the both the APP-SwDI(+) $PTP\sigma$ (+/+) mice and 15 months for the
8 APP-SwInd(+) $PTP\sigma$ (+/+) mice) (Fig. 5; Extended Data Fig. 5). Such aggregation is not
9 seen in aged-matched non-transgenic littermates (Fig. 5h), suggesting that it is a
10 pathological event downstream from the expression of amyloidogenic APP transgenes,
11 possibly a result of A β cytotoxicity. Genetic depletion of $PTP\sigma$, which diminishes A β
12 levels, suppresses Tau aggregation in both TgAPP-SwDI and TgAPP-SwInd mice (Fig.
13 5; Extended Data Fig. 5).

14 Upon closer examination, the Tau aggregates are often found in punctate shapes,
15 likely in debris from degenerated cell bodies and neurites, scattered in areas free of
16 nuclear staining (Extended Data Fig. 6a-f). Rarely, a few are in fibrillary structures,
17 probably in degenerated cells before disassembling (Extended Data Extended Data Fig.
18 6g, h). In both TgAPP-SwDI and TgAPP-SwInd mice, the Tau aggregates are found
19 predominantly in the molecular layer of the piriform and entorhinal cortices, and
20 occasionally in the hippocampal region (Fig. 5; Extended Data Fig. 5), reminiscent of the
21 early stage tangle locations in AD brains³¹. To confirm these findings, we used an
22 additional antibody recognizing the C-terminus of Tau and detected the same
23 morphologies (Extended Data Fig. 6i) and distribution pattern (Fig. 5a).

1 Consistent with the findings in postmortem AD brains, the distribution pattern of
2 Tau aggregates in the TgAPP-SwDI brain does not correlate with that of A β deposition,
3 which is pronounced in the hippocampus yet barely detectable in the piriform or
4 entorhinal cortex at the age of 9 months (Fig. 2g, h). Given that the causation of Tau
5 pathology in these mice is possibly related to the overproduced A β , the segregation of A β
6 and Tau depositions in different brain regions may indicate that the cytotoxicity
7 originates from soluble A β instead of the deposited amyloid. It is also evident that
8 neurons in different brain regions are not equally vulnerable to developing Tau
9 pathology.

10 We next examined whether the expression of APP transgenes or genetic depletion
11 of PTP σ regulates Tau aggregation by changing its expression level and/or
12 phosphorylation status. Western blot analysis of brain homogenates showed that Tau
13 protein expression is not affected by the APP transgenes or PTP σ (Extended Data Fig. 7),
14 suggesting that the aggregation may be due to local misfolding of Tau rather than an
15 overexpression of this protein. Moreover, the TgAPP-SwDI or TgAPP-SwInd transgene,
16 which apparently causes Tau aggregation, does not enhance the phosphorylation of Tau
17 residues including Serine191, Therionine194, and Therionine220 (data not shown),
18 whose homologues in human Tau (Serine202, Therionine205, and Therionine231) are
19 typically hyperphosphorylated in neurofibrillary tangles. These findings are consistent
20 with a recent quantitative study showing similar post-translational modifications in wild
21 type and TgAPP-SwInd mice³². Furthermore, unlike previously reported^{28,29}, we could
22 not detect these phosphorylated residues in the Tau aggregates, suggesting that the
23 epitopes are either missing (residues not phosphorylated or cleaved off) or embedded

1 inside the misfolding. Given the complexity of Tau post-translational modification, one
2 cannot rule out that the aggregation may be mediated by some unidentified
3 modification(s) of Tau. It is also possible that other factors, such as molecules that bind
4 to Tau, may precipitate the aggregation.

5 Although the underlying mechanism is still unclear, our finding of Tau pathology
6 in these mice establishes a causal link between the expression of amyloidogenic APP
7 transgenes and a dysregulation of Tau assembly. Our data also suggest a possibility that
8 PTP σ depletion may suppress tau aggregation by reducing amyloidogenic products of
9 APP.

10 Malfunction of Tau is broadly recognized as a neurodegenerative marker since it
11 indicates microtubule deterioration⁷. The constraining effect on Tau aggregation by
12 genetic depletion of PTP σ thus provides additional evidence for the role of this receptor
13 as a pivotal regulator of neuronal integrity.

14

15 **PTP σ deficiency rescues behavioral deficits in AD mouse models.**

16 We next assessed whether the alleviation of neuropathologies by PTP σ depletion
17 is accompanied with a rescue from AD relevant behavioral deficits. The most common
18 symptoms of AD include short-term memory loss and apathy among the earliest,
19 followed by spatial disorientation amid impairment of many cognitive functions as the
20 dementia progresses. Using Y maze and novel object assays as surrogate models, we
21 evaluated these cognitive and psychiatric features in the TgAPP-SwDI and TgAPP-
22 SwInd mice.

1 The Y-maze assay, which allows mice to freely explore three identical arms,
2 measures their short-term spatial memory. It is based on the natural tendency of mice to
3 alternate arm exploration without repetitions. The performance is scored by the
4 percentage of spontaneous alternations among total arm entries, and a higher score
5 indicates better spatial navigation. Compared to the non-transgenic wild type mice within
6 the colony, the APP-SwDI(+) $PTP\sigma$ (+/+) mice show a clear deficit in their performance.
7 Genetic depletion of $PTP\sigma$ in the APP-SwDI(+) $PTP\sigma$ (-/-) mice, however, unequivocally
8 restores the cognitive performance back to the level of non-transgenic wild type mice
9 (Fig. 6a, Extended Data Fig. 8).

10 Apathy, the most common neuropsychiatric symptom reported among individuals
11 with AD, is characterized by a loss of motivation and diminished attention to novelty, and
12 has been increasingly adopted into early diagnosis of preclinical and early prodromal AD
13 ³³⁻³⁵. Many patients in early stage AD lose attention to novel aspects of their environment
14 despite their ability to identify novel stimuli, suggesting an underlying defect in the
15 circuitry responsible for further processing of the novel information ^{33,34}. As a key feature
16 of apathy, such deficits in attention to novelty can be accessed by the “curiosity figures
17 task” or the “oddball task” in patients ^{33,34,36}. These visual-based novelty encoding tasks
18 are very similar to the novel object assay for rodents, which measures the interest of
19 animals in a novel object (NO) when they are exposed simultaneously to a
20 prefamiliarized object (FO). We therefore used this assay to test the attention to novelty
21 in the APP transgenic mice. When mice are pre-trained to recognize the FO, their
22 attention to novelty is then measured by the discrimination index denoted as the ratio of
23 NO exploration to total object exploration (NO+FO), or alternatively, by the ratio of NO

1 exploration to FO exploration. Whereas both ratios are commonly used, a combination of
2 these assessments provides a more comprehensive evaluation of animal behavior. In this
3 test, as indicated by both measurements, the expression of APP-SwDI transgene in the
4 APP-SwDI(+)PTP σ (+/+) mice leads to a substantial decrease in NO exploration as
5 compared to non-transgenic wild type mice (Fig. 6b, c; Extended Data Fig. 9). Judging by
6 their NO/FO ratios, it is evident that both the transgenic and non-transgenic groups are
7 able to recognize and differentiate between the two objects (Extended Data Fig. 9a, b).
8 Thus, the reduced NO exploration by the APP-SwDI(+)PTP σ (+/+) mice may reflect a
9 lack of interest in the NO or an inability to shift attention to the NO. Once again, this
10 behavioral deficit is largely reversed by PTP σ deficiency in the APP-SwDI(+)PTP σ (-/-)
11 mice (Fig. 6b, c; Extended Data Fig. 9), consistent with previous observation of increased
12 NO preference in the absence of PTP σ ²⁷.

13 To further verify the effects of PTP σ on these behavioral aspects, we additionally
14 tested the TgAPP-SwInd mice in both assays and observed similar results, confirming an
15 improvement on both short-term spatial memory and attention to novelty upon genetic
16 depletion of PTP σ (Extended Data Fig. 10).

17

18 **Discussion**

19 Here we report that β -amyloidosis and several downstream disease features are
20 dependent on PTP σ in two mouse models of genetically inherited AD. This form of AD
21 develops inevitably in people who carry gene mutations that promote amyloidogenic
22 processing of APP and overproduction of A β . Our data suggest that targeting PTP σ is a
23 potential therapeutic approach that could overcome such dominant genetic driving forces

1 to curtail AD progression. The advantage of this targeting strategy is that it suppresses
2 A β accumulation without broadly affecting other major substrates of the β - and γ -
3 secretases, thus predicting a more promising translational potential as compared to those
4 in clinical trials that generically inhibit the secretases.

5 PTP σ was previously characterized as a neuronal receptor of the chondroitin
6 sulfate- and heparan sulfate-proteoglycans (CSPGs and HSPGs) ^{8,9}. In response to these
7 two classes of extracellular ligands, PTP σ functions as a “molecular switch” by
8 regulating neuronal behavior in opposite manners ¹⁰. Our finding of a pivotal role for the
9 proteoglycan sensor PTP σ in AD pathogenesis may therefore implicate an involvement
10 of the perineuronal matrix in AD etiology.

11 More than 95% of AD cases are sporadic, which are not genetically inherited but
12 likely result from insults to the brain that occurred earlier in life. AD risk factors, such as
13 traumatic brain injury and cerebral ischemia ³⁷⁻⁴⁰, have been shown to induce
14 overproduction of A β in both human and rodents ⁴¹⁻⁴⁵, and speed up progression of this
15 dementia in animal models ⁴⁶⁻⁴⁸. However, what promotes the amyloidogenic processing
16 of APP in these cases is still a missing piece of the puzzle in understanding the AD-
17 causing effects of these notorious risk factors.

18 Coincidentally, both traumatic brain injury and cerebral ischemia cause pronounced
19 remodeling of the perineuronal microenvironment at lesion sites, marked by increased
20 expression of CSPGs ⁴⁹⁻⁵², a major component of the perineuronal net that is upregulated
21 during neuroinflammation and glial scar formation ⁵³⁻⁵⁵. In the brains of AD patients,
22 CSPGs were found associated with A β depositions, further suggesting an uncanny
23 involvement of these proteoglycans in AD development ⁵⁶. On the other hand, analogues

1 of heparan sulfate (HS, carbohydrate side chains of HSPGs that bind to PTP σ) were
2 shown to inhibit BACE1 activity, suggesting their function in preventing A β
3 overproduction⁵⁷. After cerebral ischemia, however, the expression of Heparanase, an
4 enzyme that degrades HS, was found markedly increased⁵⁸. Collectively, these findings
5 suggest a disrupted molecular balance between CSPGs and HSPGs in brains after lesion,
6 which may ignite insidious signaling cascades preceding the onset of AD.

7 We hence speculate upon a mechanism for further study, whereby chronic CSPG
8 upregulation or HSPG degradation in lesioned brains may sustain aberrant signaling
9 through their neuronal sensor PTP σ , leading to biased processing of APP and a
10 neurotoxic “A β cascade”. As such, altered signaling from PTP σ after traumatic brain
11 injury and ischemic stroke may explain how these risk factors can trigger subsequent
12 onset of AD. Restoring the integrity of brain microenvironment therefore could be
13 essential in preventing AD for the population at risk.

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Supplementary Materials:

Materials and Methods:

Mouse lines: Mice were maintained under standard conditions approved by the Institutional Animal Care and Use Committee. Wild type and PTP σ -deficient mice of Balb/c background were provided by Dr. Michel L. Tremblay⁵⁹. Homozygous TgAPP-SwDI mice, C57BL/6-Tg(Thy1-APPSwDutIowa)BWevn/Mmjax, stock number 007027, were from the Jackson Laboratory. These mice express human APP transgene harboring Swedish, Dutch, and Iowa mutations, and were bred with Balb/c mice heterozygous for the PTP σ gene to generate bigenic mice heterozygous for both TgAPP-SwDI and PTP σ genes, which are hybrids of 50% C57BL/6J and 50% Balb/c genetic background. These mice were further bred with Balb/c mice heterozygous for the PTP σ gene. The offspring from this mating are used in experiments, which include littermates of the following genotypes: TgAPP-SwDI(+/-)PTP σ (+/+), mice heterozygous for TgAPP-SwDI transgene with wild type PTP σ ; TgAPP-SwDI(+/-)PTP σ (-/-), mice heterozygous for TgAPP-SwDI transgene with genetic depletion of PTP σ ; TgAPP-SwDI(-/-)PTP σ (+/+), mice free of TgAPP-SwDI transgene with wild type PTP σ . Both TgAPP-SwDI(-/-)PTP σ (+/+) and Balb/c PTP σ (+/+) are wild type mice but with different genetic background. Heterozygous TgAPP-SwInd (J20) mice, 6.Cg-Tg(PDGFB-APPSwInd)20Lms/2Mmjax, were provided by Dr. Lennart Mucke. These mice express human APP transgene harboring Swedish and Indiana mutations, and were bred with the same strategy as described above to obtain mice with genotypes of TgAPP-SwInd (+/-)PTP σ (+/+) and TgAPP-SwInd (+/-)PTP σ (-/-).

Antibodies:

Primary Antibodies	Application	Clone #	Catalog #	Supplier
Mouse anti-Actin	WB	AC-40	A4700	Sigma-Aldrich
Rabbit anti-APH1	WB		PA5-20318	Thermo Scientific
Rabbit anti-APP C-term	WB, IP, IHC	Y188	NB110-55461	Novus Biologicals
Mouse anti-murine A β , 1-16	WB, IP	M3.2	805701	Biologend
Mouse anti-human A β , 1-16	WB, IP, IHC, ELISA	6E10	803001	Biologend
Mouse anti-A β , 17-24	WB, IHC	4G8	SIG-39220	Biologend
Mouse HRP-conjugated anti-A β 1-40	ELISA	11A50-B10	SIG-39146	Biologend
Mouse HRP-conjugated anti-A β 1-42	ELISA	12F4	805507	Biologend
Rabbit anti-BACE1 C-Term, B690	WB		PRB-617C	Covance
Guinea Pig anti-BACE1 C-Term	IP		840201	Biologend
Chicken anti-GFAP	IHC		ab4674	Abcam
Rabbit anti-Neuregulin	WB		sc-348	Santa Cruz Biotechnology
Rabbit anti-Nicastrin	WB		5665	Cell Signaling
Rabbit anti-Notch NICD (val1744)	WB		4147	Cell Signaling
Rabbit anti-Notch (C-20)	WB		sc-6014R	Santa Cruz Biotechnology
Rabbit anti-PEN2	WB		8598	Cell Signaling
Rabbit anti-Presenilin 1/2 NTF	WB		840201	Abcam
Rabbit anti-Presenilin 1 CTF	WB		5643	Cell Signaling
Rabbit anti-Presenilin 2 CTF	WB		9979	Cell Signaling
Mouse anti-PTP σ ICD	WB, IHC	17G7.2	MM-002-P	Medimabs
Mouse anti-PTP σ ECD	WB		ab55640	Abcam
Rabbit anti-Synaptophysin	IHC		AB9272	Millipore
Mouse anti-Tau	WB, IHC	Tau-5	MAB361	Millipore
Mouse anti-Tau	IHC	Tau-46	4019	Cell Signaling
Secondary and Tertiary Antibodies	Application	Clone #	Catalog #	Supplier
Goat anti-mouse IgG HRP-conjugated	WB		7076S	Cell Signaling
Goat anti-rabbit IgG HRP-conjugated	WB		7074S	Cell Signaling
Goat anti-mouse IgG Alexa488	IHC		A-11001	Invitrogen
Donkey anti-goat IgG Alexa488	IHC		A-11055	Invitrogen
Chicken anti-rabbit IgG CF568	IHC		SAB4600426	Sigma-Aldrich
Donkey anti-chicken IgG Cy3	IHC		703-165-155	JacksonImmunoResearch

Immunohistochemistry: Adult rat and mice were perfused intracardially with fresh made 4% paraformaldehyde in cold phosphate-buffered saline (PBS). The brains were collected and post-fixed for 2 days at 4 °C. Paraffin embedded sections of 10 μ M thickness were collected for immunostaining. The sections were deparaffinized and sequentially rehydrated. Antigen retrieval was performed at 100 °C in Tris-EDTA buffer (pH 9.0) for 50 min. Sections were subsequently washed with distilled water and PBS, incubated at room temperature for 1 hour in blocking buffer (PBS, with 5% normal donkey serum, 5% normal goat serum, and 0.2% Triton X-100). Primary antibody

incubation was performed in a humidified chamber at 4°C overnight. After 3 washes in PBS with 0.2% Triton X-100, the sections were then incubated with a mixture of secondary and tertiary antibodies at room temperature for 2 hours. All antibodies were diluted in blocking buffer with concentrations recommended by the manufacturers. Mouse primary antibodies were detected by goat anti-mouse Alexa488 together with donkey anti-goat Alexa488 antibodies; rabbit primary antibodies were detected by chicken anti-rabbit CF568 and donkey anti-chicken Cy3 antibodies; chicken antibody was detected with donkey anti-chicken Cy3 antibody. Sections stained with only secondary and tertiary antibodies (without primary antibodies) were used as negative controls. At last, DAPI (Invitrogen, 300 nM) was applied on sections for nuclear staining. Sections were washed 5 times before mounted in Fluoromount (SouthernBiotech).

Wide field and confocal images were captured using Zeiss Axio Imager M2 and LSM780, respectively. Images are quantified using the Zen 2 Pro software and ImageJ.

Protein extraction, immunoprecipitation, and western blot analysis: For the co-immunoprecipitation of APP and PTP σ , RIPA buffer was used (50 mM Tris-HCl, pH 8.0, 1 mM EDTA, 150 mM NaCl, 1% NP40, 0.1% SDS, 0.5% sodium deoxycholate). For the co-immunoprecipitation of APP and BACE1, NP40 buffer was used (50 mM Tris-HCl, pH 8.0, 1 mM EDTA, 150 mM NaCl, 1% NP40) without or with SDS at concentration of 0.1%, 0.3%, and 0.4%. For total protein extraction and immunopurification of CTF β , SDS concentration in RIPA buffer was adjusted to 1% to ensure protein extraction from the lipid rafts. Mouse or rat forebrains were homogenized thoroughly on ice in homogenization buffers (as mention above) containing protease and

phosphatase inhibitors (Thermo Scientific). For each half of forebrain, buffer volume of at least 5 ml for mouse and 8 ml for rat was used to ensure sufficient detergent/tissue ratio. The homogenates were incubated at 4°C for 1 hour with gentle mixing, sonicated on ice for 2 minutes in a sonic dismembrator (Fisher Scientific Model 120, with pulses of 50% output, 1 second on and 1 second off), followed with another hour of gentle mixing at 4°C. All samples were used fresh without freezing and thawing.

For co-immunoprecipitation and immunopurification, the homogenates were then centrifuged at 85,000 x g for 1 hour at 4°C and the supernatants were collected. Protein concentration was measured using BCA Protein Assay Kit (Thermo Scientific). 0.5 mg total proteins of brain homogenates were incubated with 5 µg of designated antibody and 30 µl of Protein-A sepharose beads (50% slurry, Roche), in a total volume of 1 ml adjusted with RIPA buffer. Samples were gently mixed at 4°C overnight. Subsequently, the beads were washed 5 times with cold immunoprecipitation buffer. Samples were then incubated in Laemmli buffer with 100 mM of DTT at 75°C for 20 minutes and subjected to western blot analysis.

For analysis of protein expression level, the homogenates were centrifuged at 23,000 x g for 30 min at 4°C and the supernatants were collected. Protein concentration was measured using BCA Protein Assay Kit (Thermo Scientific). 30 µg of total proteins were subjected to western blot analysis.

Electrophoresis of protein samples was conducted using 4-12% Bis-Tris Bolt Plus Gels, with either MOPS or MES buffer and Novex Sharp Pre-stained Protein Standard (all from Invitrogen). Proteins were transferred to nitrocellulose membrane (0.2 µm pore size, Bio-Rad) and blotted with selected antibodies (see table above) at concentrations

suggested by the manufacturers. Primary antibodies were diluted in SuperBlock TBS Blocking Buffer (Thermo Scientific) and incubated with the nitrocellulose membranes at 4°C overnight; secondary antibodies were diluted in PBS with 5% nonfat milk and 0.2% Tween20 and incubated at room temperature for 2 hours. Membranes were washed 4 times in PBS with 0.2% Tween20 between primary and secondary antibodies and before chemiluminescent detection with SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific).

Western blot band intensity was quantified by densitometry.

A β ELISA assays: Mouse forebrains were thoroughly homogenized in tissue homogenization buffer (2 mM Tris pH 7.4, 250 mM sucrose, 0.5 mM EDTA, 0.5 mM EGTA) containing protease inhibitor cocktail (Roche), followed by centrifugation at 135,000 x g (33,500 RPM with SW50.1 rotor) for 1 hour at 4°C. Proteins in the pellets were extracted with formic acid (FA) and centrifuged at 109,000 x g (30,100 RPM with SW50.1 rotor) for 1 hour at 4°C. The supernatants were collected and diluted 1:20 in neutralization buffer (1 M Tris base, 0.5 M Na₂HPO₄, 0.05% NaN₃) and subsequently 1:3 in ELISA buffer (PBS with 0.05% Tween-20, 1% BSA, and 1 mM AEBSF). Diluted samples were loaded onto ELISA plates pre-coated with 6E10 antibody (Biolegend) to capture A β peptides. Serial dilutions of synthesized human A β 1-40 or 1-42 (American Peptide) were loaded to determine a standard curve. A β was detected using an HRP labeled antibody for either A β 1-40 or 1-42 (see table above). ELISA was developed using TMB substrate (Thermo Scientific) and reaction was stopped with 1N HCl. Plates

were read at 450nm and concentrations of A β in samples were determined using the standard curve.

Behavior assays: The Y-maze assay: Mice were placed in the center of the Y-maze and allowed to move freely through each arm. Their exploratory activities were recorded for 5 minutes. An arm entry is defined as when all four limbs are within the arm. For each mouse, the number of triads is counted as “spontaneous alternation”, which was then divided by the number of total arm entries, yielding a percentage score. The novel object test: On day 1, mice were exposed to empty cages (45 cm x 24 cm x 22 cm) with blackened walls to allow exploration and habituation to the arena. During day 2 to day 4, mice were returned to the same cage with two identical objects placed at an equal distance. On each day mice were returned to the cage at approximately the same time during the day and allowed to explore for 10 minutes. Cages and objects were cleaned with 70% ethanol between each animal. Subsequently, 2 hours after the familiarization session on day 4, mice were put back to the same cage where one of the familiar objects (randomly chosen) was replaced with a novel object, and allowed to explore for 5 minutes. Mice were scored using Observer software (Noldus) on their time duration and visiting frequency exploring either object. Object exploration was defined as facing the object and actively sniffing or touching the object, whereas any climbing behavior was not scored. The discrimination indexes reflecting interest in the novel object is denoted as either the ratio of novel object exploration to total object exploration (NO/NO+FO) or the ratio of novel object exploration to familiar object exploration (NO/FO). All tests and data analyses were conducted in a double-blinded manner.

Statistics: 2-tailed Student's *t* test was used for two-group comparison. Relationship between two variables (SDS concentration and APP-BACE1 association, as in Fig 3) was analyzed using linear regression. All error bars show standard error of the means (SEM).

Figure 1. PTP σ is an APP binding partner in the brain.

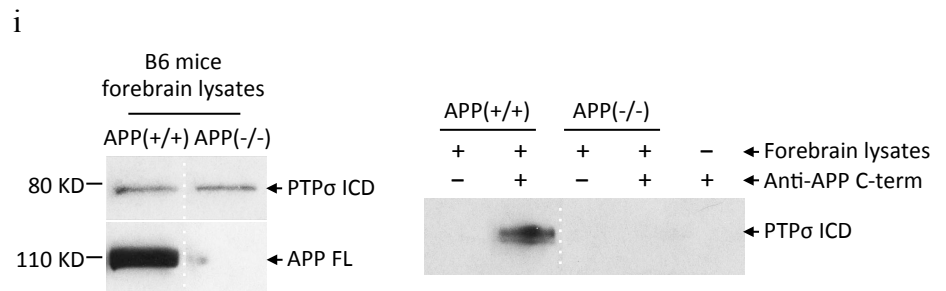
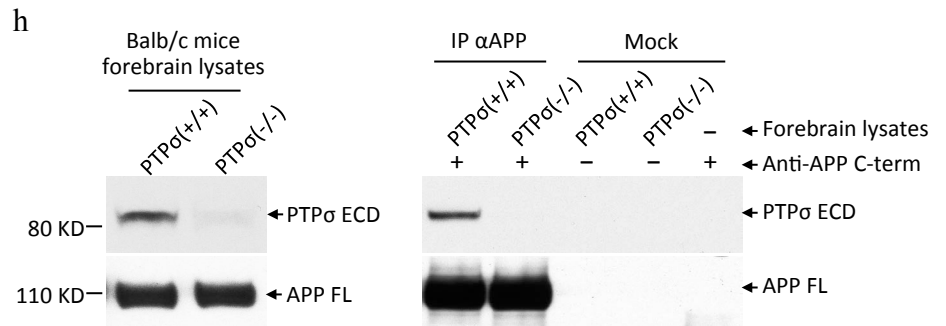
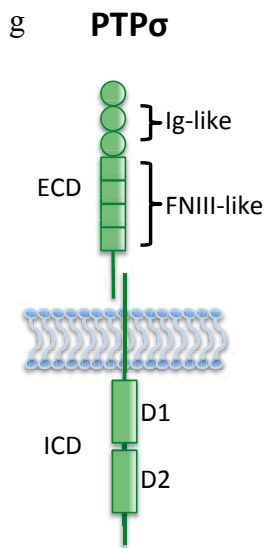
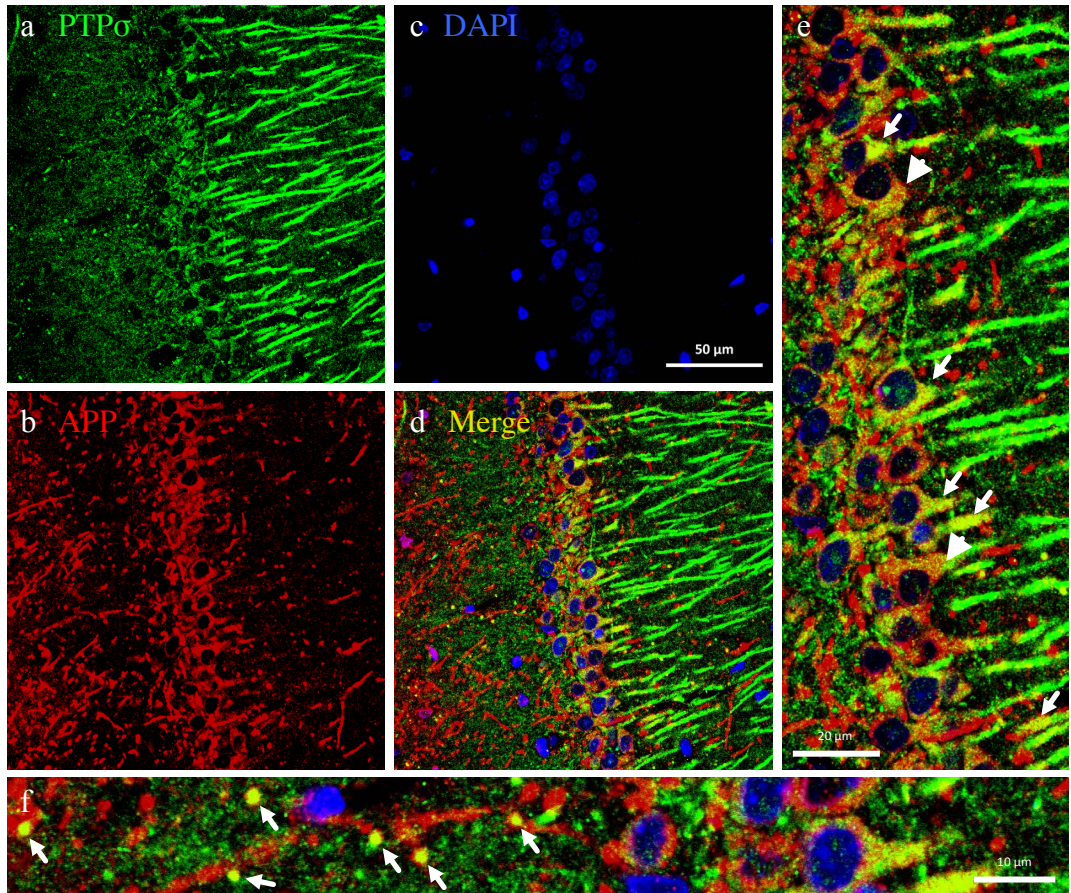
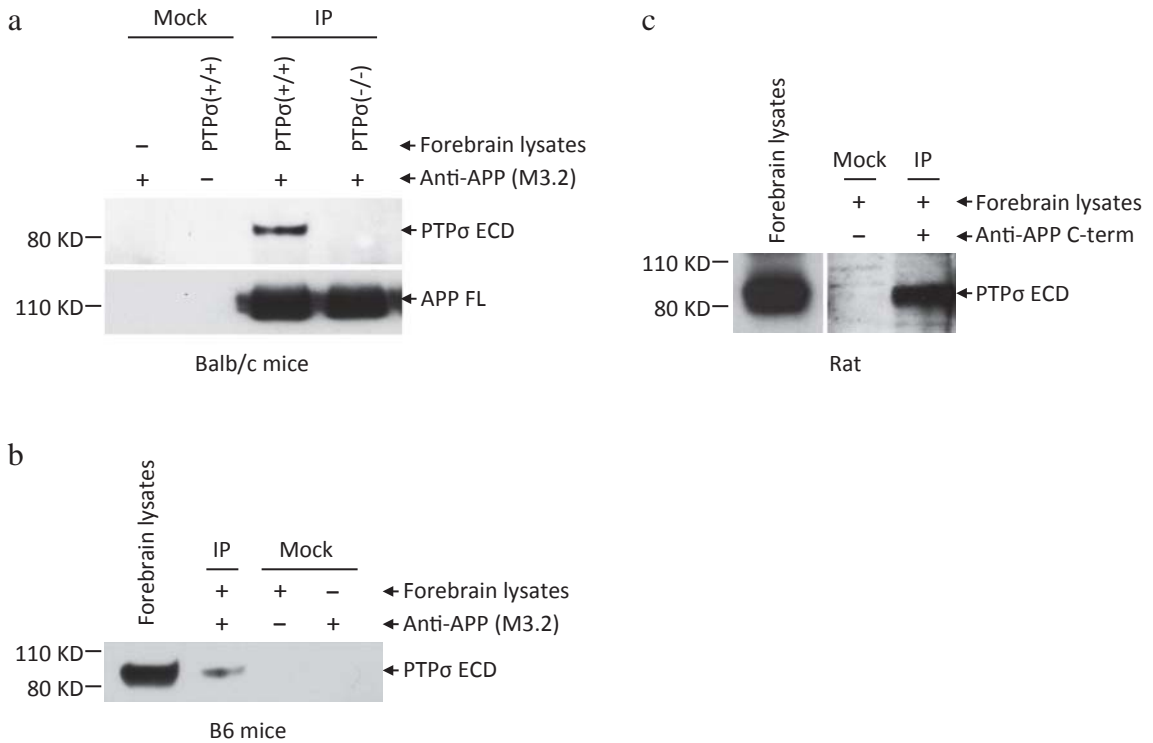


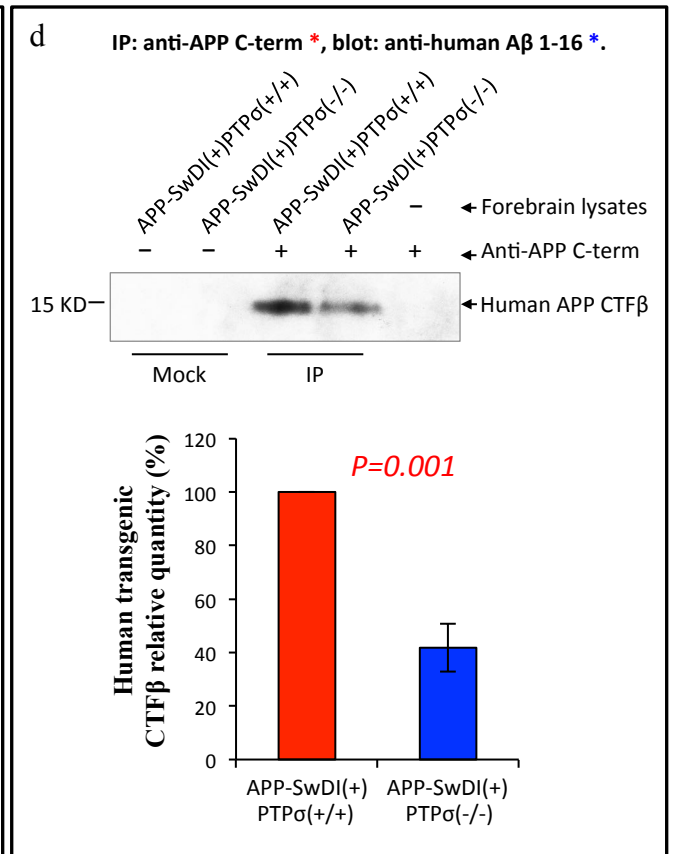
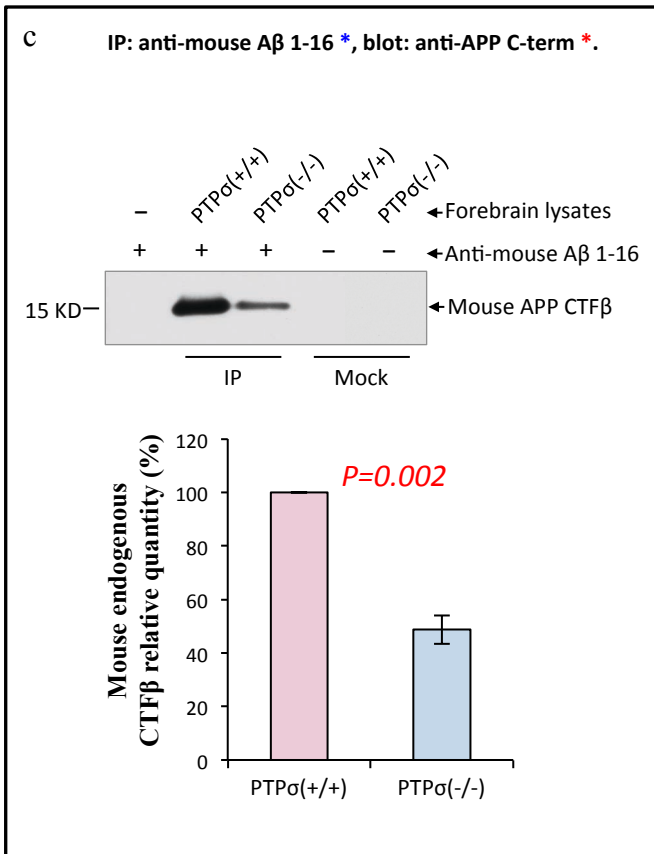
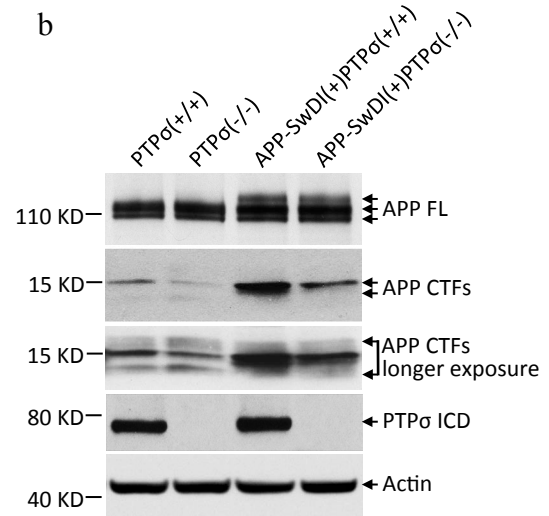
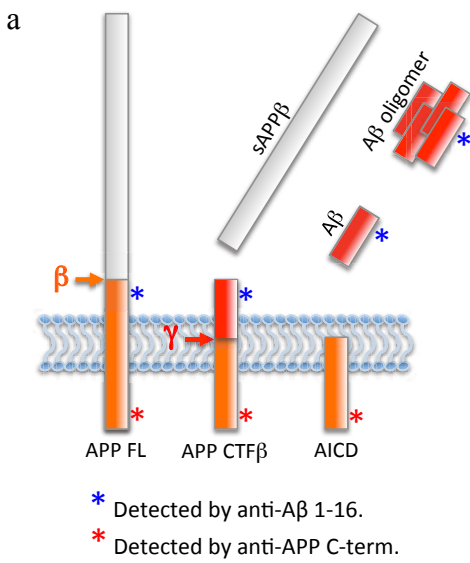
Figure 1. PTP σ is an APP binding partner in the brain. **a-f**, Colocalization of PTP σ (**a**, green) and APP (**b**, red) in hippocampal CA1 neurons of adult rat is shown by confocal imaging. Nuclei of CA1 neurons are stained with DAPI (**c**, blue). **d**, Merge of three channels. Scale bar, 50 μ m. **e**, Zoom-in image of the soma layer in **d**. Arrows, intensive colocalization of PTP σ and APP in the initial segments of apical dendrites; arrow heads, punctates of colocalization in the perinuclear regions. Scale bar, 20 μ m. **f**, Zoom-in image of the very fine grained punctates in the axonal compartment in **d**. Arrows points to the colocalization of PTP σ and APP in axons projecting perpendicular to the focal plane. Scale bar, 10 μ m. **g**, Schematic diagram of PTP σ expressed on cell surface as a two-subunit complex. PTP σ is post-translationally processed into an extracellular domain (ECD) and a transmembrane-intracellular domain (ICD). These two subunits associate with each other through noncovalent bond. Ig-like, immunoglobulin-like domains; FNIII-like, fibronectin III-like domains; D1 and D2, two phosphatase domains. **h, i**, Co-immunoprecipitation (co-IP) of PTP σ and APP from mouse forebrain lysates. Left panels, expression of PTP σ and APP in mouse forebrains. Right panels, IP using an antibody specific for the C-terminus (C-term) of APP. Full length APP (APP FL) is detected by anti-APP C-term antibody. **h**, PTP σ co-IP with APP from forebrain lysates of wild type but not PTP σ -deficient mice (Balb/c background), detected by an antibody against PTP σ -ECD. **i**, PTP σ co-IP with APP from forebrain lysates of wild type but not APP knockout mice (B6 background), detected by an antibody against PTP σ -ICD. Dotted lines in **i** indicate lanes on the same western blot exposure that were moved adjacent to each other. Images shown are representatives of at least three independent experiments.

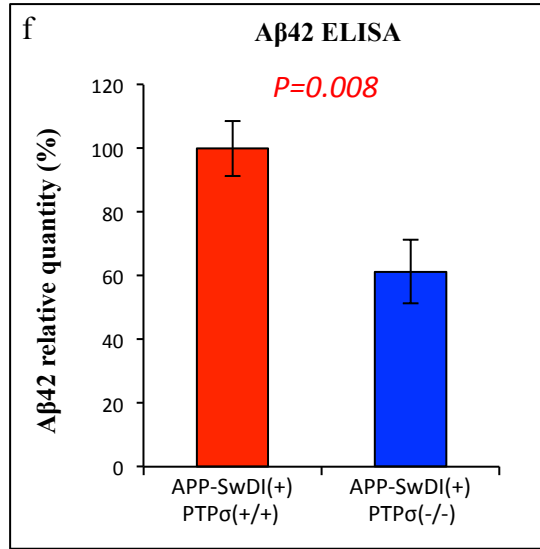
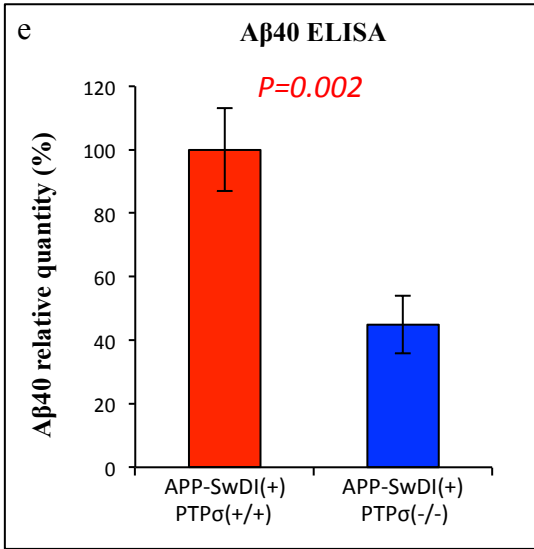
Extended Data Figure 1. Molecular complex of PTP σ and APP in brains of various rodent species.



Extended Data Figure 1. Molecular complex of PTP σ and APP in brains of various rodent species. **a, b**, Co-immunoprecipitation using an anti-APP antibody specific for amino acid residues 1-16 of mouse A β (clone M3.2). PTP σ and APP binding interaction is detected in forebrains of Balb/c (**a**) and B6 (**b**) mice. **c**, PTP σ co-immunoprecipitates with APP from rat forebrain lysates using an antibody specific for the C-terminus of APP. Images shown are representatives of at least three independent experiments.

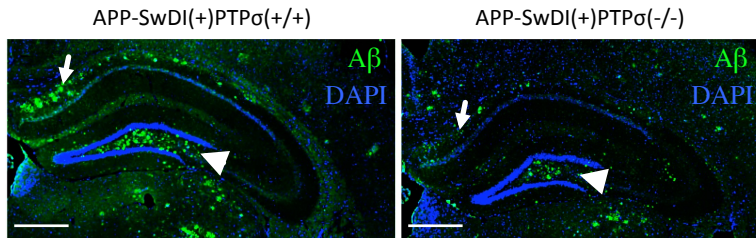
Figure 2. Genetic depletion of PTP σ reduces β -amyloidogenic products of APP.





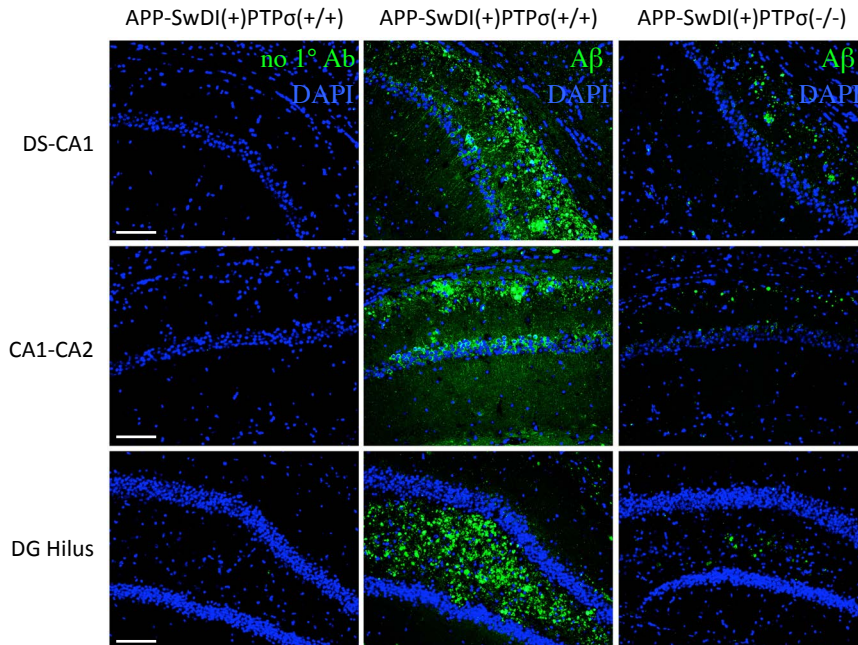
g

Anti-A β antibody 6E10 detecting A β residues 1-16



h

No primary antibody Anti-A β antibody 4G8 detecting A β residues 17-24



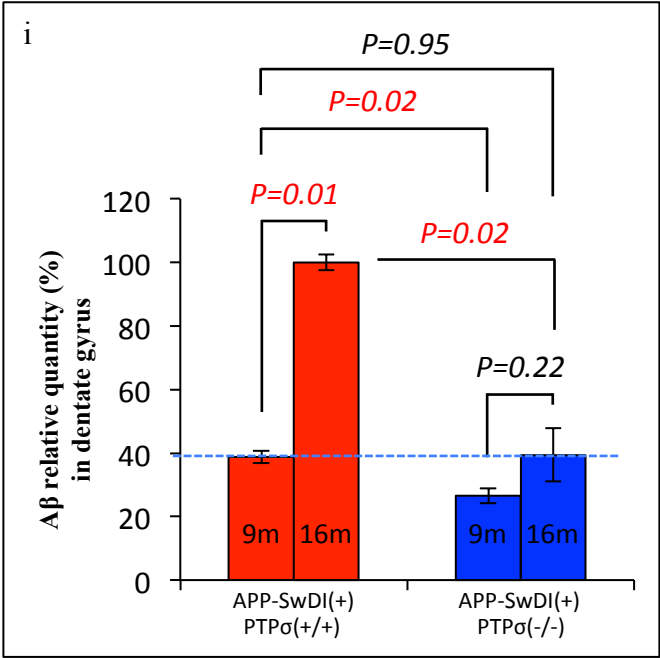
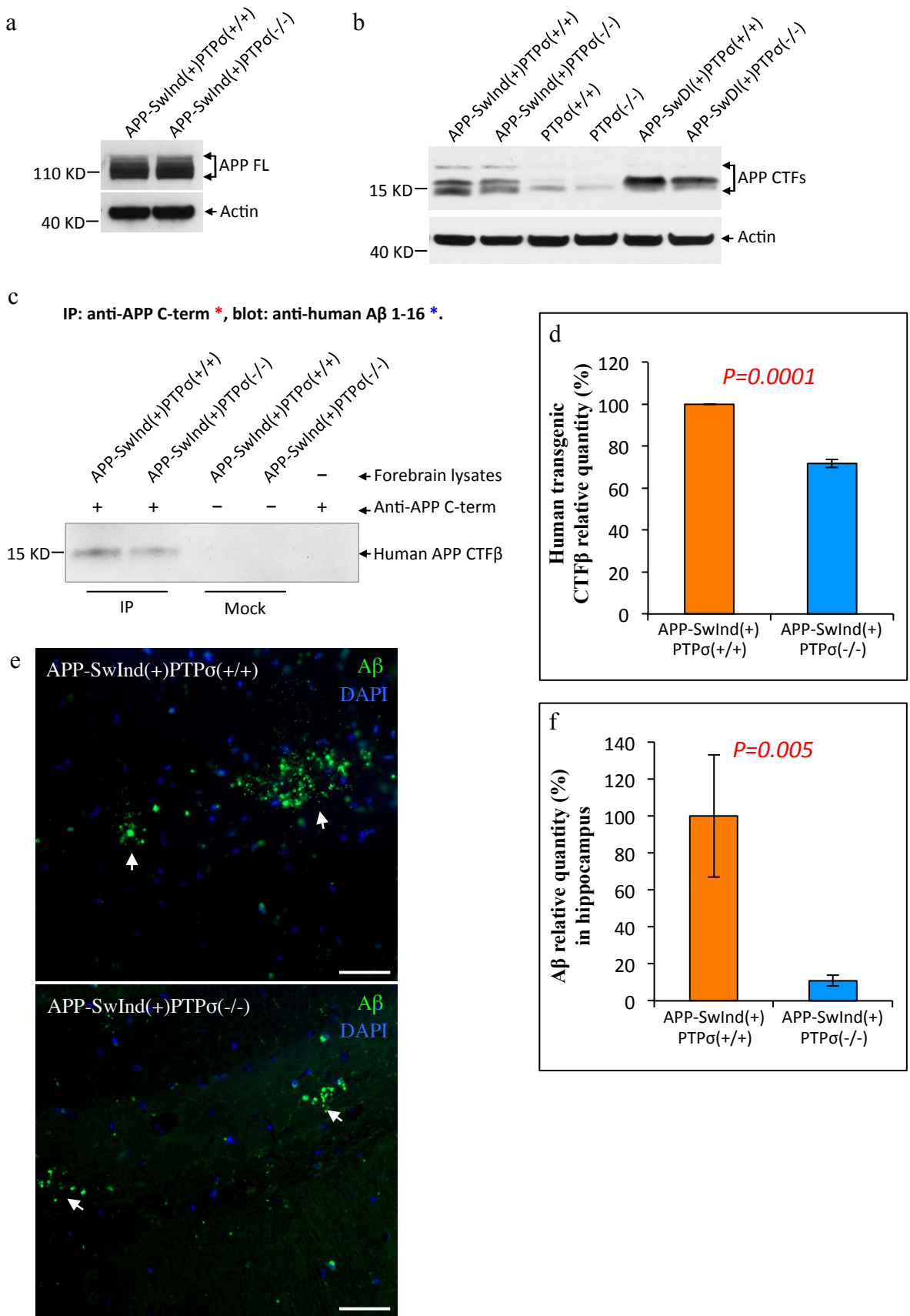


Figure 2. Genetic depletion of PTP σ reduces β -amyloidogenic products of APP. **a**, Schematic diagram showing amyloidogenic processing of APP by the β - and γ -secretases. Full length APP (APP FL) is cleaved by β -secretase into soluble N-terminal (sAPP β) and C-terminal (CTF β) fragments. APP CTF β can be further processed by γ -secretase into a C-terminal intracellular domain (AICD) and an A β peptide. Aggregation of A β is a definitive pathology hallmark of AD. **b**, PTP σ deficiency reduces the level of an APP CTF at about 15 KD in mouse forebrain lysates, without affecting the expression of APP FL. Antibody against the C-terminus of APP recognizes APP FL and CTFs of both mouse and human origins. **c** and **d**, The 15 KD APP CTF is identified as CTF β by immunoprecipitation (IP) followed with western blot analysis, using a pair of antibodies as marked in the diagram (**a**). Antibodies against amino acids 1-16 of A β (anti-A β 1-16) detect CTF β but not CTF α , as the epitope is absent in CTF α . **c**, Mouse endogenous CTF β level is reduced in PTP σ -deficient mouse brains. 4 repeated experiments were quantified by densitometry. **d**, Human transgenic CTF β level is reduced in PTP σ -deficient mouse brains harboring human APP-SwDI transgene. 6 repeated experiments were quantified by densitometry. Within each experiment in both **c** and **d**, the value from PTP σ deficient sample was normalized to that from the sample with wild type PTP σ . **e** and **f**, PTP σ deficiency reduces the levels of A β 40 (**e**) and A β 42 (**f**) in TgAPP-SwDI mice as measured by ELISA assays. n=12 for each group. The mean values from PTP σ deficient samples was normalized to that from the samples with wild type PTP σ . **g** and **h**, A β deposition in the hippocampus of 10-month old TgAPP-SwDI mice. A β (green) is detected by immunofluorescent staining using anti-A β antibodies clone 6E10 (**g**) and clone 4G8 (**h**). DAPI staining is shown in blue. PTP σ deficiency significantly decreases A β burden in the brains of TgAPP-SwDI mice. **h**, Upper panels, the stratum oriens layer between dorsal subiculum (DS) and CA1 (also shown with arrows in **g**); middle panels, oriens layer between CA1 and CA2; lower panels, the hilus of dentate gyrus (DG, also shown with arrow heads in **g**). Left column, control staining without primary antibody (no 1 $^\circ$ Ab). No A β signal is detected in non-transgenic mice (data not shown). Scale bars, 500 μ m in **G** and 100 μ m in **h**. Images shown are a representative pair among 5 pairs of age- and sex-matched mice of 9- to 11-month old. **i**, Genetic depletion of PTP σ suppresses the progression of A β pathology in TgAPP-SwDI mice. ImageJ quantification of A β immunofluorescent staining (with 6E10) in DG hilus from 9- and 16-month old TgAPP-SwDI mice. n=3 for each group. Total integrated density of A β in DG hilus was normalized to the area size of the hilus to yield the average intensity as show in the bar graph. Mean value of each group was normalized to that of 16 month old TgAPP-SwDI mice expressing wild type PTP σ . All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

Extended Data Figure 2. Genetic depletion of PTP σ reduces β -amyloidogenic products of APP.



Extended Data Figure 2. Genetic depletion of PTP σ reduces β -amyloidogenic products of APP. a and **b**, Antibody against the C-terminus of APP recognizes full length (FL) and C-terminal fragments (CTFs) of both mouse and human APP. PTP σ deficiency does not affect the expression level of APP FL (**a**), but reduces the level of an APP CTF at about 15 KD in mouse forebrain lysates (**b**). Images shown are representatives of at least three independent experiments. **c**, Human CTF β in the forebrains of APP-SwInd transgenic mice is identified using the method as described in Fig.2d. CTF β is immunoprecipitated by an antibody against the C-terminus of APP and detected by western blot analysis using an antibody against amino acids 1-16 of human A β (6E10), which reacts with CTF β but not CTF α (regions of antibody epitopes are shown in Fig. 2a). **d**, 5 repeated experiments as shown in panel **c** were quantified by densitometry. For each experiment, the value from PTP σ deficient sample was normalized to the value from the sample with wild type PTP σ . **e**, Representative images of A β immunofluorescent staining (with 6E10) in the hippocampus of 15-month old TgAPP-SwInd mice. Arrows point to A β deposits. Scale bars, 50 μ m. **f**, A β immunofluorescent staining in the hippocampus of 15-month old TgAPP-SwInd mice, as shown in panel **e**, was quantified using ImageJ. APP-SwInd(+) $PTP\sigma$ (+/+), n=7; APP-SwInd(+) $PTP\sigma$ (-/-), n=8. The mean value of APP-SwInd(+) $PTP\sigma$ (-/-) samples was normalized to that of APP-SwInd(+) $PTP\sigma$ (+/+) samples. All error bars, SEM. All *p* values, Student's *t* test, 2-tailed.

Figure 3. Lower affinity between BACE1 and APP in PTPσ-deficient brains.

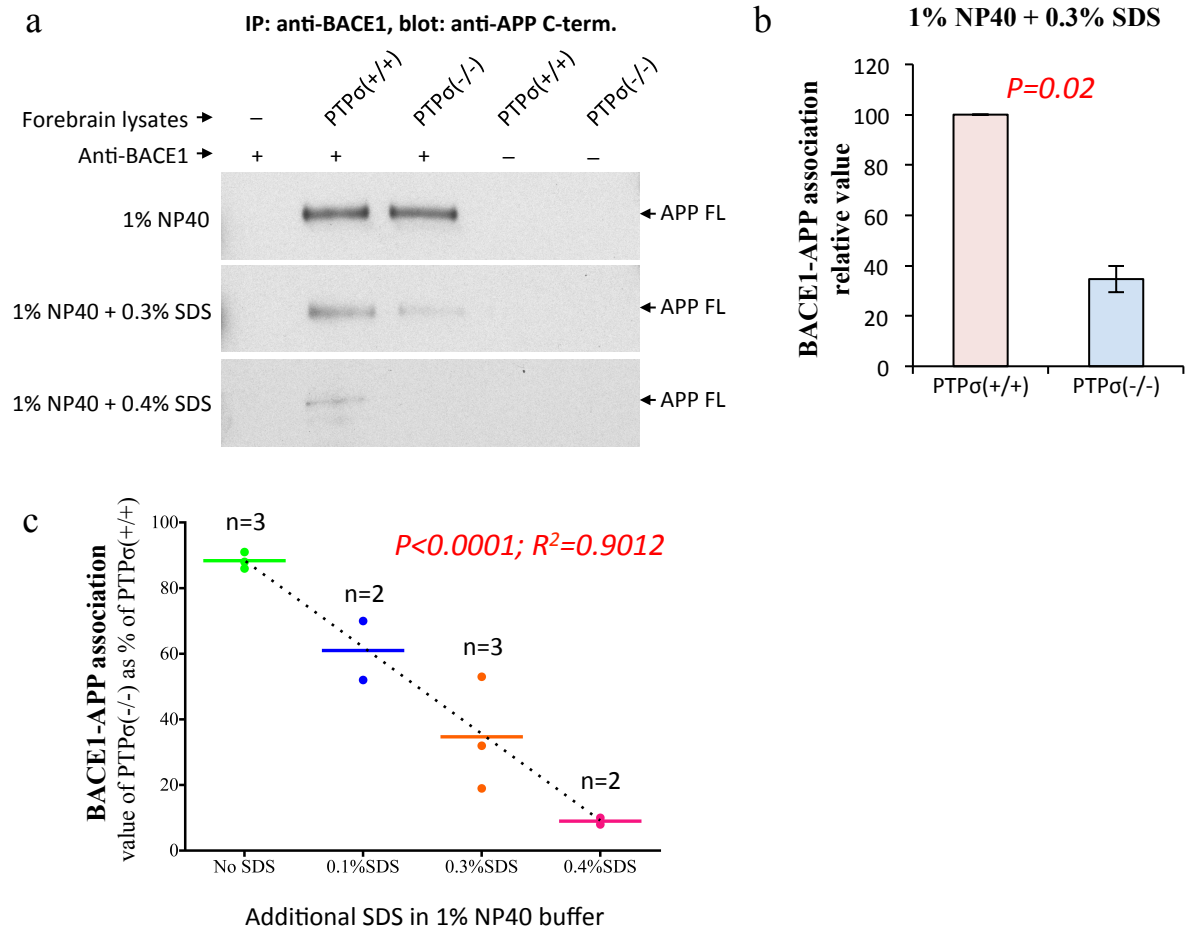


Figure 3. Lower affinity between BACE1 and APP in PTPσ-deficient brains. **a**, Co-immunoprecipitation experiments show nearly equal BACE1-APP association in wild type and PTPσ-deficient mouse brains under mild detergent condition (1% NP40). However, in PTPσ-deficient brains, BACE1-APP association detected by co-immunoprecipitation is more vulnerable to increased detergent stringency as compared to that in wild type brains. Panels of blots show full length APP (APP FL) pulled down with an anti-BACE1 antibody from mouse forebrain lysates. NP40, Nonidet P-40, non-ionic detergent. SDS, Sodium dodecyl sulfate, ionic detergent. **b**, Co-immunoprecipitation under buffer condition with 1% NP40 and 0.3% SDS, as shown in the middle panel of **a**, were repeated three times. Each experiment was quantified by densitometry, and the value from PTPσ-deficient sample was calculated as a percentage of that from the wild type sample (also shown as orange points in **c**). Error bar, SEM. *p* value, Student's *t* test, 2-tailed. **c**, Co-immunoprecipitation experiments were repeated under each detergent condition. The percentage values shown in dots are derived using the same method as in **b**. Bars represent means. Increasingly stringent buffer conditions manifest a lower BACE1-APP affinity in PTPσ-deficient brains. *p* value and R^2 , linear regression.

Figure 4. PTP σ does not generically modulate β - and γ - secretases.

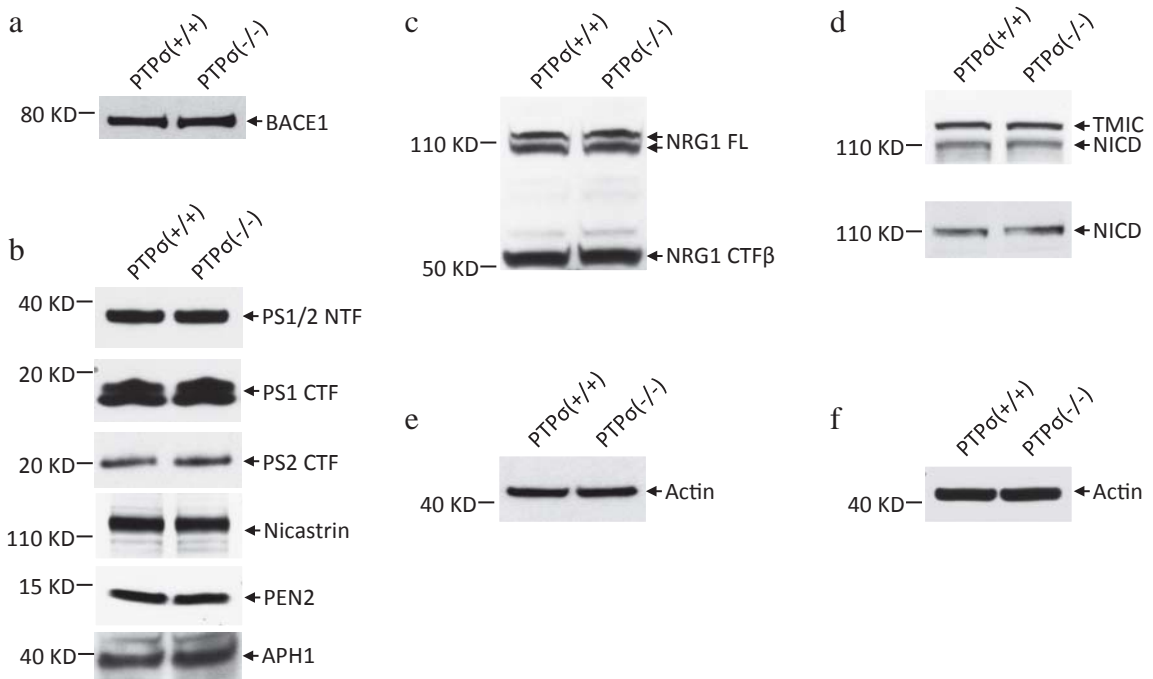
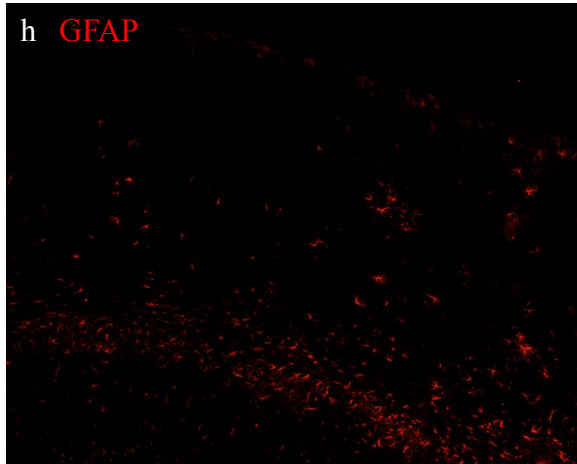
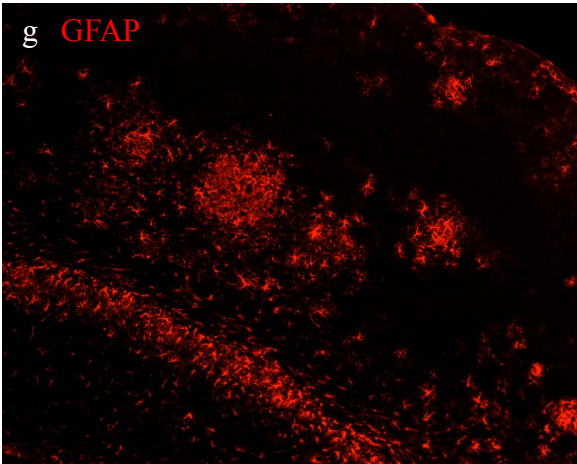
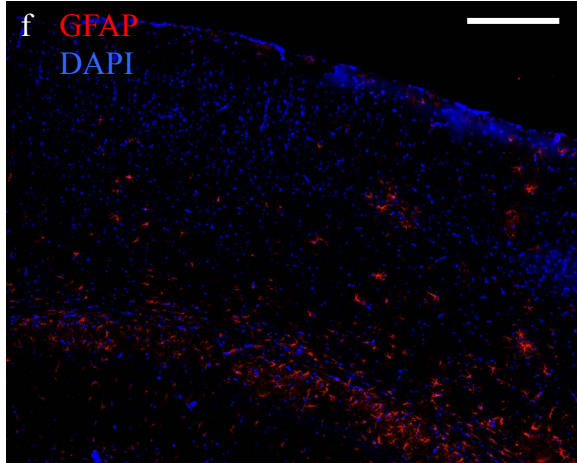
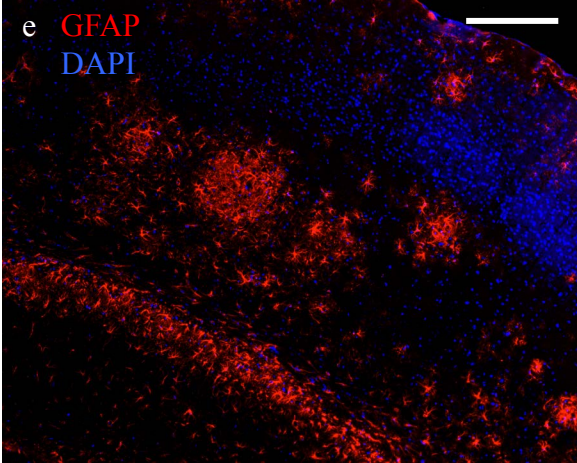
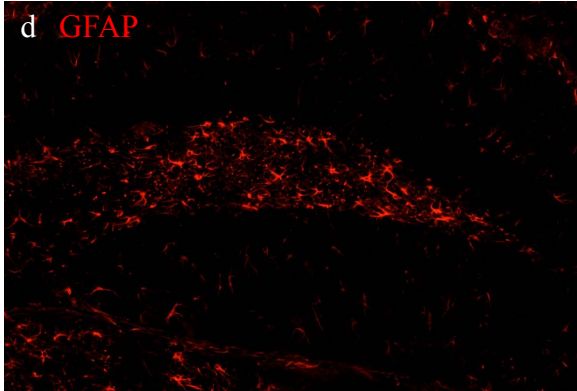
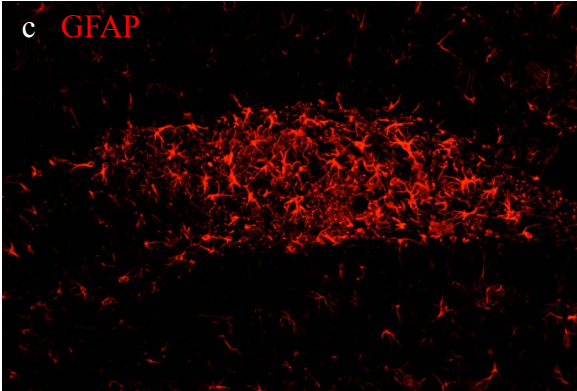
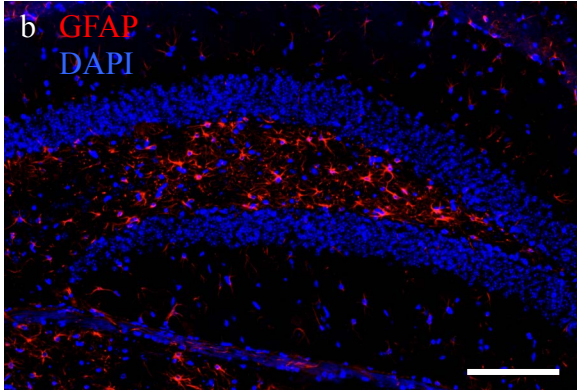
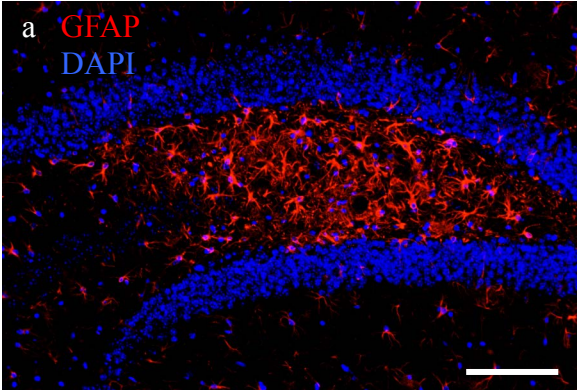


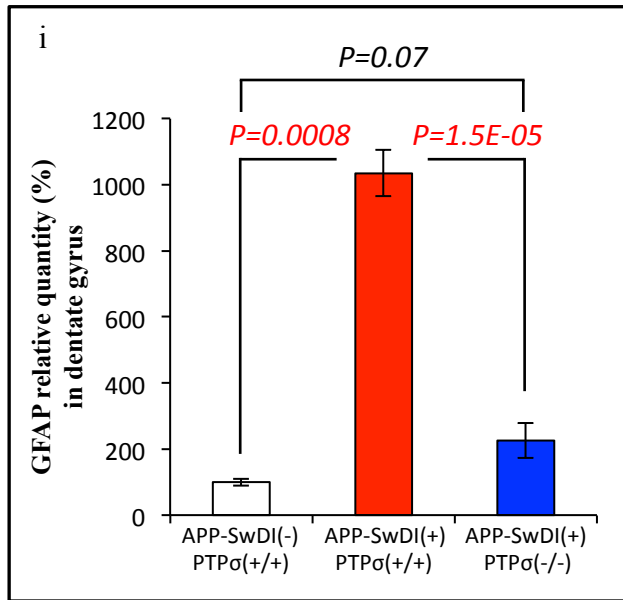
Figure 4. PTP σ does not generically modulate β - and γ - secretases. Neither expression levels of the secretases or their activities on other major substrates are affected by PTP σ depletion. Mouse forebrain lysates with or without PTP σ were analyzed by western blot. **a** and **b**, PTP σ deficiency does not change expression level of BACE1 (**a**) or γ -secretase subunits (**b**). Presenilin1 and 2 (PS1/2) are the catalytic subunits of γ -secretase, which are processed into N-terminal and C-terminal fragments (NTF and CTF) in their mature forms. Nicastrin, Presenilin Enhancer 2 (PEN2), and APH1 are other essential subunits of γ -secretase. **c**, PTP σ deficiency does not change the level of Neuregulin1 (NRG1) CTF β , the C-terminal cleavage product by BACE1. NRG1 FL, full length Neuregulin1. **d**, The level of Notch cleavage product by γ -secretase is not affected by PTP σ deficiency. TMIC, Notch transmembrane/intracellular fragment, which can be cleaved by γ -secretase into a C-terminal intracellular domain NICD (detected by an antibody against Notch C-terminus in the upper panel, and by an antibody specific for γ -secretase cleaved NICD in the lower panel). **e**, Actin loading control for **a** and **c**. **f**, Actin loading control for **b** and **d**. All images shown are representatives of at least three independent experiments. All images shown are representatives of at least three independent experiments.

Extended Data Figure 3. PTP σ deficiency attenuates reactive astrogliosis in APP transgenic mice.

APP-SwDI(+)/PTP σ (+/+)

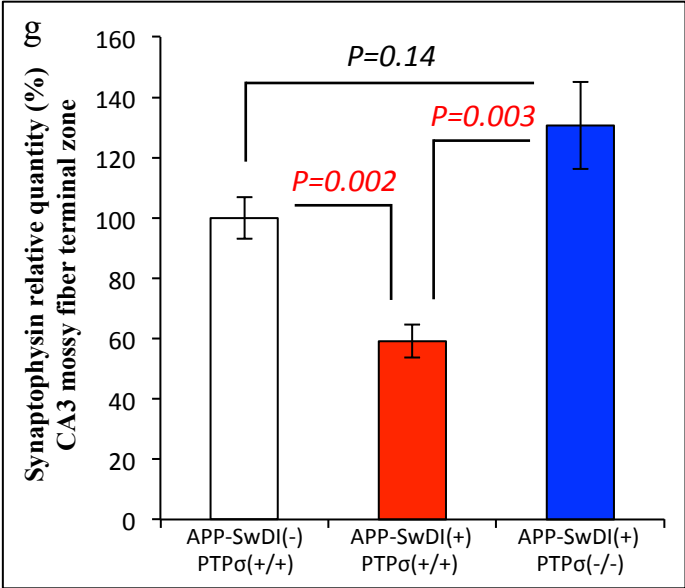
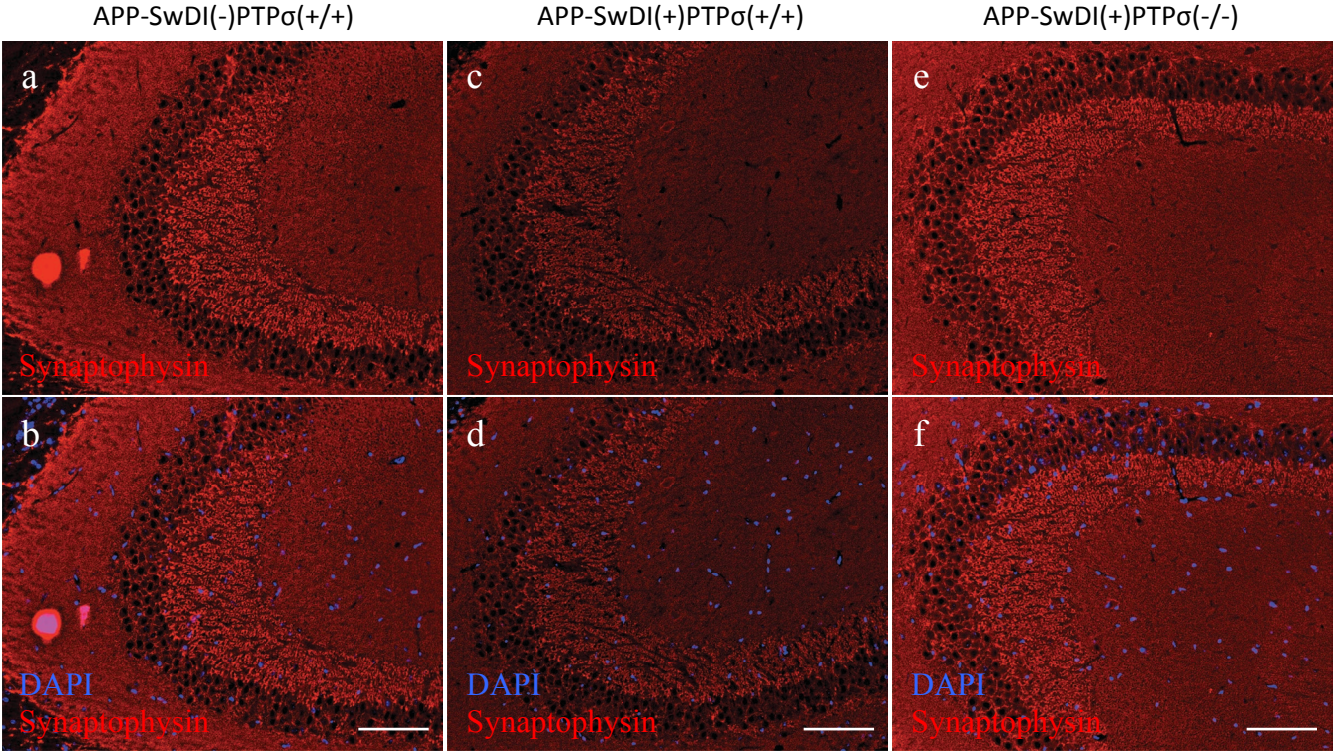
APP-SwDI(+)/PTP σ (-/-)





Extended Data Figure 3. PTPσ deficiency attenuates reactive astrogliosis in APP transgenic mice. Expression level of GFAP, a marker of reactive astrocytes, is suppressed in the brains of TgAPP-SwDI mice by PTPσ depletion. Representative images show GFAP (red) and DAPI staining of nuclei (blue) in the brains of 9-month old TgAPP-SwDI mice. **a-d**, Dentate gyrus (DG) of the hippocampus; scale bars, 100 μm. **e-h**, Primary somatosensory cortex; scale bars, 200 μm. **i**, ImageJ quantification of GFAP level in DG hilus from TgAPP-SwDI mice aged between 9 to 11 months. APP-SwDI(-)PTPσ(+/+), non-transgenic wild type littermates (expressing PTPσ but not the human APP transgene). Total integrated density of GFAP in DG hilus was normalized to the area size of the hilus to yield average intensity as shown in the bar graph. Mean value of each group was normalized to that of APP-SwDI(-)PTPσ(+/+ mice (image not shown). APP-SwDI(-)PTPσ(+/+), n=4; APP-SwDI(+), PTPσ(+/+), n=4; APP-SwDI(+), PTPσ(-/-), n=6. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

Extended Data Figure 4. PTPσ deficiency protects APP transgenic mice from synaptic loss.



Extended Data Figure 4. PTP σ deficiency protects APP transgenic mice from synaptic loss.

Representative images show immunofluorescent staining of presynaptic marker Synaptophysin in the mossy fiber terminal zone of CA3 region. **a-f**, Synaptophysin, red; DAPI, blue. Scale bars, 100 μ m. **g**, ImageJ quantification of Synaptophysin expression level in CA3 mossy fiber terminal zone from mice aged between 9 to 11 months. Total integrated density of Synaptophysin in CA3 mossy fiber terminal zone was normalized to the area size to yield average intensity as shown in the bar graph. Mean value of each group was normalized to that of wild type APP-SwDI(-)PTP σ (+/+) mice. APP-SwDI(-)PTP σ (+/+), n=4; APP-SwDI(+)PTP σ (+/+), n=6; APP-SwDI(+)PTP σ (-/-), n=6. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

Figure 5. PTP σ deficiency mitigates Tau pathology in TgAPP-SwDI mice.

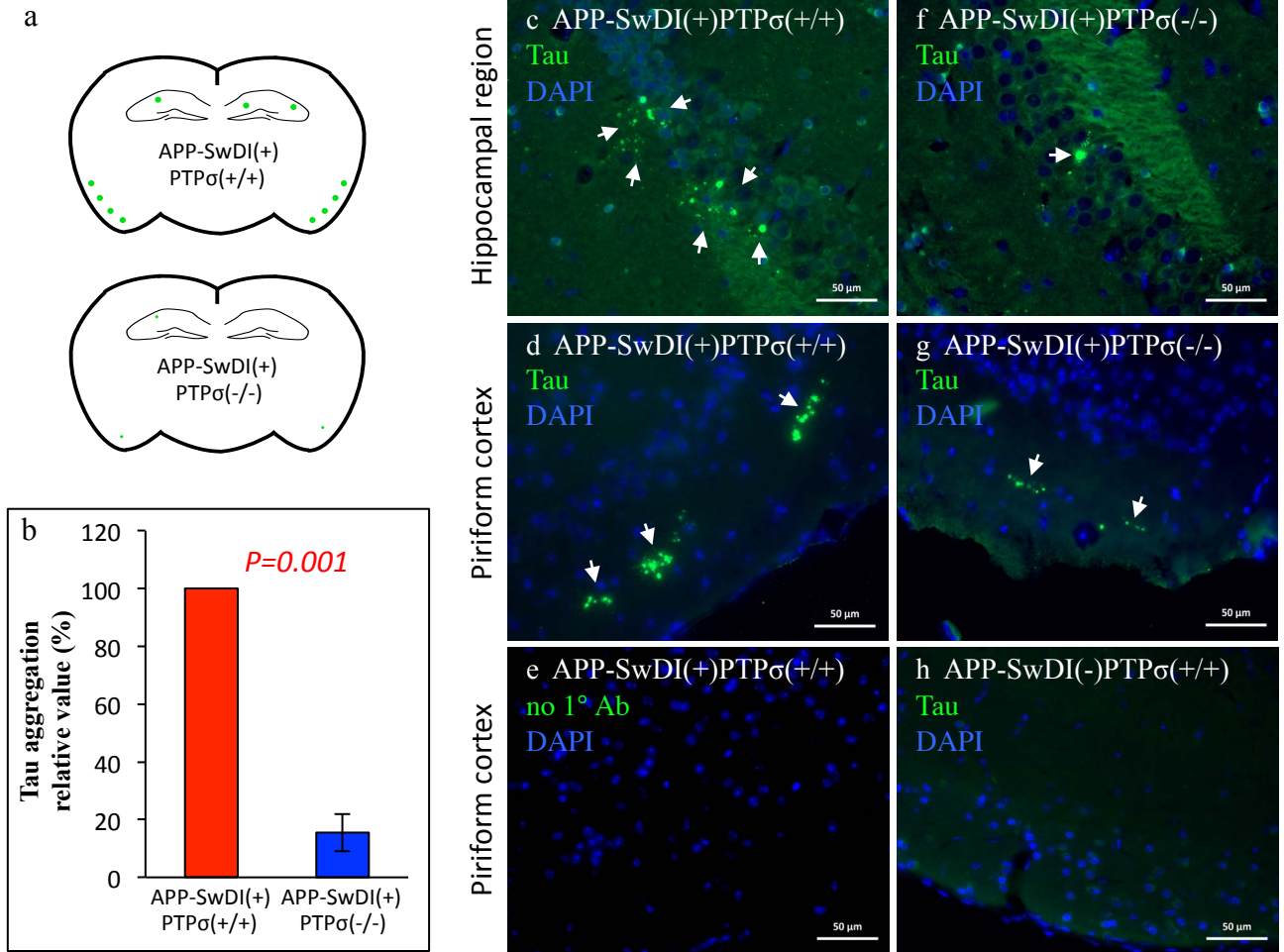
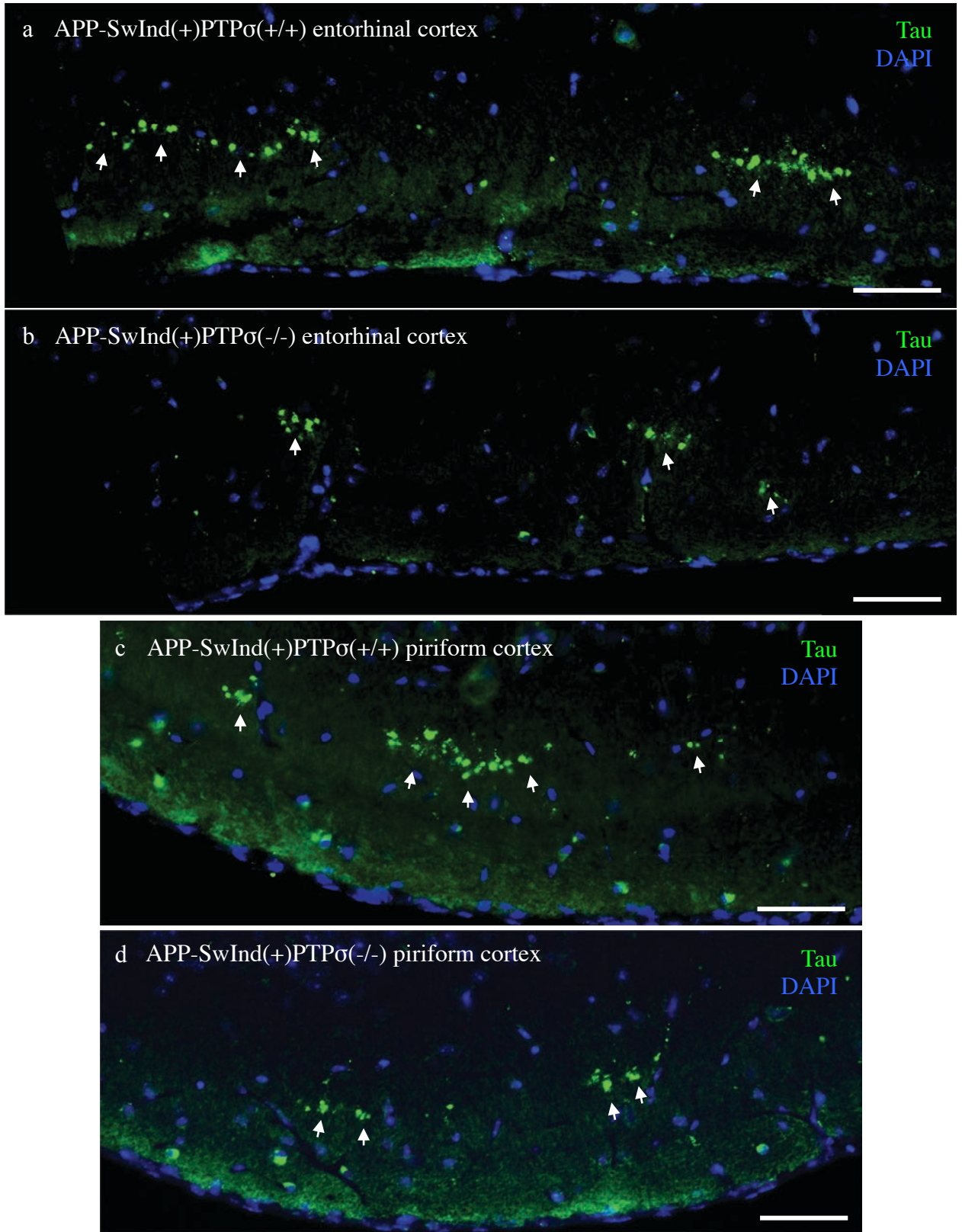
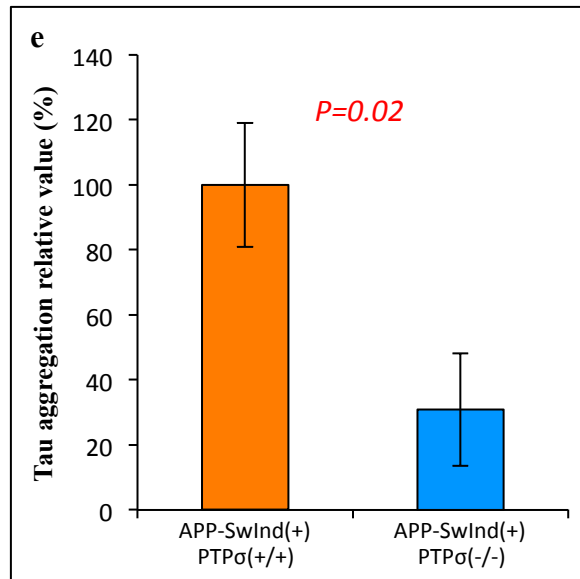


Figure 5. PTP σ deficiency mitigates Tau pathology in TgAPP-SwDI mice. **a**, Schematic diagram depicting distribution pattern of Tau aggregation (green) detected by immunofluorescent staining using an anti-Tau antibody, in brains of 9 to 11 month-old TgAPP-SwDI transgenic mice. Aggregated Tau is found most prominently in the molecular layer of piriform and entorhinal cortex, and occasionally in hippocampal regions in APP-SwDI(+) $PTP\sigma$ (+/+) mice. **b**, PTP σ deficiency diminishes Tau aggregation. Bar graph shows quantification of Tau aggregation in coronal brain sections from 4 pairs of age- and sex-matched APP-SwDI(+) $PTP\sigma$ (+/+) and APP-SwDI(+) $PTP\sigma$ (-/-) mice of 9 to 11 month-old. For each pair, the value from APP-SwDI(+) $PTP\sigma$ (-/-) sample is normalized to the value from APP-SwDI(+) $PTP\sigma$ (+/+) sample. *p* value, Student's *t* test, 2-tailed. Error bar, SEM. **c**, **d**, Representative images of many areas with Tau aggregation in APP-SwDI(+) $PTP\sigma$ (+/+) brains. **f**, **g**, Representative images of a few areas with Tau aggregation in age-matched APP-SwDI(+) $PTP\sigma$ (-/-) brains. **c** and **f**, Hippocampal regions. **d-h**, Piriform cortex. **e**, Staining of a section adjacent to **d**, but without primary antibody (no 1 $^{\circ}$ Ab). **h**, no Tau aggregates are detected in aged-matched non-transgenic wild type littermates (expressing PTP σ but not the human APP transgene). Tau, green; DAPI, blue. Arrows points to Tau aggregates. Scale bars, 50 μ m.

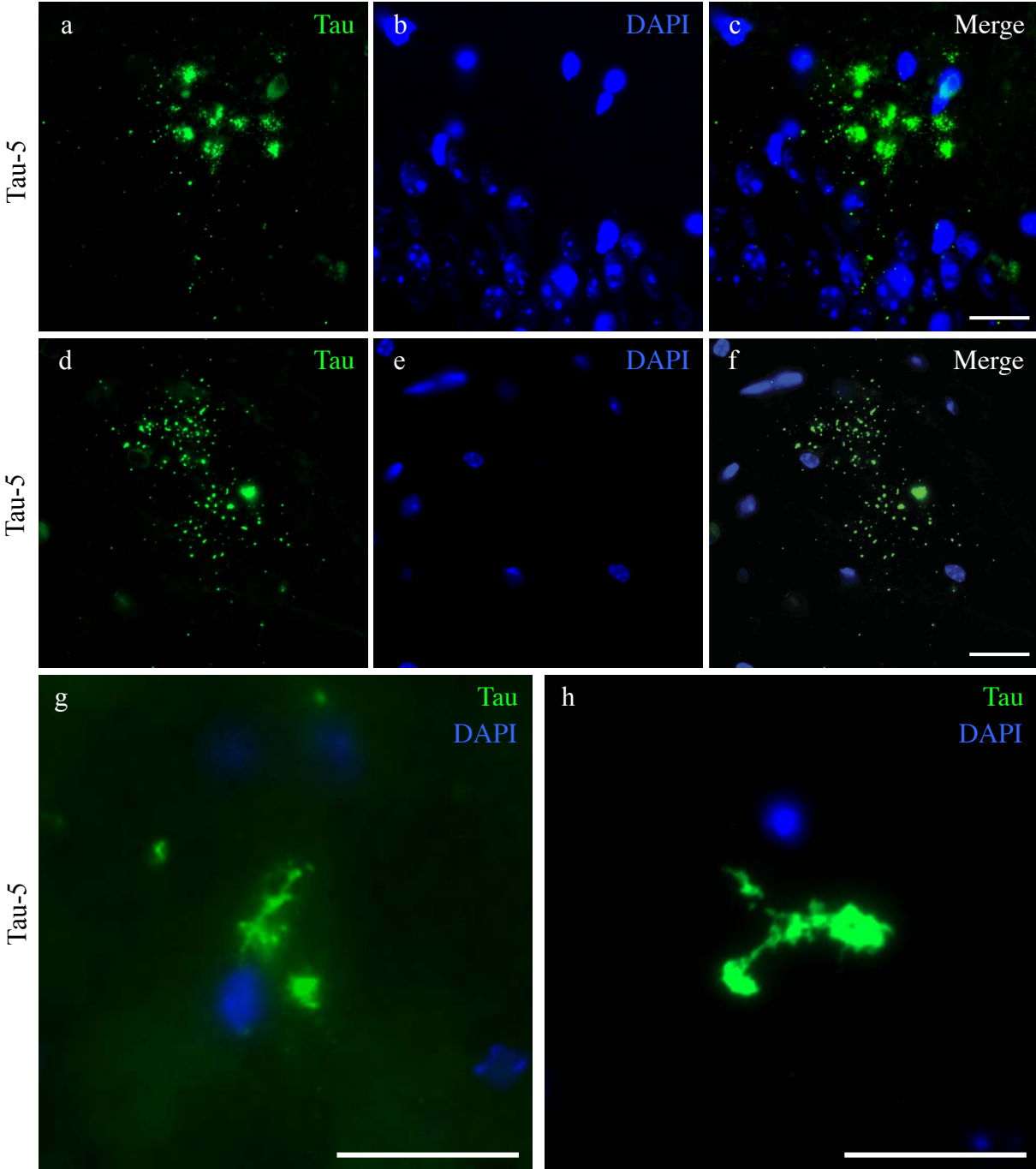
Extended Data Figure 5. PTP σ deficiency mitigates Tau pathology in TgAPP-SwInd mice.

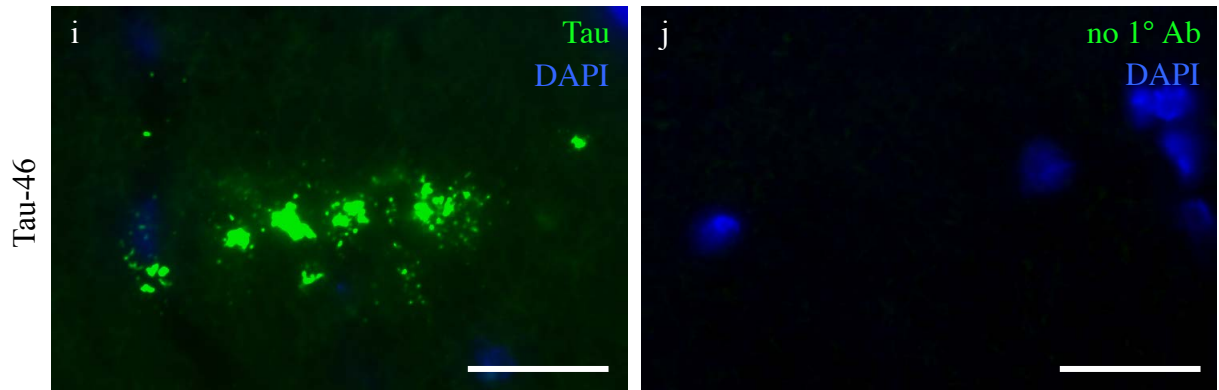




Extended Data Figure 5. PTPσ deficiency mitigates Tau pathology in TgAPP-SwInd mice. Tau aggregation (green) is detected by immunofluorescent staining, using an anti-Tau antibody (as in Fig. 5) in the brains of 15 month-old TgAPP-SwInd transgenic mice. Aggregated Tau is found most prominently in the molecular layer of the entorhinal (a, b) and piriform cortex (c, d), and occasionally in the hippocampal regions (images not shown). e, PTPσ deficiency diminishes Tau aggregation as quantified in coronal brain sections from 15 month-old APP-SwInd(+)PTPσ(+/+) (n=7) and APP-SwInd(+)PTPσ(-/-) mice (n=8). The mean value of APP-SwInd(+)PTPσ(-/-) samples is normalized to that of APP-SwInd(+)PTPσ(+/+). *p* value, Student's *t* test, 2-tailed. Error bars, SEM. Tau, green; DAPI, blue. Arrows points to Tau aggregates. Scale bars, 50 μm.

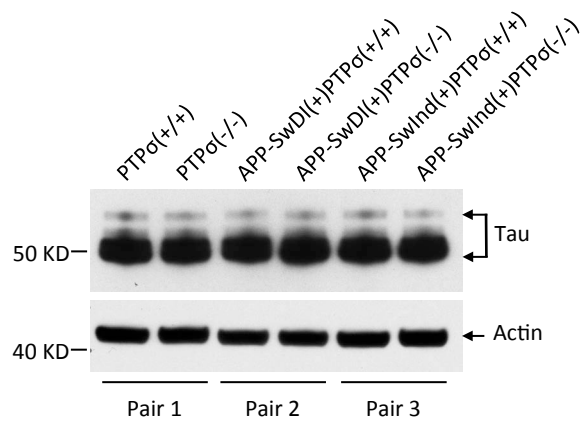
Extended Data Figure 6. Morphology of Tau aggregates found in APP transgenic brains.





Extended Data Figure 6. Morphology of Tau aggregates found in APP transgenic brains. a-h, Tau aggregation (green) is detected by immunofluorescent staining, using an anti-Tau antibody (Tau-5) against the proline-rich domain of Tau (same as in Fig. 5 and Fig. S5). Tau aggregates in TgAPP-SwDI and TgAPP-SwInd brains show similar morphologies. **a-f,** Many of the Tau aggregates are found in punctate shapes, likely as part of cell debris, in areas that are free of nuclei staining. **g, h,** Occasionally the aggregates are found in fibrillary structures, probably in degenerated cells before disassembling. **i,** An additional anti-Tau antibody (Tau-46), which recognizes the C-terminus of Tau, detects Tau aggregation in the same pattern as Tau-5. **j,** Image of staining without primary antibody at the same location of the Tau aggregates in the section adjacent to **i**. Both these antibodies recognize Tau regardless of its phosphorylation status. Tau, green; DAPI, blue. All scale bars, 20 μ m.

Extended Data Figure 7. Tau expression is not affected by PTP σ or human APP transgenes.



Extended Data Figure 7. Tau expression is not affected by PTP σ or human APP transgenes.

Upper panel, total Tau level in brain homogenates. Lower panel, Actin as loading control. Tau protein expression level is not changed by genetic depletion of PTP σ or expression of mutated human APP transgenes. All mice are older than 1 year, and mice in each pair are age- and sex matched. Images shown are representatives of three independent experiments.

Figure 6. PTP σ deficiency rescues behavioral deficits in TgAPP-SwDI mice.

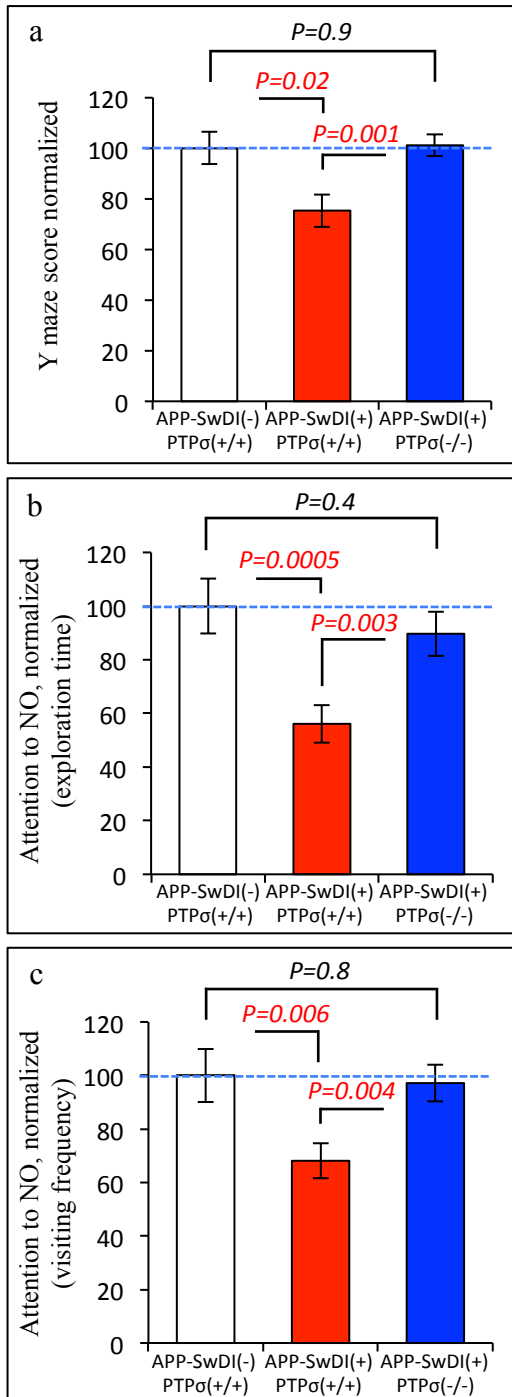


Figure 6. PTP σ deficiency rescues behavioral deficits in TgAPP-SwDI mice. **a**, In the Y-maze assay,

performance of spatial navigation is scored by the percentage of spontaneous alternations among total arm entries. Values are normalized to that of non-transgenic wild type APP-SwDI(-)PTP σ (+/+) mice within the colony. Compared to non-transgenic wild type mice, APP-SwDI(+)PTP σ (+/+) mice show deficit of short-term spatial memory, which is rescued by genetic depletion of PTP σ in APP-SwDI(+)PTP σ (-/-) mice.

APP-SwDI(-)PTP σ (+/+), n=23 (18 females and 5 males); APP-SwDI(+)PTP σ (+/+), n=52 (30 females and 22 males); APP-SwDI(+)PTP σ (-/-), n=35 (22 females and 13 males). Ages of all genotype groups are similarly distributed between 4 and 11 months. **b, c**, Novel object test. NO, novel object. FO, familiar object. Attention to NO is measured by the ratio of NO exploration to total object exploration (NO+FO) in terms of exploration

time (**b**) and visiting frequency (**c**). Values are

normalized to that of non-transgenic wild type mice.

APP-SwDI(+)PTP σ (+/+) mice showed decreased interest in NO compared to wild type APP-

SwDI(-)PTP σ (+/+) mice. The deficit is reversed by

PTP σ depletion in APP-SwDI(+)PTP σ (-/-) mice. APP-

SwDI(-)PTP σ (+/+), n=28 (19 females and 9 males);

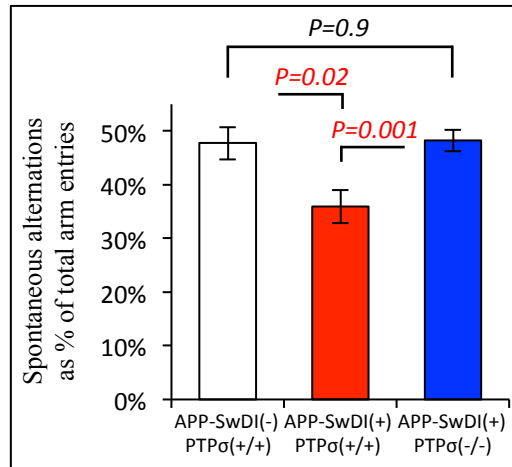
APP-SwDI(+)PTP σ (+/+), n=46 (32 females and 14

males); APP-SwDI(+)PTP σ (-/-), n=29 (21 females and

8 males). Ages of all groups are similarly distributed

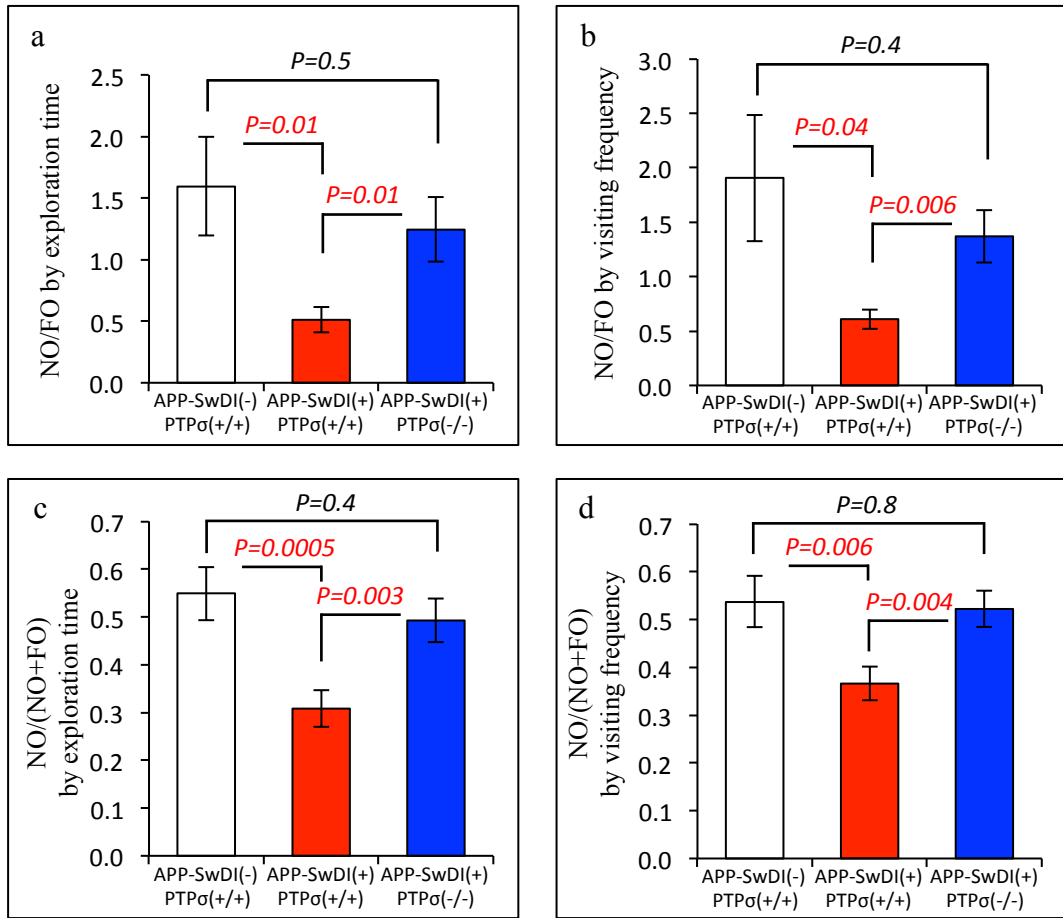
between 4 and 11 months. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

Extended Data Figure 8. PTP σ deficiency restores short-term spatial memory in TgAPP-SwDI mice.



Extended Data Figure 8. PTP σ deficiency restores short-term spatial memory in TgAPP-SwDI mice. In the Y-maze assay, performance of spatial navigation is scored by the percentage of spontaneous alternations among total arm entries. The raw values shown here are before normalization in Fig. 6a. Compared to non-transgenic wild type APP-SwDI(-)PTP σ (+/+)mice, APP-SwDI(+)PTP σ (+/+) mice show deficit of short-term spatial memory, which is rescued by genetic depletion of PTP σ . APP-SwDI(-)PTP σ (+/+), n=23 (18 females and 5 males); APP-SwDI(+)PTP σ (+/+), n=52 (30 females and 22 males); APP-SwDI(+)PTP σ (-/-), n=35 (22 females and 13 males). Ages of all genotype groups are similarly distributed between 4 and 11 months. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

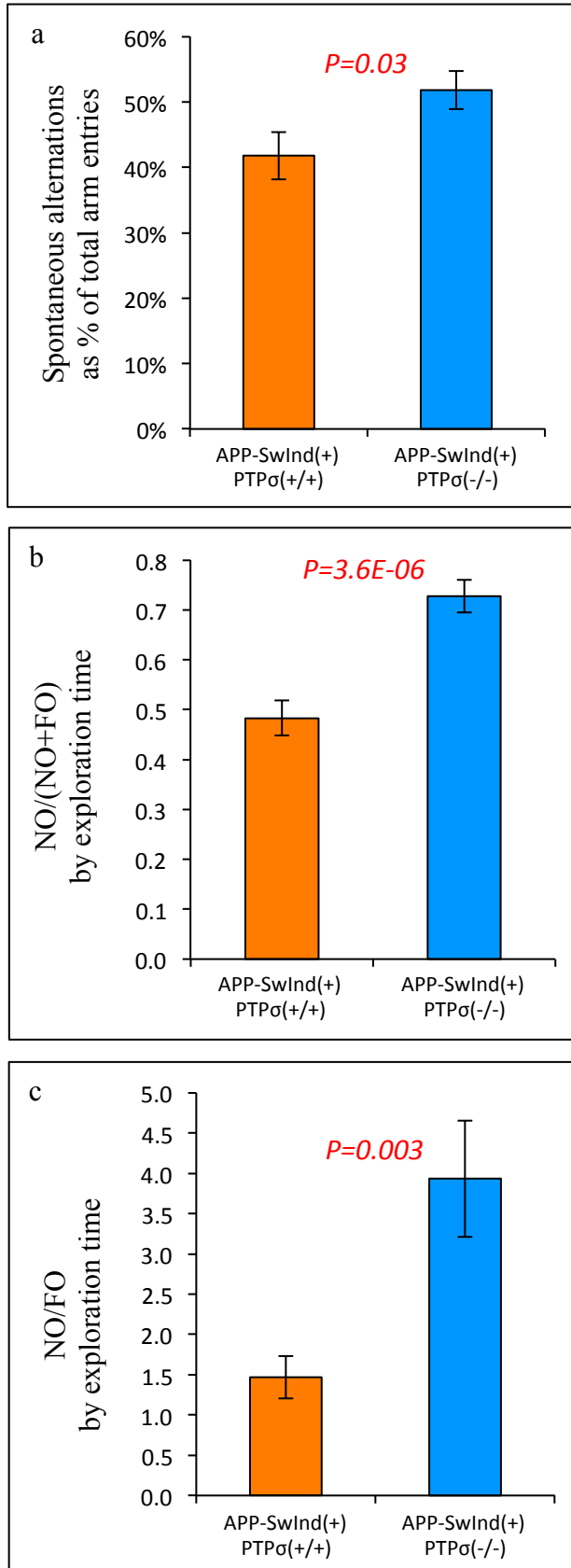
Extended Data Figure 9. PTPσ deficiency enhances novelty exploration by TgAPP-SwDI mice.



Extended Data Figure 9. PTP σ deficiency enhances novelty exploration by TgAPP-SwDI mice.

NO, novel object. FO, familiar object. **a** and **b**, In novel object test, NO preference is measured by the ratio between NO and FO exploration, where $NO/FO > 1$ indicates preference for NO. **c** and **d**, Attention to NO is additionally measured by the discrimination index, $NO/(NO+FO)$, the ratio of NO exploration to total object exploration ($NO+FO$). The raw values shown here in **c** and **d** are before normalization in Fig. 6b and c. Mice of this colony show a low baseline of the $NO/(NO+FO)$ discrimination index, likely inherited from their parental Balb/c line. For non-transgenic wild type APP-SwDI(-)PTP σ (+/+) mice, the discrimination index is slightly above 0.5 (chance value), similar to what was previously reported for the Balb/c wild type mice ²⁷. Thus, a sole measurement of the discrimination index may not reveal the preference for NO as does the NO/FO ratio. Although not as sensitive in measuring object preference, the $NO/(NO+FO)$ index is most commonly used as it provides a normalization of the NO exploration to total object exploration activity. While each has its own advantage and shortcoming, both NO/FO and NO/NO+FO measurements consistently show that the expression of TgAPP-SwDI gene leads to a deficit in attention to the NO, whereas genetic depletion of PTP σ restores novelty exploration to a level close to that of non-transgenic wild type mice. **a** and **c**, measurements in terms of exploration time. **b** and **d**, measurements in terms of visiting frequency. APP-SwDI(-)PTP σ (+/+), n=28 (19 females and 9 males); APP-SwDI(+)PTP σ (+/+), n=46 (32 females and 14 males); APP-SwDI(+)PTP σ (-/-), n=29 (21 females and 8 males). Ages of all groups are similarly distributed between 4 and 11 months. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.

Extended Data Figure 10. PTP σ deficiency improves behavioral performance of TgAPP-SwInd mice.



Extended Data Figure 10. PTP σ deficiency improves behavioral performance of TgAPP-SwInd mice. a,

Performance of spatial navigation is scored by the percentage of spontaneous alternations among total arm entries in the Y-maze assay. Compared to APP-SwInd(+)PTP σ (+/+) mice, APP-SwInd(+)PTP σ (-/-) mice showed improved short-term spatial memory. APP-

SwInd(+)PTP σ (+/+), n=40 (20 females and 20 males); APP-SwInd(+)PTP σ (-/-), n=18 (9 females and 9 males). Ages of both genotype groups are similarly distributed between 4 and 11 months. **b, c**, Novel object test. NO, novel object. FO, familiar object. NO preference is measured by the ratio of NO exploration time to total object exploration time (**b**) and the ratio of NO exploration time to FO exploration time (**c**). PTP σ depletion significantly improves novelty preference in these transgenic mice. APP-

SwInd(+)PTP σ (+/+), n=43 (21 females and 22 males); APP-SwInd(+)PTP σ (-/-), n=24 (10 females and 14 males). Ages of both groups are similarly distributed between 5 and 15 months. All *p* values, Student's *t* test, 2-tailed. Error bars, SEM.