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## **NEUROPROTECTIVE EFFECTS OF NICOTINE ON HIPPOCAMPAL LONG-TERM POTENTIATION IN BRAIN DISORDERS**

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**Non-standard abbreviations:**

AMPA:	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors
E-LTP:	early-phase LTP
fEPSP:	field excitatory postsynaptic potential
HFS:	high frequency stimulation.
L-LTP:	late-phase LTP
MHFS:	multiple high frequency stimulation
MLA:	methyllycaconitine
nAChR:	nicotinic acetylcholine receptor
NMDA:	N-methyl-D-aspartate
pspike:	population spike

## **Abstract**

Long-term potentiation (LTP) is commonly considered as the cellular correlate of learning and memory. In learning and memory impairments, LTP is invariably diminished in the hippocampus, the brain region responsible for memory formation. LTP is measured electrophysiologically in various areas of the hippocampus. Two mechanistically distinct phases of LTP have been identified: early-phase LTP (E-LTP; related to short-term memory) and late-phase LTP (L-LTP; related to long-term memory). These two forms can be severely reduced in a variety of conditions and but can be rescued by treatment with nicotine. This report reviews the literature on the beneficial effect of nicotine on LTP in conditions that compromise learning and memory.

## Introduction

Long-term potentiation (LTP) is widely deemed as the cellular correlate of learning and memory. The majority of the LTP studies have been performed in the hippocampus, a bilateral, limbic structure [Teyler and DiScenna, 1986; Sutherland et al., 1989; McNaughton and Foster, 1990]. New information is temporarily stored within the hippocampus before being transferred to the cerebral cortex for long-term storage (Ivanco and Racine, 2000). The role of the hippocampus in learning and memory is supported by direct and convincing evidence from human and animal studies.

Anatomically, the hippocampus is organized in a lamellar fashion and receives highly processed information from widespread neocortical regions. A cross-section of the hippocampus reveals its internal laminar structure with distinct areas, most prominent of which are the pyramidal cells of the Ammon's Horn or Cornu Ammonis (CA1-CA3) subfields, and the granule cell of the dentate gyrus (DG) (Amaral and Witter, 1989; Witter et al., 1989). The hippocampus is characterized by its tri-synaptic circuitry through which information flows in one direction from the entorhinal cortex to area CA1. The perforant path fibers from the entorhinal cortex synapse on the granule cells of the DG. The axons of the granule cells, forming the mossy fiber pathway synapse on the large pyramidal cells of area CA3. The pyramidal cells of area CA3 send the Schaffer collateral nerve fibers to synapse on the pyramidal cells of area CA1 (Amaral and Witter, 1989; Witter et al., 1989). Repetitive stimulation of any of these three presynaptic pathways induces long-lasting changes in synaptic responses of the neurons downstream of that particular pathway. These use-related changes are known as synaptic plasticity, of which LTP is a prime example.

The LTP of DG area is remarkably resistant to insults compared to those of other areas of the hippocampus. This protected status is perhaps due to the fact that the DG area is vital for brain function in that it is one of the few regions of the brain that has the ability for neurogenesis in adulthood. The exact mechanism for this advantaged status of the DG is complex and largely unknown; and seems to be due to a variety of factors that impart this distinction. For example, in the DG area of hypothyroid rat, we have shown a marked decrease in the basal molecular level of the phosphatase calcineurin. Thus, by restricting dephosphorylation, the level of the phosphorylated calcium-calmodulin-dependent protein kinase II (p-CaMKII), a signaling molecule essential for expression of LTP, is maintained. This compensatory mechanism is probably responsible for preservation of LTP in the DG area of the hippocampus (Gerges et al., 2005; 3003). However, in area CA1 of hypothyroid or stressed rats, there is no such compensatory mechanism. Therefore, the decreased level of calcineurin in the DG area of hypothyroid or chronically stressed rats seems to allow ample level of p-CaMKII to sustain the expression of LTP (Gerges et al., 2003, 2005, Gerges and Alkadhi, 2004). However, the mechanism of this remarkable defense in the DG area remains to be determined.

Two mechanistically discrete phases of LTP have been identified: early-phase LTP (E-LTP; related to short-term memory) and late-phase LTP (L-LTP; related to long-term memory). E-LTP is a transient phase that can be evoked by a short period of high frequency stimulation (HFS). It does not require de novo protein synthesis but requires constitutive activation of p-CaMKII, which phosphorylates and enhances the conductivity of glutamate post-synaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) (Fukunaga et al., 1996; Nayak et al., 1996; Lisman et al., 2002). L-LTP is an enduring response

to multiple high frequency stimulation (MHFS) applied over a relatively long period of time. It is a protein synthesis-dependent phase, which requires activation of calcium-calmodulin-dependent protein kinase IV (CaMKIV) and mitogen-activated protein kinase (MAPK) to phosphorylate cAMP-responsive element-binding protein (CREB); and cAMP response element (CRE)-mediated transcription of target genes (Bozon et al., 2003). CRE-mediated gene transcription is absolutely necessary for synapse formation, neuronal survival and long-term memory formation (Snyder et al., 2005).

Both forms of LTP can be measured by electrophysiological techniques in brains of anesthetized animals or in vitro from hippocampal slices. Recordings from anesthetized animals yield two measures; field excitatory postsynaptic potential (fEPSP), which is a synaptic response and population spike (pspike), which represents the number of neurons reaching threshold for action potential.

The cholinergic system in the hippocampus plays a central role in the process of learning and memory. Ample evidence shows that nicotine prevents memory impairments associated with stress (Aleisa et al., 2006a; Tipps et al., 2014), ageing (Arendash et al., 1995; Socci et al., 1995; Levin and Torry, 1996; Grilly et al., 2000; White and Levin, 2004), brain lesions (Decker et al., 1992; Levin et al., 1993b) and cognitive disorders, including Alzheimer's disease (AD) (Sahakian et al., 1989; Wilson et al., 1995; White and Levin, 1999; Newhouse et al., 2001; Srivareerat et al., 2009, 2011; Alkadhi et al., 2010, 2011), schizophrenia (Levin et al., 1996a), attention deficit/hyperactivity disorder (ADHD) (Conners et al., 1996; Levin et al., 1996b; Levin et al., 1998) and Parkinson's disease (Maggio et al., 1997, 1998; Newhouse et al., 1997). Although nicotine has been reported in some clinical (Levin et al., 1998) and animal studies (Wesnes and Warburton, 1984; Levin et al.,

1990; Levin et al., 1992, 1993a; Levin et al., 1997) to have memory enhancing abilities in normal subjects, other studies have reported no effect (Dunne et al., 1986; Parrott and Winder, 1989, Aleisa et al., 2006a, b, c) or even memory impairment (Park et al., 2000; Sorenson et al., 1991). The varying results of the effect of nicotine treatment may be due to variations in nicotine dosing, treatment duration, route of administration, and experimental memory task employed.

The effect of nicotine on LTP has been widely studied in animal models of brain disorders (e.g. Kenney and Gould, 2008). Electrophysiological studies reveal that administration of nicotine (acute or chronic) facilitates the induction of LTP in area CA1 of hippocampus by lowering its threshold of induction in slice preparations (Fujii et al., 1999; Fujii et al., 2000; Fujii et al., 2001; Matsuyama et al., 2000) as well as in anesthetized rats (Aleisa et al., et al., 2006a, b, c). The effects of nicotine on memory and LTP are prevented by mecamylamine, a non-selective nicotinic acetylcholine receptor (nAChR) antagonist, indicating that nicotine induces its effects on memory and LTP by acting on nAChRs in the hippocampus (Levin et al., 1987; Levin et al., 1993a; Levin and Torry, 1996; Levin et al., 1997; Fujii et al., 1999; Matsuyama et al., 2000; Levin et al., 2002; Rezvani et al., 2002).

The nAChR belongs to a family of ligand gated ion channels that mediate fast synaptic transmission in the central nervous system (CNS). Structurally, nAChRs are comprised of homologous or heterologous combinations of five polypeptide subunits arranged around a central water-filled pore, like staves of a barrel. Each subunit is composed of four transmembrane (TM1-4) domains. The extracellular N-terminal of each of the five subunits may form the agonist binding (receptor) site (Cooper et al., 1991). Three rings of negative charges, positioned along the inner pore of the channel, constitutes the cationic selectivity of

nAChR. The nAChRs can be of three major classifications based on their pharmacological and physiological properties: the heteropentameric nAChRs ( $\alpha$ ,  $\beta$ ,  $\delta$ ,  $\sigma$ ,  $\epsilon$ ), which exist in endplates of skeletal muscles, the standard neuronal nAChRs formed from  $\alpha$  and  $\beta$  combinations, and the homopentameric nAChRs, formed from  $\alpha 7$  or  $\alpha 9$  subunits (Colquhoun and Patrick, 1997). The hippocampus contains a large number of nAChR subtypes; however, based on electrophysiological and in situ hybridization studies, the heteropentameric  $\alpha 4\beta 2$  and homopentameric  $\alpha 7$  nAChR subtypes are the most abundant receptor subtypes in the hippocampus (Wada et al., 1989; Seguela et al., 1993).

Nicotine activates presynaptic nAChRs on the Schaffer collateral nerve terminals in area CA1 resulting in increased release of glutamate and the consequent pyramidal cell excitation. Moreover, chronic nicotine treatment upregulates  $\alpha 4\beta 2$  and  $\alpha 7$  nAChR subtypes in most brain regions including the hippocampus (Ridley et al., 2001; Mugnaini et al., 2002; Parker et al., 2004). The effects of nicotine on memory and LTP are blocked by the  $\alpha 4\beta 2$  nAChRs antagonist dihydro- $\beta$ -erythroidine (Bancroft and Levin 2000; Fujii et al., 2000; Levin and Rezvani 2000; Arthur and Levin 2002), suggesting that nicotine improves memory and LTP by activation of nAChRs, mainly the  $\alpha 4\beta 2$  subtypes.

The involvement of  $\alpha 7$ -nAChRs in memory and LTP is debatable. Whereas blocking  $\alpha 7$ -nAChRs by methyllycaconitine (MLA) impairs memory and inhibits nicotine action on memory in the radial arm maze (Levin and Rezvani, 2000; Bettany and Levin, 2001; Levin et al., 2002), MLA facilitates the generation of LTP in hippocampal slices (Fujii et al., 2000). The MLA-induced facilitation of LTP is explained by the finding that chronic nicotine treatment induces desensitization of  $\alpha 7$ -nAChRs in GABAergic interneurons, which reduces the release

of gamma-aminobutyric acid (GABA) from these interneurons, hence indirectly promoting pyramidal cell excitability (Alkondon et al., 2000a, 2000b). Consequently, LTP expression is facilitated by lowering its threshold of induction (Fujii et al., 1999, 2000a, 2001).

Therefore, changing the dynamics of nAChR activation and distribution influences the release of neurotransmitters and affects memory and activity-dependent synaptic plasticity. Furthermore, in addition to modulating the activity of neuronal circuits in hippocampal and cortical brain regions, nAChRs appear to be involved in neuronal survival. For example, in the brains of old mice that lack  $\beta 2$ -nAChRs, Xu et al., reported astrogliosis, and microgliosis with neocortical hypertrophy and hippocampal neuronal loss resulting in impaired spatial learning (Xu et al., 1999).

In this review, the neuroprotective effects of nicotine on LTP in certain brain disorders is recounted with emphasis on electrophysiological work reported from my laboratory.

### **Alzheimer's disease**

Alzheimer's disease (AD) is characterized by dysfunctional cholinergic mechanisms as is common in some other dementia disorders (Kasa et al., 1997; Perry et al., 2000). Examination of neocortical and hippocampal regions in brains of AD patients reveals a marked loss of  $\alpha 7$ - and  $\alpha 4\beta 2$ -nAChRs (Pettit et al., 2001; Auld et al., 2002; Lahiri et al., 2002; Utsuki et al., 2002; Mattson, 2004) and of pre-synaptic terminals in neocortical and hippocampal regions (Terry et al., 1991; Sze et al., 1997), which are correlated with progressive cognitive decline. We have reported similar loss of nAChRs in an animal model of AD (Srivareerat et al., 2011). Immunohistochemical, biochemical, and pharmacological

data suggest that the high affinity binding of the neurotoxic protein A $\beta$ <sub>1-42</sub> to  $\alpha$ 7- and  $\alpha$ 4 $\beta$ 2-nAChRs has an important role in AD pathogenesis, including formation of extracellular amyloid plaques and deterioration of cholinergic neurons (Wang HY et al., 2000b; Wang HY et al., 2000a; Ikonomovic et al., 2009). It has been proposed that chronic stimulation of  $\alpha$ 7-nAChRs by A $\beta$ <sub>1-42</sub> protein accelerates disorder of ERK2-MAPK signaling pathway (Dineley et al., 2002), promotes internalization and intracellular accumulation of A $\beta$ <sub>1-42</sub> (Nagele et al., 2002), interferes with GABAergic signaling (Alkondon et al., 2000a) and/or furthers excessive stimulation of glutamate receptors (Parpura-Gill et al., 1997). Experiments in exogenous A $\beta$  administration, transgenic mice, and gene-targeting mouse AD models demonstrate correlations among excessive A $\beta$  accumulation, impaired nAChR function (Mattson, 2004; Srivareerat et al., 2011) and deficits in learning, memory, and LTP (Cullen et al., 1997; Itoh et al., 1999; Chen et al., 2000; Freir et al., 2001; Srivareerat et al., 2011; Alzoubi et al., 2013). Collectively, the data suggest that A $\beta$  disrupts memory and LTP by impairing nAChR function.

Numerous epidemiological studies have reported a highly significant negative correlation between cigarette smoking and AD (Brenner et al., 1993; Hillier and Salib, 1997; Ulrich et al., 1997; Potter et al., 1999). In laboratory and clinical studies (Emilien et al., 2000; Moreira et al., 2006), nicotine has been shown to improve cognitive function in AD subjects (Potter et al., 1999) and attenuate A $\beta$ -induced amnesia in rodent models of AD (Newhouse et al., 1988; Maurice et al., 1996; Srivareerat et al., 2011; Gao et al., 2014). Although the mechanism of the neuroprotective effects of nicotine is unknown, one possibility might involve the desensitization and upregulation of nAChRs induced by chronic exposure to the drug.

In A $\beta$ -treated rat models of AD, both E-LTP and L-LTP are severely suppressed as measured by extracellular recording from brains of anesthetized animals (Srivareerat et al., 2009; 2011; Chen et al., 2010; Alkadhi et al., 2011). However, chronic nicotine treatment (1mg/kg s.c. twice per day for 6 weeks prior and during A $\beta$ -infusion) completely prevents the deleterious effects of A $\beta$  on both E-LTP and L-LTP of CA1 (Fig 1) (Srivareerat et al., 2009; 2011; Alkadhi et al., 2011) and DG areas of the hippocampus (Alkadhi, 2018). Comparable results have been reported in streptozotocin model of AD in anesthetized rats where chronic nicotine also prevents inhibition of LTP in area CA1 (Esteves et al., 2017). In area CA1 slices from A $\beta$  treated rats, nAChR agonists completely preserve E-LTP and L-LTP (Kroker et al., 2013).

In contrast to the preponderance of published reports, some laboratories reported that nicotine neither enhances nor depresses stimulation-induced LTP in normal animals (Freir et al., 2001; Itoh et al., 1999). For instance, Itoh et al. report that in slices from A $\beta$ -infused rats, perfusion of 50 mM of nicotine for 10 min diminishes population spike amplitude in area CA1 of control rats. In similar studies, Freir et al. report that injection of nicotine and A $\beta$ , 1 hour before HFS, diminishes LTP much more than does A $\beta$  alone.

## Mental Stress

Stress ranges from mild to post-traumatic stress disorder (PTSD) and negatively affects normal brain structure and function (McEwen 2000). The hippocampus is highly sensitive to damage during repeated stress (Sapolsky 1993, 2000; Smith 1996). Chronic psychosocial stress impairs hippocampus-dependent learning and memory in animal models (Holscher 1999; Park et al., 2000; Gerges et al., 2004a) and in humans (Lupien et al.,

1997). Additionally, stress markedly inhibits LTP of area CA1 of the hippocampus in anesthetized rats (Gerges et al., 2001) and in hippocampal slices (Foy et al., 1987). However, in the DG area the great majority of reports show no impairment (Bramham et al., 1998; Gerges et al., 2001; Alkadhi, 2018; but see Vereker et al., 2001).

The mechanism of impairment of memory and LTP by stress is not well understood. A suggested contributing mechanism is the increased levels of excitatory amino acids and glucocorticoids during stress (Watanabe et al., 1992a; Magarinos and McEwen 1995). Elevation of excitatory amino acids and glucocorticoid levels during stress is known to induce hippocampal atrophy and promote neuronal death due to excitotoxicity (Watanabe et al., 1992a, b; Magarinos and McEwen 1995; Magarinos et al., 1996; McEwen 1997).

Stress and stress hormones downregulate nAChRs and impair memory (Pauly and Collins, 1993; Diamond et al., 1994; Luine et al., 1994; Takita and Muramatsu, 1995; Takita et al., 1999; Gerges et al., 2001, 2004b; Aleisa et al., 2006c). The finding that chronic nicotine treatment prevents stress-induced downregulation of nAChRs (Takita et al., 1999; Srivareerat et al., 2011), suggests a possible mechanism by which nicotine exerts its neuroprotective effects on stress-induced impairment of memory and LTP. Stress-induced atrophy of hippocampal neurons (e.g. Schoenfeld et al., 2017; Gilabert-Juan et al., 2016) results in impairment of cognitive function, which suggests that chronic nicotine treatment may reduce the impact of excitotoxic amino acids and glucocorticoids, thus, preventing permanent damage and cognitive decline. From this lab, we report that chronic psychosocial stress severely diminishes E-LTP in hippocampal area CA1, without affecting that of the DG area (Gerges et al., 2001, 2004a; Aleisa et al., 2006 b, d), a hippocampal region known to be resistant to a variety of insults. On the other hand, chronic nicotine treatment completely

prevented the stress-induced impairment of E-LTP (Aleisa et al., 2006 b, d). Interestingly, we show that acute bolus nicotine treatment fails to reverse the deleterious effects of stress on E-LTP (Aleisa et al., 2006d).

### **Co-occurrence of Alzheimer's disease and chronic stress**

Chronic stress exacerbates the severity of cognitive decline in a variety of disorders (Vanitallie, 2002), including Cushing's syndrome (Starkman et al., 1999), PTSD (Yehuda, 2001), hypothyroidism (Gerges et al., 2001; Gerges et al., 2004b), depression (McEwen, 1999; Meyer et al., 2001) as well as AD (Srivareerat et al., 2009; , 2011, Tran et al., 2011a, b). The physiological consequences of stress depend on the intensity and duration of the stressor and upon how the organism perceives and reacts to the noxious stimulus (Gold et al., 1984; Diamond et al., 1992; Joels, 2006).

Chronic stress is a serious risk factor for AD (Wilson et al., 2003; Wilson et al., 2005, Tran et al., 2010, 2011a, b) since elevated glucocorticoid levels are correlated with increased A $\beta$  deposition (Kulstad et al., 2005; Green et al., 2006), enhanced A $\beta$ -mediated neurotoxicity, and accelerated cognitive decline (Aisen et al., 2000; Pedersen et al., 2006; Srivareerat et al., 2009, 2011, Alkadhi et al., 2010a, 2011; Tran et al., 2010, 2011a,b). In AD, the presence of stress may further reduce the ability of neurons to survive coincident insults, thus intensifying A $\beta$ -mediated neurotoxicity and impairment of memory and synaptic plasticity (Foy et al., 1987; Shors et al., 1990; Diamond et al., 1992; Shors and Thompson, 1992). Therefore, any exposure to stress is a threat to cellular metabolic activity and CNS function.

We studied the effect of chronic psychosocial stress in a preclinical (at-risk) model of AD (subA $\beta$  model). This model involves infusion of subtoxic dose of A $\beta$ 1-42 peptide that does not affect normal cognition or synaptic plasticity (Tran et al., 2010, 2011a, Alkadhi and Tran,

2014a). In area CA1 of chronically stressed preclinical (Stress/subA $\beta$ ) AD model, E-LTP is more severely diminished than with stress alone. The effect of stress on L-LTP of hippocampal area CA1 of this model is even more dramatic; although neither stress nor subA $\beta$  model alone affects L-LTP, the combination of the two conditions produces a marked depression of this form of synaptic plasticity. Even in the insult resistant DG area, the combination of chronic stress and subA $\beta$  severely impacts E-LTP, while having no effects on L-LTP of the same area.

In the full toxic dose of our A $\beta$  rodent model, E-LTP of area CA1 in the A $\beta$  treated stressed rat (stress/A $\beta$ ) is more severely blocked than those treated with either A $\beta$  or stress alone. Chronic nicotine treatment completely prevents the effects of the combination (fig 1A). Similarly, in area CA1 the L-LTP of stressed/A $\beta$  rat is more severely blocked in the combination treatment than that with A $\beta$  treatment alone and nicotine totally prevented the effect of the combination. We also studied the effect of the combination on DG area in the same model. The effect of the combination on E-LTP in the stress-resistant DG area is not significantly different than that of the A $\beta$  treatment alone (Alkadhi, 2018). However, the effect of the combination on L-LTP of the DG is markedly more severe than that of the A $\beta$  treatment alone and is prevented by chronic treatment with nicotine (Alkadhi, 2018).

## Hypothyroidism

Thyroid disorders are the second most common endocrine disorder in the United States, with an increased prevalence in elderly (Helfand and Crapo, 1990; Elliott, 2000; Hueston, 2001). Hypothyroidism is an endocrine disorder characterized by reduced normal levels of thyroid hormone (thyroxin, T4). When it develops during infancy or early childhood, hypothyroidism results in cretinism, which is characterized by impaired

development of skeletal system and central nervous system resulting in severe mental retardation among other symptoms (David and Nathaniel, 1983; Porterfield and Hendrich, 1991; Porterfield, 1994; Rovet, 1999).

Adult-onset hypothyroidism displays a wide range of CNS dysfunctions including severe cognitive impairments manifested as inability to concentrate, slow mentation and poor memory for recent events (Haggerty et al., 1990; Mennemeier et al., 1993; Leentjens and Kappers 1995; Burmeister et al., 2001). Older adults with hypothyroidism show impairment of learning, visual-spatial relationship abilities, and attention (Osterweil et al., 1992).

In experimental animals, we have shown that hypothyroidism severely impairs learning as well as short-term and long-term memory in adult rats (Gerges et al., 2004b; Alzoubi et al., 2006b). Synaptic plasticity impairment has been also reported in hypothyroidism. Hippocampal E-LTP is shown to be impaired during hypothyroidism at the neonatal stages (Niemi et al., 1996; Gilbert and Paczkowski 2003) as well in adulthood (Gerges et al., 2001, 2005; Vara et al., 2003; Alzoubi et al., 2006b). Interestingly, impairment is reported in the pspike amplitude, but not in the fEPSP of E-LTP and L-LTP during adulthood of developmental-onset hypothyroidism (Gilbert 2004; Sui et al., 2005), which suggests impairment of generation of nerve action potentials.

We have reported that hypothyroidism abolishes both E-LTP and L-LTP in area CA1 (Gerges et al., 2001; Gerges and Alkadhi. 2004; Alzoubi et al, 2006a, b; 2007b). However, in hypothyroid animals chronically treated with nicotine, both E-LTP and L-LTP of the CA1 are normal indicating that nicotine protects this area of the hippocampus (Fig 2) (Alzoubi et al, 2006a, b; 2007b). A striking example of the resistance of the DG area to insults is the total

lack of effect of hypothyroidism or hypothyroidism in the presence of chronic stress on both E-LTP and L-LTP of this area as expressed in the effect on the fEPSP or population spike (Gerges et al., 2001; Gerges and Alkadhi. 2004).

## **Sleep deprivation**

Sleep is characterized by cyclic occurrence of two major types of sleep: rapid eye movement (REM) and non-REM (slow wave or delta). Studies have shown that in the course of the night, the two sleep stages are expressed and alternate regularly. A night of sleep consists of five to six cycles, each lasting 90 minutes. Although all sleep cycles in a night last about 90 minutes, the duration of each of the two major sleep types in the cycle changes as the night progresses with REM sleep duration increasing and non-REM duration decreasing. The deepest and most restorative sleep occurs during stage 3 (formerly stages 3 and 4) of non-REM sleep, which is characterized by low overall brain activity. In contrast, REM sleep, which starts after non-REM sleep, is characterized by increased brain activity similar to wakefulness. (McCarley, 2007). Each sleep type seems to impact certain memory mode; for instance, non-REM sleep strengthens declarative memory whereas procedural memory is strengthened with REM sleep (Diekelmann and, Born, 2010). Compelling evidence suggests a strong correlation between sleep deprivation (SD) and cognitive impairment in both animals and humans (Polzella, 1975; Youngblood et al., 1997; Smith et al., 1998; McDermott et al., 2003; Guan et al., 2004; Tartar et al., 2006; Ferrara et al., 2008, Alhaider et al. 2010b; 2011, Aleisa et al., 2011a, b; Alkadhi et al., 2012; Zagaar et al., 2012, 2013a). Animal studies of REM SD using the multiple columns-in-water method showed impaired spatial memory

as tested in the Morris water maze and radial arm water maze (fig 3) (Wang et al., 2009; Alhaider et al., 2010b, 2011; Zagaar et al., 2012, 2013a).

Sleep deprivation suppresses both E-LTP and L-LTP in hippocampal area CA1 (McDermott et al., 2003; Kim et al., 2005; Kopp et al., 2006; Tartar et al., 2006; Alhaider et al., 2010b, 2011, Zagaar et al., 2012, 2013a) and DG areas (Marks and Wayner, 2005; Ishikawa et al., 2006; Alhaider et al., 2010a, 2015; Zagaar et al., 2016, 2013b). The negative effect that SD has on synaptic plasticity is believed to be due to detrimental changes in intracellular signaling. For instance, after 24 hours of REM SD, subunit composition and turnover of glutamate N-methyl-D-aspartate (NMDA) receptors, which are critical to LTP induction, are negatively impacted (Chen et al., 2006). Additionally, as brief as 12 hours of SD impairs phosphorylation of hippocampal glutamate AMPARs, which are central in initiating synaptic plasticity signaling (Hagewoud et al., 2010). Molecular studies in the hippocampus have revealed that the expression of important signaling molecules and growth factors (e.g. MAPK, CREB and BDNF) implicated in LTP and memory are reduced after 8, 24 and 48 hours of SD (Guan et al., 2004; Guzman-Marin et al., 2006; Alhaider et al., 2010a, 2011; Zagaar et al., 2012, 2013a, b). Above all, the expression of p-CaMKII is significantly decreased after 24 hours of SD whereas the levels and activity of calcineurin are increased (Wang et al., 2009; Alhaider et al., 2010a, b; Zagaar et al., 2012, 2013b; alkadhi and Alhaider, 2016).

We have also studied the neuroprotective effects of nicotine on E-LTP of the hippocampal DG and CA1 areas in rats REM sleep deprived for 24hr or 48hr. While SD prevents E-LTP expression in both CA1 and DG areas, chronic nicotine treatment completely prevents the deleterious effects of SD on this response (fig 4) (Aleisa et al., 2011a).

Interestingly, even an acute dose of nicotine (1 mg/kg given 3 times during the 24hr SD period) is able to prevent the effects of post-learning SD on long-term memory (Aleisa et al. 2011b). This may suggest that in SD, even acute nicotine can protect L-LTP, which is the cellular correlate of long-term memory.

## **Schizophrenia**

Individuals with mental illnesses are particularly likely to be heavy smokers; for example, heavy tobacco use among people with schizophrenia is prevalent (Ziedonis et al., 2008). It has been suggested that this may be a form self-medication to ameliorate common cognitive dysfunction seen in schizophrenia. It is indicated that the cognitive dysfunction and inhibition of synaptic function may be due to excessive schizophrenia-linked neuregulin 1 (NRG1) signaling through its receptor ErbB4. LTP, recorded from area CA1 pyramidal cells in acute hippocampal slices, is significantly reduced in NRG1 $\beta$  treated rats. Chronic nicotine treatment (subcutaneous injection of nicotine; 0.5-1 mg/kg, twice daily for 10-15 days) prevents impairment of LTP in NRG1 $\beta$  treated rats (Yamazaki et al., 2017).

## **Other conditions**

Various other conditions where LTP is impaired and brain function compromised have been shown to be restored with nicotine treatment in experimental settings. For example, status epilepticus can cause serious brain damage resulting in cognitive dysfunction including impairment of memory and attention. In experimental convulsive status epilepticus, recordings from acute hippocampal slices show severe impairment of LTP, which is reversed in the presence of nicotine (Xu et al., 2017). Even the effects of aging on cognitive function seem to be reduced with nicotine. Experiments in hippocampal area CA1 slices of aged F44 rats reveal significant decline in synaptic plasticity. These age-related

alterations seem to involve both presynaptic and postsynaptic mechanisms, which may be related to the observed poor spatial memory acquisition and retention in these aged rats (Deupree et al., 1993). The threshold for induction of LTP increases with age. This age-induced impairment of LTP induction is reversed with nicotine treatment (Fujii and Sumikawa, 2001). The age-related inhibition of LTP in the DG is also attenuated by nicotine (Curran and O'Conner, 2002). Environmental contaminants such as the heavy metal Lead can cause marked cognitive impairments in children (Lidsky & Schneider, 2003; Meng et al., 2005) and experimental animals (Lasley & Gilbert, 1999; Ruan et al., 2000). Previous studies have reported that chronic lead exposure during development impairs the induction of LTP in the rat hippocampus (Lasley & Gilbert, 1999; Ruan et al., 2000). Nicotine attenuates deficits in spatial learning in rats chronically exposed to lead (Zhou & Suszkiw, 2004) and rescues LTP (Wang et al., 2006).

### **Concluding remarks**

Most reports have shown that nicotine does not improve cognition in healthy animals but seems to have a protective effect against conditions that impair cognitive abilities. Only high doses of nicotine (e.g. 5 mg/kg and higher) have been reported to enhance memory performance of “normal” animals in the radial arm maze task (Bancroft and Levin 2000; Bettany and Levin 2001). However, it has been suggested that environmental conditions, such as noise stress, are necessary for revealing the positive effects of nicotine on memory (Grobe et al., 1998), therefore, since stress impairs short-term memory, which is prevented by nicotine; this neuroprotective effect of the drug may appear as enhancement in these seemingly normal animals.

It has been reported that smokers have a lower risk of developing neurodegenerative diseases and other neuropsychiatric disorders. For example, schizophrenic patients seemingly relieve the symptoms of the disorder with tobacco smoking. Thus, the increase in the rate of tobacco products use during conditions such as chronic stress and schizophrenia could be a self-medication to counteract the harmful effect of these conditions on cognitive function. Therefore, nicotine and nicotine-like compounds have been proposed as potential treatment for neuropsychiatric conditions. These suggestions, however, raise serious ethical issues, because nicotine is a potentially toxic substance and tobacco smoking is a major risk factor for cancers and heart and lung diseases.

In addition to other effects, studies have shown that nicotine increases the levels of neuronal growth factors (Maggio et al., 1997; Belluardo et al., 1998). Among the neuronal growth factors that are affected by nicotine is brain-derived neurotrophic factor (BDNF), which plays a principal role in the expression and support of synaptic plasticity including LTP (Figurov et al., 1996; Ying et al., 2002). BDNF is the most abundant neuronal growth factor in the brain (Webster et al., 2002; reviewed in: Cunha et al., 2010, Machaalani and Chen, 2018). BDNF produces its positive effects on neuronal development, growth and synaptic plasticity through activation of tyrosine kinase receptor B (TrkB) (Fayard et al., 2005), which eventually leads to involvement of cAMP-response-element-binding protein (CREB) to regulate genes expression involved in the expression and support of LTP (Ernfors and Bramham, 2003).

The majority of studies provides strong evidence showing that exposure to nicotine leads to increased brain BDNF levels (Zhang et al., 2010; Suriyaprom et al., 2013; Jamal et al., 2015; Neves et al., 2017; See Machaalani and Chen, 2018 for review). The expression of BDNF

and its TrkB receptor are linked to  $\alpha 7$ nAChRs where evidence shows BDNF and nAChRs mutually influencing each other (Freedman et al., 1993; Zhou et al., 2004). Thus, the role of BDNF in the neuroprotective effects of nicotine merits further investigation.

In summary, this short review discusses the effects of nicotine on LTP, which is widely considered as a correlate of learning and memory is described. The efficacy of neuroprotective effect of nicotine in preventing LTP impairment associated with a variety of models of disease conditions is discussed. Reports from this lab as well as others have shown that chronic nicotine treatment prevented memory deficits seen in animal models of AD, stress, hypothyroidism, sleep deprivation, schizophrenia among others, likely by preventing impairment of LTP.

**Authorship contribution:**

Dr. Karm Alkadhi wrote the manuscript

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**Footnotes:**

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## Figures Legends

**Figure 1:** The protective effect of nicotine on synaptic plasticity in area CA1 of A $\beta$  rat model of Alzheimer's disease with chronic stress. (A) Chronic nicotine treatment prevents impairment of early phase LTP (E-LTP) caused by i.c.v. infusion of A $\beta$  in A $\beta$  rat model of Alzheimer's disease. E-LTP of the CA1 region was evoked by HFS (applied at time 0) of the Schaffer collateral/commissural pathway of urethane-anesthetized rats. (B) Nicotine prevents stress-exacerbated impairment of hippocampal late-phase long-term potentiation (L-LTP) in area CA1 of A $\beta$  rats. L-LTP was induced by multiple high frequency stimulation (MHFS) applied at time 0. Both E-LTP and L-LTP were measured as increases in slope of field excitatory postsynaptic potential (fEPSP). Each point is the mean  $\pm$  S.E.M. from 5-7 rats. \* Indicates points are significantly different from control group and # indicates points are significantly different from all other groups; (p<0.05). Modified from (Srivareerat et al., 2011; Alkadhi et al., 2011).

**Figure 2:** Chronic nicotine treatment reverses hypothyroidism-induced impairment of synaptic plasticity in area CA1 of rat hippocampus. (A) E-LTP was measured as an increase in f-EPSP slope. The fEPSP slope in all points after HFS was significantly (p<0.05) lower in the hypothyroid group compared with the other groups. E-LTP magnitude, in nicotine-treated hypothyroid rats, was comparable with that in control or nicotine-treated rats. Similar results were obtained with L-LTP of area CA1(B). Each point in each group is the mean  $\pm$  SEM from 6 to 7 rats. Methods details are as in Figure 1. Adapted from (Alzoubi et al., 2006 a, b). \* Indicates points are significantly different from all other groups .

**Figure 3:** Nicotine treatment (24 h) prevents sleep deprivation (SD 24 hour)-induced impairment of spatial learning and short-term memory (30-min) (A) as tested in the radial arm water maze. The RAWM is a black circular pool filled with water at room-temperature containing six swim paths from one open central area. The experiments are carried out in a dimly lit room with visual cues placed on the surrounding walls. Each rat is randomly assigned a goal arm, which contains a hidden black platform (2 cm below the water level) near the end of the arm. The rats are randomly released at an arm different from the goal arm where they would swim and locate the platform, which is submerged about 1 cm under the water. The rats were allowed a maximum time of 1 minute for each learning trial or memory tests. An error was counted when the rat entered more than halfway into an arm other than the goal arm. The number of errors ranged from 1 to a maximum of 7, as the rat could only swim into 7 arms within 1 minute. If the rat failed to locate the platform within 1 minute, the rat was manually guided to the platform and is scored with 7 errors. Upon reaching the platform, the rat was allowed 15 seconds sitting time on the platform before the next trial began. The effect of SD on short-term memory is also depicted in (B). Note impaired learning by SD in the second half of the trials. Nicotine administration (SD+Nic) prevents effects of SD on learning and memory. Data are presented as mean  $\pm$  SEM (N= 9–11 rats). \* Indicates significant difference from control, Nic and SD/Nic group. (from Aleisa et al., 2011a)

**Figure 4:** E-LTP of area CA1 was absent in rats sleep deprived for 24h (A) and 48h (B). Nicotine treatment completely prevented sleep deprivation-induced blockade of E-LTP. Each

point is the mean $\pm$  SEM from four to seven rats. \* Indicates points are significantly different from all other groups . Methods details are as in Figure 1. (Adapted from Aleisa et al., 2011).

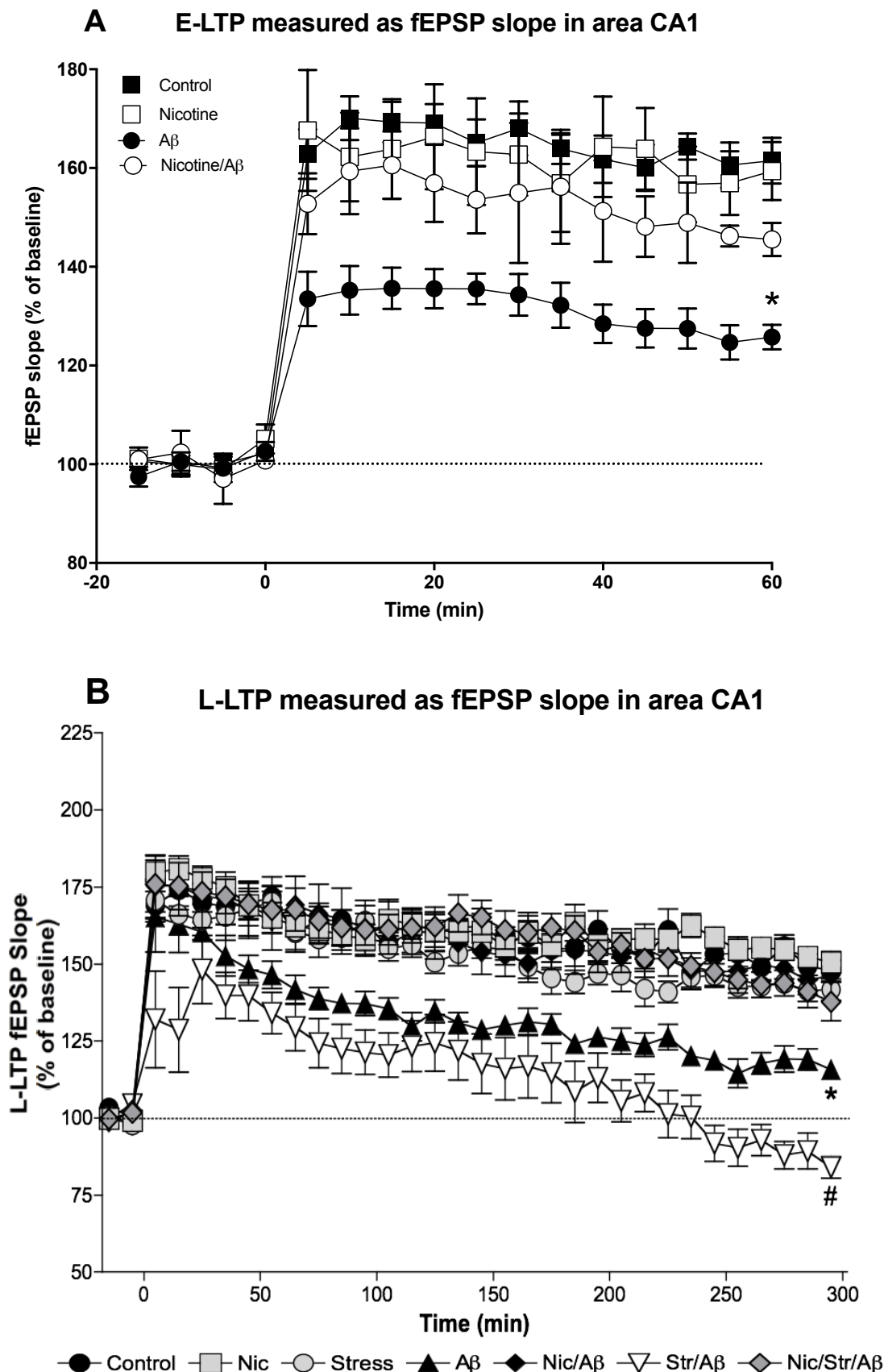


Fig 2

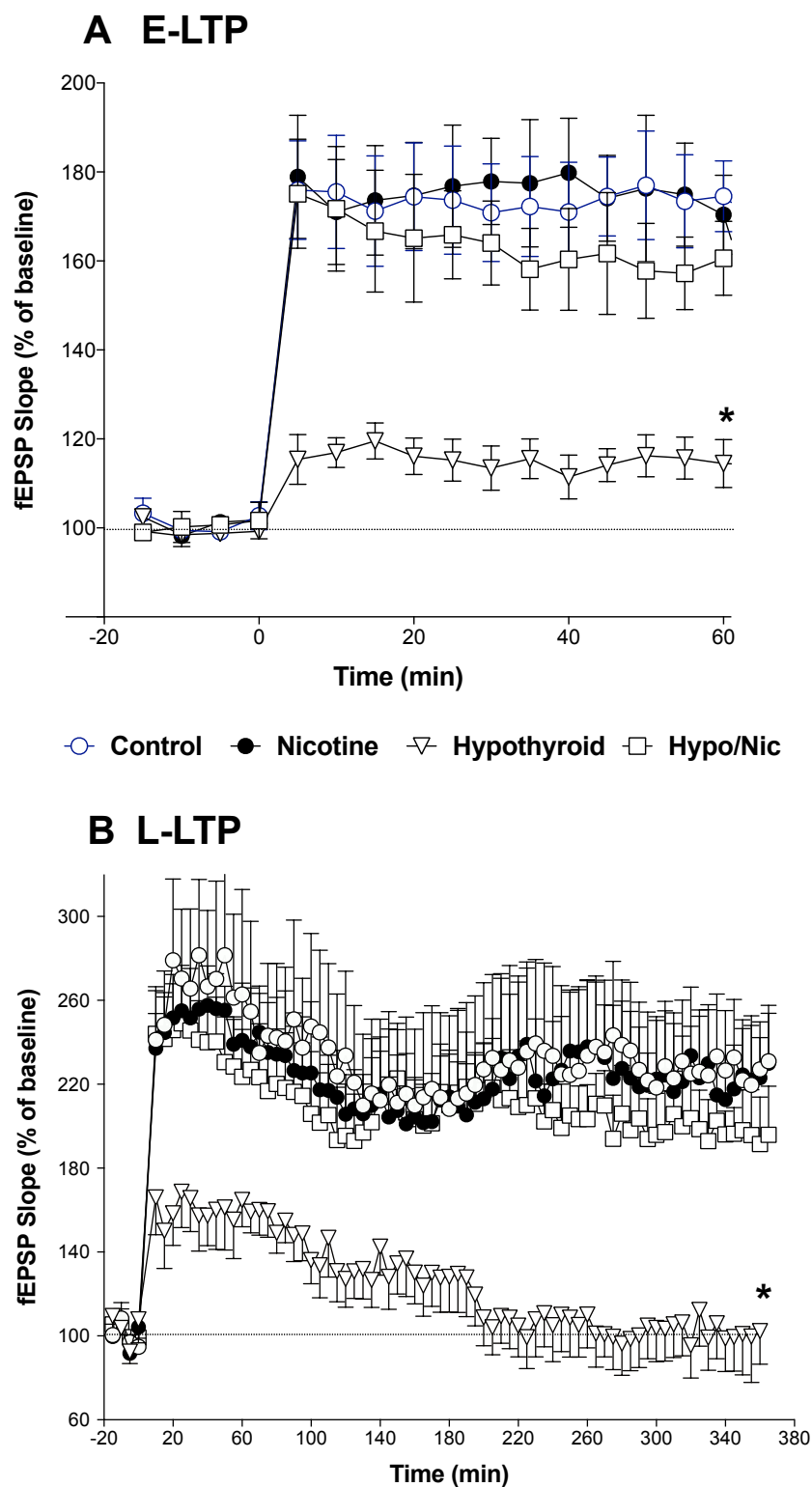


Fig 3

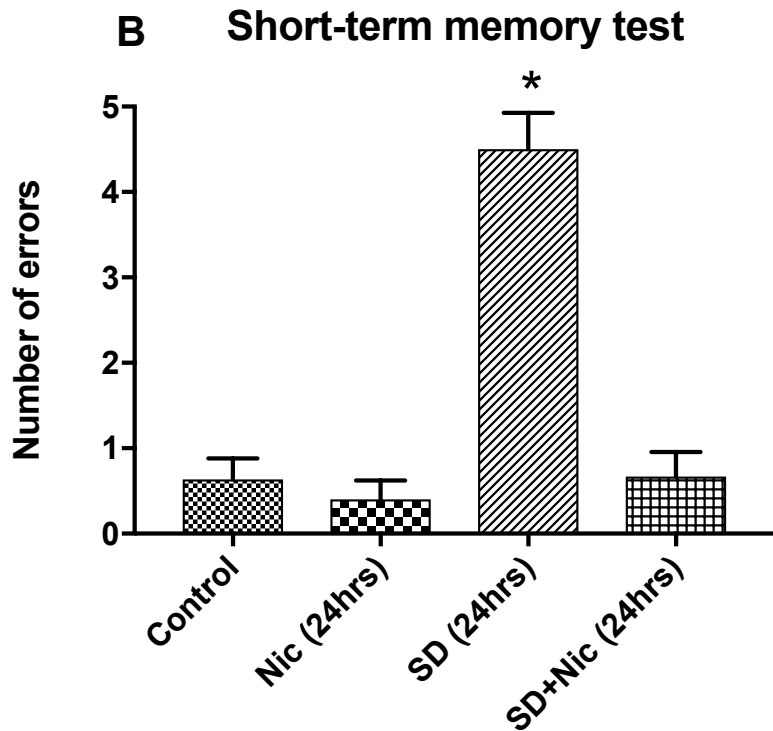
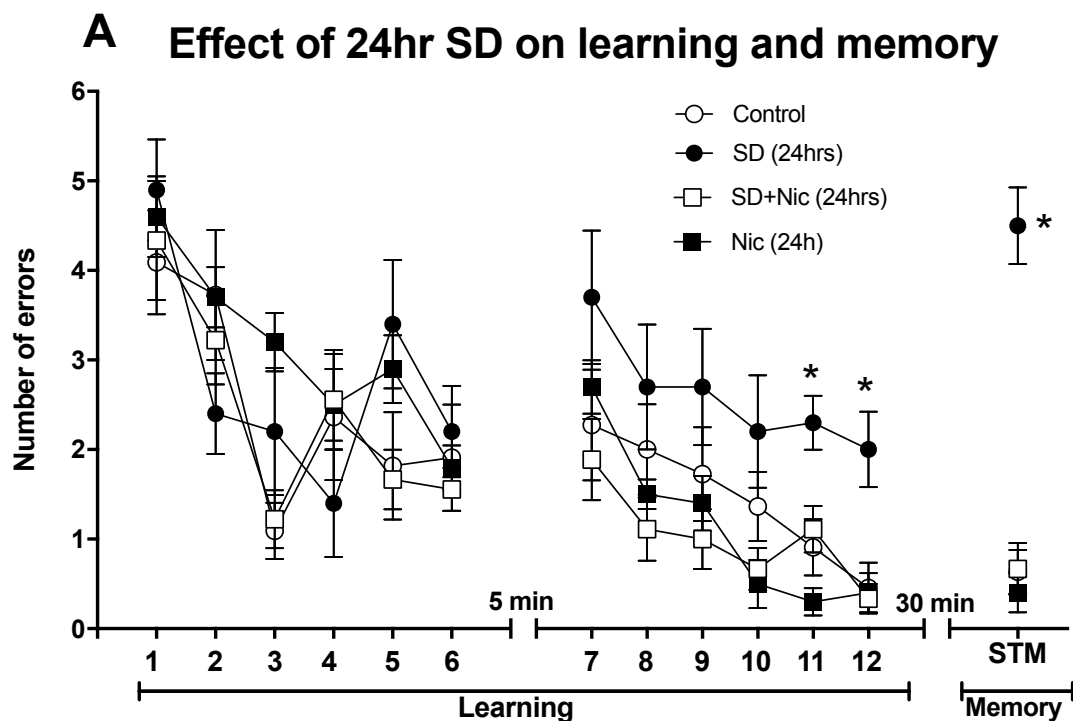


Fig 4

