and irritability symptoms, ii) have little to no effect on inappropriate speech or social withdrawal, and iii) show significant weight gain and sedative side effects. A recent study with autistic individuals showed that D-cycloserine (DCS), an NMDAR glycine-site partial agonist, significantly improved social withdrawal (Posey et al., 2004).

[0006] Viable therapy for neuronal dysfunction associated with memory loss (e.g., memory loss that accompanies early stage Alzheimer's disease) is another area with limited success. Long-term potentiation in hippocampal slices however has emerged as a model system for study of physiological and molecular mechanisms that underlie normal learning and memory processes. For example, naturally secreted oligomers of amyloid beta protein (Aβ) have been shown to inhibit long-term potentiation in hippocampal slices.

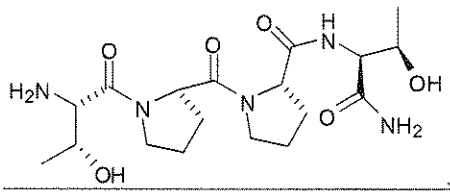
[0007] Huntington's disease (HD) is an autosomal dominant disorder caused by an expanded and unstable CAG trinucleotide repeat that causes a progressive degeneration of neurons, primarily in the putamen, caudate nucleus, and cerebral cortex. HD is characterized by movement abnormalities, cognitive impairments, and emotional disturbances, which eventually culminates in death around 15-20 years after the onset of motor symptoms.

[0008] The HD 51 CAG rat utilizes a human HD mutation containing an allele with 51 CAG repeats. This animal model exhibits progressive neurological, neuropathical, and neurochemical phenotypes that closely resemble the late manifesting and slow progression of HD found in humans, and displays HD-like symptoms, such as cognitive impairments and progressive motor dysfunction, as well as neuropathological characteristics, such as neuronal intranuclear inclusions and enlarged lateral ventricles. The HD 51 CAG rat closely resembles the human condition, making it a good candidate to study behavioral, cellular, and molecular markers of the disease.

[0009] Known therapies underscore the need for improved approaches to the treatment of autism, Huntington's disease, and associated disorders and/or conditions with compounds that can provide improved efficacy and/or reduced undesirable side effects.

SUMMARY

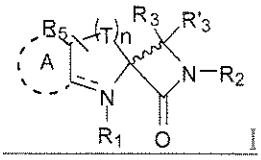
[0009a] In one aspect, there is provided the use of GLYX-13:



, or pharmaceutically acceptable salt thereof,

or

a pharmaceutically effective amount of a compound represented by Formula I:



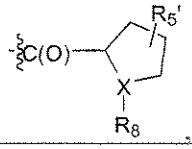
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and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof; wherein

T is, independently for each occurrence, CR_4R_4', and n is 0, 1, 2 or 3;

A is optionally present and is selected from phenyl or pyridine, wherein A is optionally substituted by one or more substituents selected from R_a;

R_1 is selected from the group consisting of H, hydroxyl, $-S(O)_2-C_{1-4}$alkyl; $-SO_2$, C_{1-4}alkyl, C_2-C_4alkenyl, phenyl, R_7, or



, wherein C_{1-4}alkyl, C_{2-4}alkenyl, or phenyl is optionally substituted by one or more substituents selected from R_a;

X is CH or N;

R_3 and R_3' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, C_{1-4}alkyl, amido, amine, or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_4 and R_4' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, C_{1-4}alkyl, amido, amine, C_{1-4}alkoxy or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, and phenyl are optionally substituted by one or more substituents selected from R_a;

R_5 is selected from the group consisting of H, R_7, $-S(O)_2$, $S(O)_2-C_1-C_4$alkyl, C_{1-4}alkyl, hydroxyl, or phenyl wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_5 and R_5' are each independently selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, cyano, amino, phenyl, and hydroxyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_7 is selected from group consisting of $-C(O)-R_9$, $-C(O)-O-R_9$, or $-C(O)-NR_9-R_9$,

R_9 is selected from the group consisting of H, C_{1-4}alkyl, phenyl, or heterocyclic, wherein C_{1-4}alkyl, phenyl or heterocyclic is optionally substituted by 1, 2 or 3 substituents selected from R_b

R_8 is selected from group consisting of H, $-C(O)-C_{1-4}$alkyl or $C(O)-O-C_{1-4}$ alkyl, wherein C_{1-4}alkyl is optionally substituted by 1, 2 or 3 substituents selected from R_a;

R_a is selected, independently for each occurrence, from carboxy, hydroxyl, halogen, amino, phenyl, C_{1-4}alkyl, and C_{1-4}alkoxy;

R_b is selected, independently for each occurrence, from the group consisting of carboxy, hydroxyl, halogen, amino, phenyl, C_{1-4}alkyl, C_{1-4}alkoxy, and $-NH-R_c$;

R_c is selected, independently for each occurrence from the group consisting of: $-C(O)-O-C_{1-4}$alkyl; and $-C(O)-C_{1-4}$alkyl; and

R_d is selected, independently for each occurrence, H and C_{1-4}alkyl;

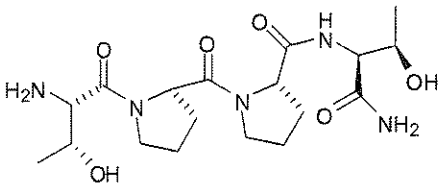
and pharmaceutically acceptable salts, N-oxides or stereoisomers thereof, in the manufacture of a medicament for treating autism in a patient in need thereof.

[0010] A method for treating autism in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a NMDA receptor glycine site partial agonist, is provided herein. For example, the present ~~invention~~disclosure is directed in part to

a method for treating autism by administering a therapeutically effective dose of GLYX-13, as disclosed herein, or derivative thereof, for example, a compound having NMDA receptor glycine site partial agonist activity, *e.g.*, a compound that binds to the glycine site of a NMDA receptor, such as a compound disclosed herein. For example, provided herein is a method for treating autism in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound that modulates a glycine site on a NMDA receptor.

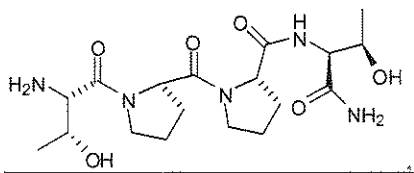
[0011] In other embodiments, methods of treating conditions selected from the group consisting of epilepsy, AIDS, AIDS dementia, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, autism (and autism spectrum disorder subtypes), fragile X syndrome, tuberous sclerosis, attention deficit disorder, olivio-ponto-cerebellar atrophy, cerebral palsy, Parkinson's disease, drug-induced optic neuritis, peripheral neuropathy, myelopathy, ischemic retinopathy, glaucoma, cardiac arrest, stroke, ischemia, behavior disorders, impulse control disorders, frontal temporal dementia, schizophrenia and bipolar disorders are provided, comprising administering a NMDA receptor partial agonist such as GLYX-13 or a compound disclosed herein, to a patient in need thereof.

[0012] For example, in some embodiments, a contemplated compound that is capable of modulating the glycine site of a NMDA receptor is represented by (GLYX-13):



or pharmaceutically acceptable salts thereof.

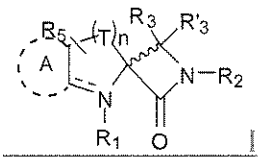
[0012a] In one aspect, there is provided the use of GLYX-13:



, or pharmaceutically acceptable salt thereof,

or

a pharmaceutically effective amount of a compound represented by Formula I:



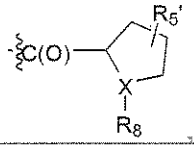
I

and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof; wherein

T is, independently for each occurrence, CR_4R_4', and n is 0, 1, 2 or 3;

A is optionally present and is selected from phenyl or pyridine, wherein A is optionally substituted by one or more substituents selected from R_a;

R_1 is selected from the group consisting of H, hydroxyl, $-S(O)_2-C_{1-4}$alkyl; $-SO_2$, C_{1-4}alkyl, C_2-C_4alkenyl, phenyl, R_7, or



, wherein C_{1-4}alkyl, C_{2-4}alkenyl, or phenyl is optionally substituted by one or more substituents selected from R_a;

X is CH or N;

R_3 and R_3' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, C_{1-4}alkyl, amido, amine, or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_4 and R_4' are independently selected from the group consisting of H, halogen, hydroxyl, phenyl, C_{1-4}alkyl, amido, amine, C_{1-4}alkoxy or C_{2-4}alkenyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, and phenyl are optionally substituted by one or more substituents selected from R_a;

R_2 is selected from the group consisting of H, R_7, $-S(O)_2$, $S(O)_2-C_1$-C_4alkyl, C_{1-4}alkyl, hydroxyl, or phenyl wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_5 and R_5' are each independently selected from group consisting of H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, cyano, amino, phenyl, and hydroxyl, wherein C_{1-4}alkyl, C_{2-4}alkenyl and phenyl are optionally substituted by one or more substituents selected from R_a;

R_7 is selected from group consisting of –C(O)-R_9, -C(O)-O-R_9, or -C(O)-NR_6-R_9;

R_9 is selected from the group consisting of H, C_{1-4}alkyl, phenyl, or heterocyclic, wherein C_{1-4}alkyl, phenyl or heterocyclic is optionally substituted by 1, 2 or 3 substituents selected from R_b

R_8 is selected from group consisting of H, –C(O)- C_{1-4}alkyl or C(O)-O- C_{1-4} alkyl, wherein C_{1-4}alkyl is optionally substituted by 1, 2 or 3 substituents selected from R_a;

R_a is selected, independently for each occurrence, from carboxy, hydroxyl, halogen, amino, phenyl, C_{1-4}alkyl, and C_{1-4}alkoxy;

R_b is selected, independently for each occurrence, from the group consisting of carboxy, hydroxyl, halogen, amino, phenyl, C_{1-4}alkyl, C_{1-4}alkoxy, and -NH-R_c;

R_c is selected, independently for each occurrence from the group consisting of: -C(O)-O-C_{1-4}alkyl; and –C(O)-C_{1-4}alkyl; and

R_d is selected, independently for each occurrence, H and C_{1-4}alkyl;

and pharmaceutically acceptable salts, N-oxides or stereoisomers thereof, in the manufacture of a medicament for treating memory loss that accompanies early stage Alzheimer's disease in a patient in need thereof.

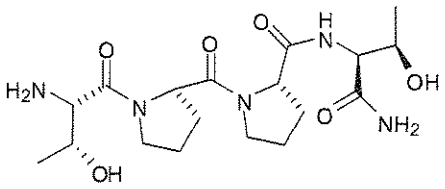
[0013] Also contemplated herein is a method of treating Alzheimer's disease, or a method of treating memory loss that accompanies early stage Alzheimer's disease in a patient in need thereof, comprising administering to the patient a disclosed compound.

[0014] In another embodiment, methods are provided herein of treating attention deficit disorder, ADHD, schizophrenia, anxiety, amelioration or treatment of addiction, e.g., of opiate, nicotine and/or ethanol addiction, traumatic brain injury, post-traumatic stress syndrome and/or Huntington's chorea (i.e., Huntington's disease) in a patient in need thereof, comprising administering to the patient a compound disclosed herein.

[0015] In some embodiments, a contemplated compound is administered intravenously, intraperitoneally, intramuscularly, or subcutaneously, for example, a contemplated method may include administering a single-dose of said compound. In some embodiments, disclosed methods may provide, after about 1 day, or even after 8 days of administration of a disclosed compound, substantial improvement in one or more autism symptoms of a patient.

[0016] In some embodiments, disclosed compounds may be administered daily. A pharmaceutically effective amount of a disclosed compound may be about 0.01mg/kg to about 1000 mg/kg.

[0017] Also provided herein is a method of treating autism in a patient in need thereof, comprising administering to said patient a single dose of a compound represented by:



(GLYX-13)

[0018] or pharmaceutically acceptable salts thereof, wherein after 1 day, or after 8 days, the patient has substantial improvement in autism symptoms. A single dose may include for example, about 0.01 mg/kg to about 1000 mg/kg of a disclosed compound.

[0019] In another embodiment, the disclosed ~~invention~~disclosure relates to administering a di-pyrrolidine peptide compound comprising the sequence Thr-Pro-Pro-Thr, or exemplified by Formula A (GLYX-13) for the treatment of autism in mammals including humans.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIGURE 1 depicts Mean ± SEM (A) time spent in direct social contact in adult male Long Evans rats selectively bred for low or random rates of play-induced pro-social USVs. Animals were tested in pairs with a conspecific of the same selectively bred line. (B) Rates of conspecific play induced pro-social USVs (frequency-modulated 50 kHz calls) in adult male low and random-line animals. (C) Proportion of total conspecific play induced USVs that are monotonous (i.e., bandwidth less than 7 kHz; n = 14-20 per group. * $P < .05$ Fisher PLSD post hoc test, 2 tailed.

[0021] FIGURE 2 depicts Mean ± SEM (A) rates of conspecific play induced pro-social USVs (frequency-modulated 50 kHz calls) in adolescent male low-line rats pretreated with