Do cortical plasticity mechanisms differ between males and females?

by James Dachtler[1] and Kevin Fox[2]

[1]Department of Psychology, Durham University, South Road, Durham, DH1 3LE, UK.

[2]School of Biosciences, Cardiff University, Museum Avenue, Cardiff, CF10 3AX, UK.

Address for correspondence: Prof. Kevin Fox, School of Biosciences, Cardiff University, Museum Avenue, Cardiff, CF10 3AX, UK. foxkd@cardiff.ac.uk, telephone: +44 (0)29 2087 4632, fax: +44 (0)29 2087 4744.

Running Title: Sex differences in cortical plasticity.

Significance Statement: In this review we explore the question of whether male and female brains differ at the synaptic level. The significance of evaluating this question is two-fold; first, because plasticity is important in memory disorders, psychiatric conditions such as autism and schizophrenia and for recovery from stroke, we need to know whether therapies for these conditions should stratified by biological sex. Second, reviewing the evidence will help those researchers studying plasticity and memory conditions to plan whether sex should be included as a variable in the experimental design.

Authors contributions: JD and KF both wrote the review, JD conducted the original research on autism and NOS1 as cited, KF conceived and designed experiments for the NOS1 experiments as cited.

Abstract

The difference between male and female behaviour and male and female susceptibility to a number of neuropsychiatric conditions is not controversial. From a biological perspective one might expect to see at least some of these differences underpinned by identifiable physical differences in the brain. In this review, we focus on evidence that plasticity mechanisms differ between males and females and ask at what scale of organisation the differences might exist, at the systems level, the circuits level or the synaptic level. Emerging evidence suggests that plasticity differences may extend to the scale of synaptic mechanisms. In particular, the CaMKK, NOS1 and oestrogen receptor pathways show sexual dimorphisms with implication for plasticity in the hippocampus and cerebral cortex.

Introduction

The difference between male and female animals is unmistakable on the outside and from a biological perspective one might expect to find many differences on the inside too. It is not controversial that male and female behaviour is different both in humans and less sentient animals, and highly likely that many of those behavioural differences can be attributed to differences in brain structure. Over what spatial scale might such differences occur? At the systems level, male and female brains differ in size (Goldstein et al., 2001; Gur et al., 2012) and connectivity (Ingalhalikar et al., 2014); the hypothalamic structures and circuits are different due to their roles in reproduction and hormone regulation (Scott et al., 2015; Simerly, 2002), and sex hormones are known to have effects on the function and development of neuronal circuits (Dohler et al., 1986; Scharfman and MacLusky, 2006). But is it also possible that differences between the sexes exist on a finer scale, perhaps down to the level of individual synapses and the molecular mechanisms that are involved in synaptic plasticity.

To date, sex differences remain relatively under-explored in Neuroscience. The relative lack of exploration may partly rest on practical reasons such as the belief that biological results are more variable in females than in males, which leads to experimental designs employing only male animals. In a similar vein, since at least twice as many animals would be required to test for a difference in the role of a particular variable between male and female mice, the financial cost of so doing is twice as high and requires twice the time and the subsequent cost may discourage the practice. In addition to errors of commission there may also be errors of omission. Pogun, noted as recently as 2001 that

"Although males and females are unmistakably different, the recognition of sex as a key variable in science and medicine is considered a revolution in some circles. Sex differences transcend reproductive functions, are evident in the structural and functional organization of the brain, and are reflected in group differences in cognitive abilities and behavior." (Pogun, 2001).

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Indeed, given the finding in mouse studies that genetic background can have a large effect on learning, plasticity and behaviour (Nguyen et al., 2000; Ranson et al., 2013), it would almost seem inevitable that a far less subtle genetic difference between animals such as an entire chromosome difference would have some effect. In this article we explore some of the evidence for differences in plasticity at the cellular level and how those differences might impact on learning and memory at the behavioural level. Particular attention is given to the role of oestrogen in structural plasticity of dendritic spines and the differing degrees to which nitric oxide synthase (NOS) plays a role in synaptic potentiation in males versus females. Given recent findings showing that synaptic proteins are major factors in mental health conditions (Hall et al., 2015; Reichelt et al., 2012) we further explore the evidence for sex differences in schizophrenia and autism spectrum disorders (ASD) as a possible cause. We begin by summarising some of the molecular differences reported to date between synapses in males and females.

1. Molecular organisation of the synapse in males and females

Calcium/calmodulin kinase kinase (CaMKK) signalling has been found to differ in males and female mice, both in behavioural and plasticity studies (Figure 1). The two isoforms of CaMKK, CaMKKα and CaMKKβ, act by phosphorylating CaMKI and CaMKIV, which in turn modulate the activity of the transcription factor cAMP-responsive element binding protein (CREB) (Bito et al., 1997), most likely by calcium entry into the cytoplasm through NMDA receptors and L-type calcium channel (Deisseroth et al., 1998). Mice lacking either CaMKKα or CaMKKβ reveal striking sex differences in tests of behaviour and hippocampal synaptic plasticity (for review, see (Mizuno and Giese, 2010)). Male mice lacking CaMKKα have deficits in contextual fear conditioning, which may relate to the lack of up-regulation of brain derived neurotrophic factor (BDNF) by CaMKKα in males that would normally accompany this task in females (Mizuno et al., 2006). Male CaMKKβ deficient mice are impaired in spatial learning and lack hippocampal CREB activation compared to female null mice, and also lack late-phase hippocampal LTP (Mizuno et al., 2007). Baseline sex differences in CREB signaling also exist, with male neonatal rodents having greater

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phosphorylated CREB expression in hippocampal CA1 (Auger et al., 2001). It is known that CREB is involved in neocortical experience dependent plasticity (Barth et al., 2000; Glazewski et al., 1999), but it is not known if the hippocampal differences in CaMKK and CREB signalling extend to neocortical circuits. These studies provide clear evidence for the basis of sex differences in synaptic plasticity, but further work is required to (i) determine whether CaMKK differences generalise to other brain regions, including the cortex, and (ii) identify further sex-related protein candidates for differences in plasticity.

2. Sex differentiation of the role of α-Nitric Oxide Synthase-1 in cortical plasticity

Studies in the barrel cortex have shown that both pre- and post-synaptic mechanism are activated during expression of cortical synaptic potentiation (Hardingham and Fox, 2006). The post-synaptic aspect of potentiation is dependent on αCaMKII autophosphorylation and GluA1 (GluR1), while the presynaptic component depends on post-synaptically located αNOS1 (Hardingham and Fox, 2006; Hardingham et al., 2003). Studies from hippocampus, cerebral cortex and several other brain structures all suggest that nitric oxide is involved in increasing transmitter release, most likely through a coordinated and synergistic action on several components of the presynaptic release machinery (Hardingham et al., 2013). Theoretically, both activity dependent isoforms of Nitric Oxide Synthase (NOS1 and NOS3) could be the source of the nitric oxide signal and indeed, there is evidence that NOS3 and αNOS1 are involved in providing a tonic and phasic release of nitric oxide respectively (Hopper and Garthwaite, 2006).

The phasic component of nitric oxide release is calmodulin and αNOS1-dependent and can be triggered by NMDA receptor activation. Early indications that the function of αNOS1 might be different between males and females came from studies showing that knocking out αNOS1 confers some neuroprotection from ischaemic damage produced by stroke in the male brain, but has no protective effect on the female brain (Huang et al., 1994; McCullough et al., 2005). Subsequently, it was found that αNOS1 is also necessary for LTP in males, but not female mice (Dachtler et al., 2012). The residual LTP in female mice is not susceptible to a general NOS antagonist suggesting

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that the main component of LTP does not rely on nitric oxide signalling at all in female animals (Figure 2). The dependency of male plasticity on NO may relate to baseline differences between the sexes. Within the hippocampus, females have less abundance of NO and reduced NOS1 expression compared to males, although the application of estradiol increased hippocampal NOS1 expression (Hu et al., 2012). Therefore a possible explanation for this sex difference is that females lack available NO for the induction of plasticity, and thus rely upon other molecular pathways instead. It is conceivable that the sex differences in plasticity and susceptibility to stroke damage are related. If nitric oxide is released during ischaemic damage, it would tend to potentiate excitatory transmission in the male brain thereby leading to greater NMDA receptor activation, greater calcium entry and greater excitotoxic damage.

Experience-dependent potentiation in the somatosensory cortex depends on many of the same factors as LTP. For example, both αNOS1 and GluA1 are required for pre- and post-synaptic components of LTP respectively and both are important for experience dependent plasticity in the barrel cortex (Dachtler et al., 2011). Knocking out both GluA1 and αNOS1 abolishes experience-dependent potentiation in the cortex, whereas knocking out either gene individually produces a reduction in but not a complete elimination of plasticity (Dachtler et al 2011). Subsequent, experiments showed that the αNOS1 component of experience-dependent plasticity was also sex-dependent in common with LTP (Dachtler et al., 2012). Depriving mice of all but one whisker for a period of 3-4 weeks normally results in expansion of the spared whisker domain within the barrel cortex, such that neurones located in barrels surrounding the spared whisker's home barrel are far more sensitive to spared whisker stimulation than in a normal animal (Glazewski et al., 1996). This process is dependent on intracortical circuits and crucially, on excitatory connections between cortical columns (Fox, 1994; Glazewski et al., 2000). Studies comparing experience-dependent plasticity in male and female αNOS1 knockout mice showed that experience-dependent potentiation was almost completely absent in αNOS1$^{-/-}$ males and intact in αNOS1$^{-/-}$ females (Dachtler et al., 2012). Taken together with the lack of LTP in the male αNOS1 knockouts, these findings suggest that either potentiation is αNOS1 dependent only in male mice, or that females have an alternate (or compensating) mechanism that comes into play when αNOS1 is knocked out

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and this compensation system is absent in males. In either case, these studies provide evidence for the theory that cortical synaptic plasticity is differentiated at the level of the synapse between the two sexes.

3. The role of oestrogen in synaptic plasticity

CaMKK and αNOS1 are examples of distinct, sexually dimorphic molecular pathways underpinning synaptic plasticity. However, the most obvious difference between the sexes is the presence of circulating oestrogen (predominantly as 17β-estradiol (E2)), a molecule that is known to directly affect synaptic plasticity (Cordoba Montoya and Carrer, 1997). High levels of oestrogen are present in the female brain from circulating hormone, and non-circulating oestrogen is also present in the male brain, albeit at far lower concentrations, where testosterone acts as a precursor to oestrogen by aromatase catalysis (Gillies and McArthur, 2010).

3.1. Does oestrogen have a direct role in synaptic plasticity?

Warren et al. (1995) performed a simple assay to examine whether oestrogen has a role in LTP by testing females at different points in their oestrous cycle. They found that when females were at proestrus, the magnitude of hippocampal LTP was greater than that at either diestrus or oestrus (Warren et al., 1995). Prior to this study, others had noted that the abundance of E2 was correlated with dendritic spine plasticity in the hippocampus; spine density was 32% lower at oestrus compared to the proestrus phase of the cycle, (Woolley and McEwen, 1992). The E2-dependent increase in spine density at proestrus could be stabilised by NMDA receptors as it was prevented by NMDA receptor antagonists, whereas AMPA or muscarinic receptor antagonists had no effect (Woolley and McEwen, 1994). E2 acted to increase the sensitivity of synapses to NMDA receptor mediated input (Woolley et al., 1997); LTP increased only when both spine density increases and there was an enhancement of NMDA receptor transmission relative to AMPA receptor transmission (Smith and McMahon, 2005). Indeed, though E2 was found to cause spinogenesis, synapses remained 'silent' unless NMDA receptor activation occurred, allowing the spine to

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stabilise (Srivastava et al., 2008). Specifically, E2-dependent facilitation of LTP appears to act through GluN2B-containing (also known as NR2B) NMDA receptors (Smith and McMahon, 2006). Taken together, acute treatment of E2 causes increases in spine density and facilitation of LTP through GluN2B receptors, which could be linked to the oestrus cycle in females.

3.2. Sex difference in oestrogen and plasticity

E2 treatment in slices of hippocampal CA1 acutely potentiates glutamatergic synapses of both sexes. Whilst males and females arrive at the same plasticity outcome of E2 treatment, the mechanisms by which they do it vary. The compound WAY20070 is an agonist of the β form of the estrogen receptor (ERβ) and causes an increase in the frequency of miniature excitatory post-synaptic currents (mEPSCs) in females but not males, whilst conversely, increasing the amplitude of mEPSCs in males but not females. An ERα agonist (PPT) only increases mEPSC frequency in males (Oberlander 2016). Hence, E2 acts via distinct estrogen receptors at pre- and post-synaptic locations. Furthermore, an agonist to the G-protein couple estrogen receptor-1 (GPER1), causes increases in mEPSC amplitude in females but not males (Oberlander 2016). Therefore at glutamateric synapses, in females, E2 facilitates potentiation by post-synaptic GPER1 and pre-synaptic ERβ, whilst in males, E2 acts through post-synaptic ERβ and pre-synaptic ERα (Figure 1). Currently it is unclear what advantage this sex difference would convey, and whether the recruitment of other downstream elements of the pre- and post-synaptic machinery (such as NOS) are consequently differentially modulated as a result.

Recent studies have also demonstrated a role for E2 in inhibition and begun to reveal that not only is this sex specific, but that E2 acts through distinct molecular pathways. Acute E2 application to hippocampal slices has revealed a rapid suppression of GABAergic inhibitory synaptic transmission at perisomatic inputs to pyramidal cells within the hippocampal CA1, specifically through a molecular cascade including the α form of estrogen receptor (ERα), metabotrophic glutamate receptor 1 (mGluR1) and endocannabinoid receptor 1 (Huang and Woolley 2012). Remarkably, this inhibitory effect was only evident in females; E2 had no effect upon inhibitory

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postsynaptic currents (IPSCs) in males (Huang and Woolley 2012). Further work revealed this was because E2 promotes an ERα-mGluR1 interaction only in females, which in turn stimulates production of phospholipase C and inositol triphosphate (IP_3), leading to postsynaptic endocannabinoid release (Tabatadze, 2015).

3.3 Is circulating oestrogen the source of the sex difference?

Theoretically, the sex differences in ER receptors discussed in the previous section could account for different effects in oestrogen from the common source of aromatase, present in males and females. However, a number of studies suggest that circulating oestrogen is in practice the cause of the spinogenic differences in hippocampal plasticity. First, E2 levels are very much lower in males (below detection limits (0.07pM)) than in females. Second, *in vivo* E2 only increases spine density in females. Third, spinogenesis still occurs if you block aromatase with tetrazole in cycling females but has no effect in males (Fester et al., 2012) and finally, E2 only increases LTP sensitivity in females (Vierk et al., 2015). While these findings do not preclude aromatase generated E2 as a determinant of other sex differences, they do imply that the major difference in LTP between the sexes can be attributed to the action of circulating hormone.

4. Sex differences in behaviour and neuropsychiatric disorders involving the cortex.

As behaviour is the final output of all the upstream synaptic functions, sex differences in behaviour can reveal insights into how cortical activity differs between males and females. Likewise, aberrations in behaviour caused by certain psychiatric conditions tend to be sex specific in their expression, which can provide insight into which cortical circuits and synaptic mechanisms differ between the sexes.

4.1. Sex differences in cortex-dependent behaviours.

Males and females show differences in cortical connectivity that develop early in adolescence (Ingalhalikar et al., 2014). In particular, prefrontal cortical areas appear to be more strongly linked across hemispheres in females and more strongly linked within hemispheres in males (Ingalhalikar et al., 2014). Prefrontal cortical function also differs between males and females. The Iowa gambling task (IGT), probes probabilistic learning, whereby the subject is asked to win as much money as possible without initial knowledge of a winning strategy. A winning strategy is to select cards from a pack that yields smaller rewards but overall monetary gain rather than packs containing larger rewards to avoid overall monetary loss. Studies show that the winning strategy is adopted before the subject is aware of it (Bechara et al., 1997). fMRI measurements show that the IGT engages the dorsolateral prefrontal cortex, the insula and posterior cingulate cortex and the orbitofrontal and ventromedial prefrontal cortex (Li et al., 2010). Males consistently perform better than females by learning more quickly to avoid the card selections that cause the greater monetary punishment (van den Bos et al., 2013). fMRI studies suggests that male and females engage different parts of the cortex during the IGT, which might explain the sex difference. Males show activity in the left and right lateral orbitofrontal cortex and the right dorsolateral prefrontal cortex, while females show activation of the left dorsolateral prefrontal cortex, left frontal gyrus and temporal lobe (Bolla et al., 2004). In a rat-based version of the IGT, performance is modulated by both serotonin and dopamine signalling (Zeeb et al., 2009) and similar to humans, male rats perform better than females (van den Bos et al., 2012). Further work is required to understand the why males and females engage different parts of their brains during certain cortical behaviours, and whether each sex employs different neurotransmitters and different synaptic plasticity mechanisms. Nevertheless, these studies do emphasise that in addition to the sex differences seen at the synaptic scale, sex differences may also manifest themselves at the systems level and indeed the two may interact. The sex differences seen in prefrontal cortex may be a factor in sex differences seen in psychiatric diseases as discussed in the following sections.

4.2. Sex differences in cortical function in neurobehavioural disorders.

4.2.1. Schizophrenia.

Schizophrenia is a psychiatric disorder that has a clear association with cortical impairments. In particular, changes to the structure and function of the prefrontal cortex are particularly characteristic of schizophrenia, with studies noting cortical thinning (Kuperberg et al., 2003), alterations in neural density (Heckers, 1997) and reduced activity during prefrontal-dependent tasks (Weinberger et al., 1986). The risk ratio of developing schizophrenia in males compared to females is approximately 1.4 (Aleman et al., 2003), with males tending to develop schizophrenia at an earlier age (Faraone et al., 1994), suggesting there could be underlying sex differences in cortical abnormalities that affect the disease expression. Indeed, there is evidence for this hypothesis. Gross anatomical sex differences in the schizophrenic brain as detected by MRI remains controversial (in part due to the lack testing of sex balanced groups), but studies suggest female-specific reductions and male-specific enlargements in white matter volume within the occipito–parietal lobe (Highley et al., 2003), reduced temporal lobe (Bryant et al., 1999) and anterior cingulate cortex volume (Bryant et al., 1999) in male patients. Differences in molecular signalling may also be sex-dependent. Altered expression of GABAergic genes in the anterior cingulate cortex of schizophrenic patients vary by sex; in males, GABA-Aα5, GABA-Aβ1, and GABA-Aε had reduced expression, while in females, GABA-Aβ1 and GAD67 were upregulated (Bristow et al., 2015).

Mouse models of schizophrenia have revealed sex-dependent effects. Female mice carrying a missense mutation within the C-terminal of Disrupted-in-Schizophrenia-1 (*Disc1*) had altered sociability, hyperlocomotion and heightened anxiety (Dachtler et al., 2016), a similar profile to elderly females harboring single nucleotide polymorphisms within *DISC1* (Harris et al., 2010). A separate mouse model expressing inducible truncated *Disc1* also showed sex-specific behaviours, with males having enhanced spontaneous locomotor activity and alterations in social interaction, and females having deficient reference spatial memory in the Morris water maze (Pletnikov et al., 2008). Recent evidence has highlighted that without the normal expression of *DISC1* during

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development, adult *in vivo* and *in vitro* synaptic plasticity is impaired in both the somatosensory (Greenhill et al., 2015) and visual cortex (Tropea et al., 2016). Hence, *DISC1* may contribute to genesis of sex differences in schizophrenia.

4.2.2. Autism Spectrum Disorders.

Autism is a heterogeneous cluster of behavioural abnormalities, which correspondingly has a differing diagnosis depending upon the severity of these symptoms. Males consistently have a substantially greater incidence of autism compared to females, with male/female ratios up to 15:1, although on average this is closer to 4:1 (Wing, 1981). A possible cause of this sex difference could lie in hormonal effects during development and has been discussed in terms of the 'extreme male brain' theory (Baron-Cohen et al., 2011), which itself is underpinned by the foetal testosterone theory and the X chromosome theory. A number of recent reviews have been published on this topic (Mottron et al., 2015; Schaafsma and Pfaff, 2014; Werling and Geschwind, 2013) and so here we focus instead on other possible factors that may contribute to sex differences in autism.

Research into the causative factors explaining male bias in autism have pointed towards sex differences in the structure and function of the cortex. It is well established that brain enlargement occurs in autism, with enlargement of the cerebral cortex evident before the second year of life (Hazlett et al., 2011). Widespread differences in cortical grey matter have observed across the frontal (Abell et al., 1999; McAlonan et al., 2002), parietal (McAlonan et al., 2002) and temporal (Boddaert et al., 2004; Hazlett et al., 2011) lobes. However, some of these differences vary by sex. Comparing autistic girls and boys, significant differences in grey matter were observed in the motor cortex, supplementary motor area, insular cortex and amygdala (Supekar and Menon, 2015). In males but not females, a significant negative correlation has been observed between behavioural autism traits and default-mode functional connectivity of the medial prefrontal cortex (Jung et al., 2015), along with reduced gyrification in the ventromedial prefrontal and orbitofrontal cortex (Nordahl et al., 2015). Diffusion tenor imaging derived fibre tracking has revealed subtle differences in the corpus callosum of preschool aged children with autism. Males have a smaller

callosal projection region to the orbitofrontal cortex, while females had a smaller region projecting to the anterior frontal cortex (Nordahl et al., 2015).

Sex differences in cortical function in autism may pertain to altered gene expression at the synapse. Retinoic acid-related orphan receptor alpha (*RORA*), a gene found to be downregulated in autistic patients (Nguyen et al., 2010), is upregulated by E2 but if the protein is deficient, will cause an accumulation of testosterone through the lack of suppression of *CYP19A1* activity (encoding aromatase) (Sarachana et al., 2011). The regulation of *RORA* and its transcriptional targets, including *CYP19A1*, are tightly regulated in the male cortex but less so in females (Hu et al., 2015), suggesting that *RORA* dysregulation could have greater impact upon E2 and testosterone regulation and aromatase activity in male cortex of autism patients. Dysregulation of synaptic genes in autism mouse models have revealed sex differences in autistic-like phenotypes. Mutations within the neurexin genes (*NRXN1-3*) have been widely associated with autism (Chen et al., 2014), and female mice containing deletions of *αNrxn1* exhibit impairments in fear learning, whilst female *αNrxn2* knockout mice have reduced sociability and increased repetitive behaviours (Born et al., 2015; Dachtler et al., 2015). Deficiency of *Nrxn2* has been shown to impair NMDA receptor function, short term plasticity and excitatory transmitter release in cortical layer V cells (Born et al., 2015), implying that some of the behavioural effects of *NRXN* deletion could be related to impaired cortical function.

Taken together, these studies show that differences at the synaptic level play a part in explaining some of the behavioural impairments associated with autism differences between males and females, in addition to differences in cortical structure and connectivity.

5. Conclusions

We began this review by posing the question of whether sex differences might extend down to the synaptic scale and whether plasticity might differ between males and females as a result. The

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current literature yields a number of examples of such differences at synaptic level, most notably the CaMKK pathway, the NOS1 pathway and the differential effect of circulating oestrogen on synaptogenisis, NOS1 and GABAergic transmission. The NOS1, CaMKK and oestrogen effects are all capable of influencing the exact nature of plasticity and hence of affecting learning, memory and cognition. It remains to be determined to what extent these are general cortical mechanistic differences however, as some features such as the effects of oestrogen on spinogenesis have only thus far been documented in the hippocampus.

Recent studies have shown that many of the risk factors for psychiatric diseases affect synaptic proteins. Furthermore, studies are now emerging that show plasticity is altered or impaired in mouse models of psychiatric diseases. For example, a transient disruption of normal DISC1 activity during a critical period of early development affects cortical plasticity into adulthood. It is well known that schizophrenia and ASD show different prevalence across males and females. We therefore raise the possibility here that some of the differential susceptibility to neuropsychiatric disorders seen between males and females may arise from sex differences in the plasticity mechanisms that are perturbed in those conditions.

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Figure legends

Figure 1

Summary of synaptic plasticity and molecular pathways that differ between the sexes. Neocortical αNOS1 in males has been shown to be involved in *in vitro* and *in vivo* synaptic plasticity, with NO acting both pre- and postsynaptically. NO and αNOS1 are also more abundant in the male than female hippocampus. CaMKKα and CaMKKβ are also more crucial in the male brain for memory tasks, LTP and CREB transcription. E2 acts via different pre- and postsynaptic disposition of oestrogen receptors between the sexes to facilitate increased presynaptic glutamate release and greater postsynaptic glutamate sensitivity; males require presynaptic ERα and postsynaptic ERβ, while females employ presynaptic ERβ and postsynaptic GPER1. Deletions of *αNrxn1* and *αNrxn2* have been shown to impair female behaviours including anxiety, sociability and memory, whilst a loss of presynaptic NRXN2 impairs glutamate release and postsynaptic NMDA receptor function in the neocortex. Dashed line represents the effect of mutations in the NRXN genes that would impair synaptic function. NB: the molecules depicted are expressed in males and females but only have specific actions or pre/post-synaptic locations in one or the other as shown.

Figure 2

LTP is reduced in αNOS1 knockouts in a sex specific manner. **A** LTP is reduced in αNOS1 knockouts compared to wild-types (sexes combined). **B** Male and female WTs showed similar magnitudes of LTP. **C** Male αNOS1s show no significant LTP while female α NOS1 knockouts do show LTP. **D** L-NNA has no effect on LTP in female αNOS1 knockouts or **E** male αNOS1 knockouts (that already lack LTP). **F** Average level of potentiation observed at 60 minutes, showing within group significance (++$p < 0.01$ +++$p < 0.001$, paired t-test) and comparisons between genotypes or sexes (* $p < 0.05$, **$p < 0.01$, ***$p < 0.005$). Scale bar 100ms/5mV for example paired pulse EPSPs. Reproduced from Dachtler et al (2012) with permission.
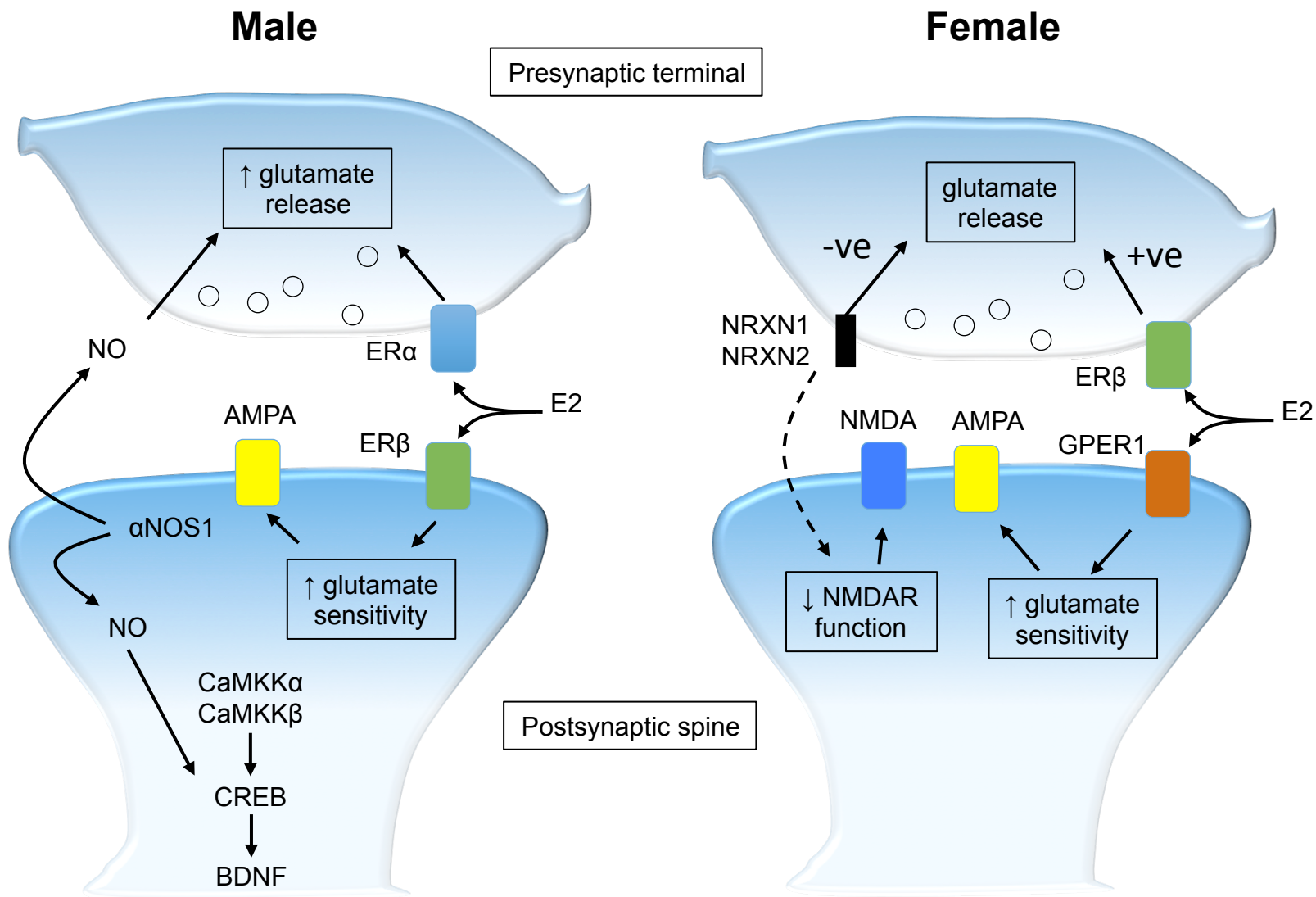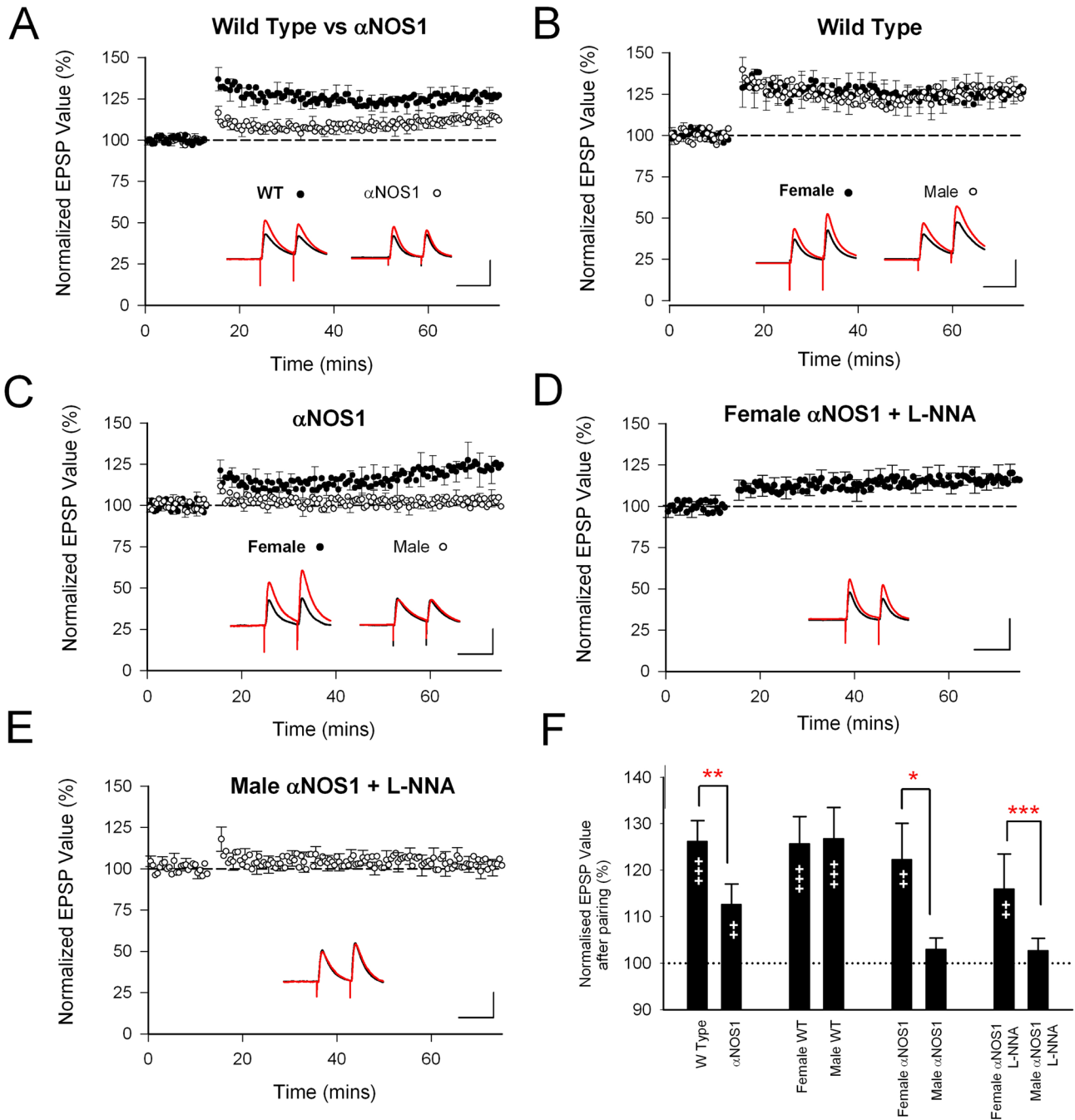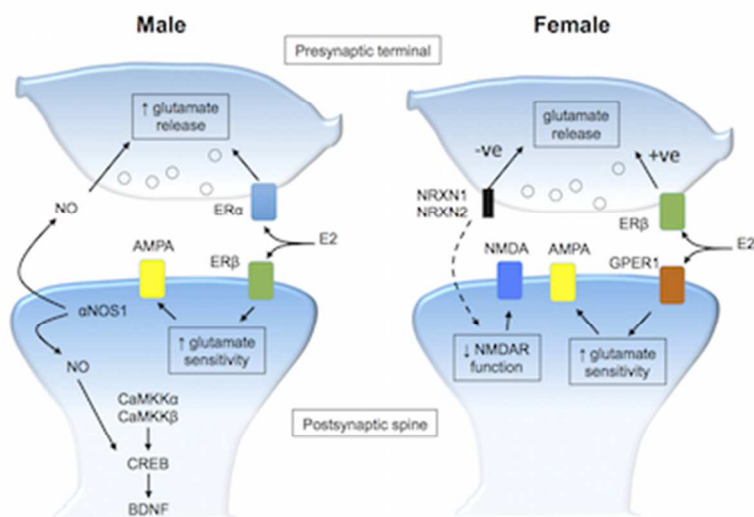
Sex differences at the synaptic level

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Graphical Abstract: This review explores the evidence that male and female brains differ at the synaptic level and that synaptic plasticity mechanism differ between sexes. The review focuses on NOS1, CaMKK and oestrogen differences. Implications for stroke therapies and autism research are discussed.