



Review article

The Role of Glutamate in Language and Language Disorders - Evidence from ERP and Pharmacologic Studies

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ABSTRACT

Current models of language processing do not address mechanisms at the neurotransmitter level, nor how pharmacologic agents may improve language function(s) in seemingly disparate disorders. L-Glutamate, the primary excitatory neurotransmitter in the human brain, is extensively involved in various higher cortical functions. We postulate that the physiologic role of L-Glutamate neurotransmission extends to the regulation of language access, comprehension, and production, and that disorders in glutamatergic transmission and circuitry contribute to the pathogenesis of neurodegenerative diseases and sporadic-onset language disorders such as the aphasic stroke syndromes. We start with a review of basic science data pertaining to various glutamate receptors in the CNS and ways that they may influence the physiological processes of language access and comprehension. We then focus on the dysregulation of glutamate neurotransmission in three conditions in which language dysfunction is prominent: Alzheimer's Disease, Fragile X-associated Tremor/Ataxia Syndrome, and Aphasic Stroke Syndromes. Finally, we review the pharmacologic and electrophysiologic (event related brain potential or ERP) data pertaining to the role glutamate neurotransmission plays in language processing and disorders.

Our understanding of human language and language disorders has steadily increased in the past several decades. The advent of functional neuroimaging has significantly expanded upon the classical lesion-based neuroanatomical models of language processing to include widely-distributed functional language networks. However, these network models do not address language regulation at a neurotransmitter level, or how pharmacologic agents such as the NMDA antagonist memantine may improve language function(s) in disorders as seemingly disparate as Alzheimer's disease and aphasic stroke syndromes.

In this article, intended for clinicians and scientists, we offer a complementary perspective to current network models by reviewing language processing and its regulation at the neurotransmitter level. We focus on the primary excitatory neurotransmitter in the human brain, L-Glutamate, and pharmacologic and electrophysiologic data pertaining to its role in language disorders. Glutamate neurotransmission has long been implicated in synaptic plasticity and memory formation (Traynelis

et al., 2010) and is extensively involved in various higher cortical functions. We postulate that the physiologic role of glutamate neurotransmission extends to the regulation of language access, comprehension, and production*, and that disorders in glutamatergic transmission and circuitry contribute to the pathogenesis of neurodegenerative and sporadic-onset language disorders such as the aphasic stroke syndromes.

In this review, we use 'language processing' to denote the general access, comprehension, and production of language. We define language 'access' as the retrieval of stored semantic and lexical information, and 'comprehension' as the ability to manipulate lexical and semantic linguistic components (e.g., syntax, context, and word meaning) to decode and interpret incoming information. Language 'production' is defined as the ability to generate novel phrases or sentences *de novo* or by manipulating existing clauses (motor aspects of speaking and writing are outside the scope of this discussion).

As there are no comparable animal or basic neuroscience models to

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establish a direct link between glutamatergic neurotransmission and language, we support their hypothesized association by combining clinical data with relevant basic science data (Section I) and data from preclinical investigations (Section II). We focus on three disorders in which language dysfunction is prominent: Alzheimer's Disease (AD), Aphasic Stroke Syndromes, and Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) to make a case that dysregulation in glutamate neurotransmission, which seems to play a role in the pathogenesis of these diseases, also may be responsible for their disorders of language processing. We also evaluate clinical data from *N*-Methyl-D-Aspartate (NMDA) receptor antagonists memantine and ketamine in event-related brain potential (ERP) studies (Section III) showing that glutamate-modulating drugs may improve outcome in language disorders. We conclude with a brief discussion of future directions in evaluating the role of glutamate neurotransmission in language disorders and introduce other diseases and pharmacologic agents which also may prove useful in assessing this hypothesized association (Section IV).

To our knowledge, this is the first article to combine basic science, pre-clinical, and clinical data from ERP and pharmacologic studies linking glutamate neurotransmission to language processing and disorders. Our aim is to spur more research interest in the proposed association between glutamate and language, so as to provide new insights and more effective therapies for the language disorders.

*Glutamate's involvement is particularly likely in distributed language network models. One early example is Quillian's 1967 spreading activation model, in which semantic memory and search are conceptualized as a cortically spreading wave of excitation from two or more concept nodes in a semantic network; activation propagates until an intersection representing the concept/word of interest is found (Quillian, 1967a; Collins and Loftus, 1975). A similar model of "automatic spreading activation" suggests that a word or concept may prime a distributed network of semantically related concepts by spreading outward from a prime concept to the rest of the semantic network in a hub and spoke fashion. Kiefer gives the example of the word "sour" priming the word "lemon" and supports it with data from an N400 congruity paradigm (Kiefer, 2002). Although neither Quillian nor Kiefer mention neurotransmitters, as the most prominent excitatory neurotransmitter in the human cortex, glutamate is the ideal candidate for propagating such a wave of spreading activation.

1. Overview of Glutamate Receptors

Glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS); it is involved in a variety of higher functions including memory, learning, and attention (Traynelis et al., 2010). The precise role of glutamatergic neurotransmission in language, however, has not been well established. This is in part because language is almost exclusively a human form of communication and research has been limited by the lack of an animal model. Despite these challenges, studies have begun to shed light on the role of glutamatergic neurotransmission in language. Here, we review the literature and posit that the physiologic regulation of glutamate neurotransmission is essential to the proper access, comprehension, and production of linguistic information.

We begin with a review of the four classes of glutamate receptors. We describe the putative mechanisms by which these receptors are involved in language processing using predominantly data from basic research. We will elaborate on these using specific disease models in section two.

1.1. α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Receptor

Endogenous glutamate receptors include three major families of glutamate-gated ion channels and a family of G protein-coupled metabotropic receptors that act through cytoplasmic secondary messengers or by direct influence of membrane-bound ion channels (Meldrum, 2000).

α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) are ubiquitous in the adult human brain. They are the primary mediators of fast excitatory synaptic transmission in the CNS. AMPARs are predominantly located postsynaptically on pyramidal neurons and inhibitory interneurons, but may also be expressed on astrocytes (Meldrum, 2000). Structurally, AMPARs are tetrameric ligand-gated sodium (Na^+) and potassium (K^+) channels assembled from subunits GluA1, 2, 3, and 4. (Fig. 1a) AMPAR subunit compositions (and therefore roles) vary based on anatomic location as well as stage of cortical development.

Learning induces changes in the number of AMPARs at synapses via synaptic plasticity. Activity-induced trafficking of AMPARs in and out of synapses form the basis of long-term potentiation (LTP), a persistent increase in synaptic strength, and long-term depression (LTD), a persistent decrease in synaptic strength. During the induction of LTP, AMPARs are inserted into the post-synaptic membrane from a combination of lateral diffusion from extrasynaptic sites and the exocytosis of AMPARs from intracellular membrane compartments (Makino and Malinow, 2009). Secondary stabilization of newly inserted AMPARs on the postsynaptic membrane (and hence LTP stabilization) is achieved through interactions between activated transmembrane AMPAR regulatory proteins (TARPs) and scaffolding proteins in the postsynaptic density (Chen et al., 2000). AMPARs also undergo post-translational modifications at synapses; CaMKII and protein kinase A (PKA) can phosphorylate GluA1 subunits of synaptic AMPARs, increasing channel conductance and opening probabilities (Banke et al., 2000). Dephosphorylation of AMPARs leads to receptor endocytosis and lysosomal degradation in an activity-dependent manner, which is thought to play a role in LTD (Fortin et al., 2010). Together, these post-translational modifications and receptor trafficking mechanisms are crucial to the LTP and LTD processes.

Diseases that interrupt AMPAR trafficking or modification naturally disrupt homeostasis between LTP and LTD. For example, in Alzheimer's disease synaptic AMPAR density is reduced; A β oligomers bind to AMPAR subunits disrupting receptor trafficking and hyperphosphorylated tau (hTau) disrupts receptor anchoring to post synaptic density proteins (PSD) (D'Amelio et al., 2011).

1.1.1. Calcium-Permeable AMPA Receptors

Most AMPARs are impermeable to Ca^{2+} ions due to the presence of the GluA2 subunit. This is because the mRNA for the GluA2 subunit becomes edited post-transcriptionally resulting in a positively-charged arginine (R) in the ion channel that blocks Ca^{2+} (Huettner, 2015; Wollmuth, 2018). Thus, GluA2-lacking AMPARs are permeable to Ca^{2+} and have been identified in various brain regions (Henley and Wilkinson, 2016). Although the precise function of these calcium-permeable AMPARs (CP-AMPA) remains poorly understood, there is accumulating evidence for their roles in synaptic plasticity and pathologic disease states such as AD and ischemic stroke.

CP-AMPA may be involved in the early phases of synaptic plasticity (Shi et al., 2001). Phosphorylation of membrane-bound, perisynaptic CP-AMPA leads to preferential integration at PSD sites and enhanced synaptic calcium entry, contributing to the induction of LTP (Fortin et al., 2010; Yang et al., 2010). CP-AMPA may also be involved in the induction of late phase-LTP, as Ca^{2+} entry via CP-AMPA has been shown to trigger de novo protein synthesis of new AMPARs via a PI3K (phosphoinositide 3-kinases) and MAPK (mitogen-activated protein kinase) mediated pathway (Park et al., 2018). In the lateral amygdala, physiologic increases in CP-AMPA expression may play a role in the consolidation of emotional (but not neutral) memories and memory retrieval and updating (Torquatto et al., 2019).

On the other hand, excessive increases in CP-AMPA activity contribute to the pathogenesis of multiple diseases such as AD, ischemic/hypoxic brain injury, fragile X syndrome, and epilepsy (Towmey et al., 2018). In early Alzheimer's disease, intracellular oligomeric A β may induce overexpression of synaptic CP-AMPA, which may lead

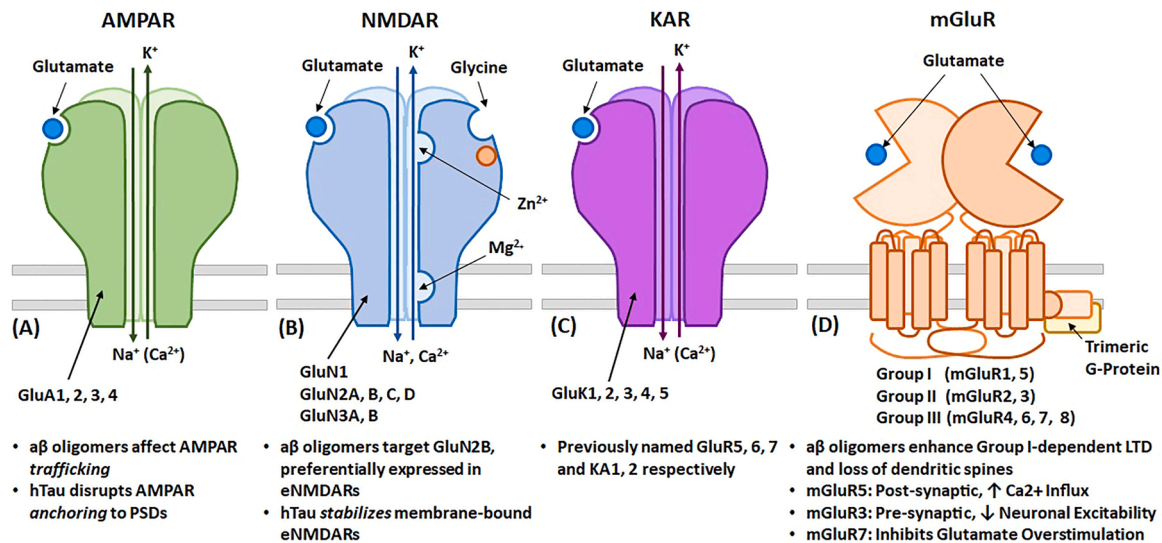


Fig. 1. Glutamate Receptor Compositions.

(A) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Receptor (B) N-Methyl-D-Aspartate (NMDA) Receptor, (C) Kainate Receptor, and (D) Metabotropic Glutamate (mGlu) Receptor

to excitotoxicity (Whitcomb et al., 2015). This may be further amplified by disruption of Ca²⁺ homeostasis, resulting in accelerated disease progression. Epidemiologic research has demonstrated a correlation between low serum vitamin D (specifically 25-Hydroxyvitamin D) levels and increased risk of Alzheimer's Disease and cognitive decline with aging (Miller et al., 2015). Although the pathogenic link between vitamin D and AD is not fully understood, disruption of Ca²⁺ homeostasis may be one among a host of potential mechanisms. Vitamin D is integral to maintaining Ca²⁺ homeostasis in addition to regulating certain epigenetic processes (Berridge, 2016) and low serum vitamin D levels can lead to dysregulation of intracellular Ca²⁺ in neurons as well as accompanying glial cells (Brawek and Garaschuk, 2014).

In ischemic stroke, increased CP-AMPA expression increases neuronal oxidative stress contributing to post-stroke excitotoxicity, cell damage, and degeneration (Twomey et al., 2018; Noh et al., 2005). These mechanisms likely work in concert with NMDAR dysregulation and contribute to the pathogenesis of language dysfunction in these and other diseases. More on this in the upcoming Alzheimer's Disease and Ischemic Stroke Syndromes sections.

1.2. N-Methyl-d-Aspartate (NMDA) Receptors

N-Methyl-D-Aspartate receptors (NMDAR) are ligand-gated calcium (Ca²⁺) channels that are crucially involved in the regulation of synaptic strength. NMDARs are heterotetramers of two obligatory GluN1 subunits and two additional regulatory subunits. These regulatory subunits are primarily GluN2 subunits, of which there are four genes GluN2 (A, B, C, or D), or GluN3 (A or B) (Sanz-Clemente et al., 2013) (Fig. 1b) Like AMPARs, NMDAR function is dictated by its subunit composition, and expression of specific subunits is based on CNS location and changes throughout stages of brain development from embryo to adulthood, as well as synaptic versus extrasynaptic location (Henson et al., 2008).

In addition to ligand binding, NMDAR function is regulated by voltage as the channel pore is blocked at rest by a Mg²⁺ ion removed only upon postsynaptic depolarization (Sanz-Clemente et al., 2013), allowing NMDARs to act as a coincidence detector for both presynaptic and postsynaptic activity. NMDARs are also unique in being the only receptor to require a co-ligand, which can be either glycine or D-serine, though the mechanisms regulating co-ligand availability are not well understood (Sanz-Clemente et al., 2013). Due to these additional gating mechanisms, NMDARs possess a higher activation threshold than other glutamate receptors, but once activated they trigger a cascade of

downstream effects that mediate synaptic plasticity and help maintain neuronal health, though overactivation and influx of Ca²⁺ can lead to excitotoxicity.

1.2.1. Synaptic NMDARs

At most excitatory synapses in the brain, NMDAR activation is important for both LTP and LTD. This bidirectional regulation of synaptic strength is thought to be the neurochemical basis of learning and memory (Broutman and Baudry, 2001). (Fig. 2a) Synaptic NMDARs (sNMDARs) are clustered in large macromolecular signaling complexes, held together by scaffolding proteins such as postsynaptic density-95 (PSD-95). Activation of sNMDARs results in an influx of Ca²⁺ into the dendritic spine, triggering various intracellular signaling cascades, notably, Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC)-mediated pathways, as well as changes in the number of postsynaptic AMPARs (Lau et al., 2009).

A separate but related role for sNMDARs is to promote activity-dependent neuronal survival and protection against cell death. Synaptic NMDAR-dependent Ca²⁺ influx promotes gene transcription via activation of the transcription factor cyclic-AMP responsive element binding (CREB) protein which in turn upregulates pro-cell survival genes such as brain-derived neurotrophic factor (BDNF) (Hardingham and Bading, 2010). BDNF has been implicated in rescuing neurons from NMDAR blockade-induced neuronal death and in regulating all phases (induction, maintenance, and synaptic consolidation) of LTP (Panja and Bramham, 2014). The sNMDAR-CREB pathway also upregulates the expression of activity-regulated inhibitors of death (AID) genes, which may render mitochondria more resistant to cellular stress and toxic insults (Zhang et al., 2009).

Synaptic NMDARs also suppress expression of pro-apoptotic mechanisms in a CREB-independent manner. One such mechanism is via suppression of the pro-apoptotic Bcl2 homology domain 3 (BH3)-only member gene (Puma), which is upstream of a cytochrome C release-mediated, p53-independent, apoptotic cascade (Léveillé et al., 2010). Another sNMDAR pathway leads to suppression of the transcription factor forkhead box protein O (FOXO), which promotes neuronal death following excitotoxic injury and oxidative stress (Dick and Bading, 2010).

These transcription-dependent changes work in concert with the receptor level-changes to maintain activity-dependent synapses and in turn, promotes consolidation of LTP and memory. Failure to maintain synaptic connections may lead to a breakdown of globally-distributed

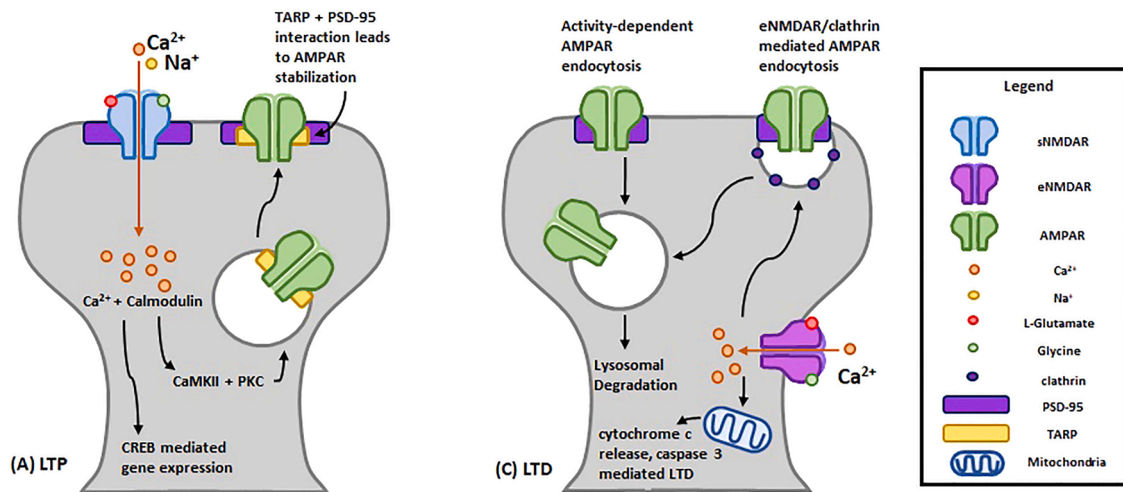


Fig. 2. LTP and LTD.

N-Methyl-D-Aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Receptor-mediated (A) Long-Term Potentiation (LTP) and (B) Long-Term Depression (LTD).

cortical networks, including those responsible for language storage and access; such disruptions may present clinically as a failure to retrieve relevant semantic information.

1.2.2. Extrasynaptic NMDARs

In contrast to synaptic NMDARs, extrasynaptic NMDARs (eNMDAR) are typically located in clusters at the peri-synaptic zone or the dendritic shaft, usually in a contact area between the dendrite and adjacent astrocytes. (Petralia et al., 2010) eNMDARs preferentially express the GluN2B subunit, which as we discuss later, may be a target for beta-amyloid ($A\beta$) oligomers in Alzheimer's Disease (Papouin and Oliet, 2014; Ferreira et al., 2012). From an electrophysiological perspective, eNMDARs were initially defined as NMDARs not activated by low frequency afferent stimulation, or lacking in response to spontaneous glutamate release producing miniature EPSPs (Papouin and Oliet, 2014). This distinction is not entirely accurate* but is useful in thinking of eNMDAR activation as the product of excessive synaptic stimulation and the resultant glutamate spillover at synaptic junctions.

Selective activation of eNMDARs has been associated with inducing LTD via signaling cascades that lead to destabilization of AMPAR-binding membrane anchoring proteins and clathrin-mediated AMPAR endocytosis (Liu et al., 2013; Collingridge et al., 2010). (Fig. 2b) eNMDAR activation also seems to favor neuronal death by suppressing pro-survival gene expression - inactivating CREB and extracellular signal-regulated kinases Erk1/2 (Papouin and Oliet, 2014) and promoting apoptotic cell-death signaling through upregulation of caspase-3 (Hardingham and Bading, 2010).

That there is a receptor dedicated to promoting neuronal death and attenuating synaptic transmission seems counterintuitive, but this pathway may serve as a last-ditch effort to prevent runaway propagation of excitotoxic impulses throughout the CNS by curtailing aberrantly firing synapses at its source. Indeed, data suggest that extrasynaptic NMDARs trigger glutamate-induced cell death only when co-activated with pathologically activated synaptic NMDARs (e.g. by excessive synaptic stimulation), but that isolated eNMDAR activation does not result in excitotoxicity (Zhou et al., 2015). This seems to support the idea of eNMDAR-associated neuronal death as a fail-safe mechanism that specifically affects neurons at risk for excessive activation.

Taken together, NMDARs may contribute to global language processing and the integrity of semantic information storage and retrieval: activation of synaptic NMDARs is largely beneficial to neuronal survival and maintenance of LTP, whereas extrasynaptic NMDAR activation plays an antithetical role, promoting LTD and neuronal death. It is

reasonable to assume that in certain disease processes, selective suppression of eNMDARs is neuroprotective and ameliorates or prevents symptom progression, e.g. language deficits. This hypothesis provides a basis for clinical studies using the selective NMDAR antagonists, ketamine and memantine. Both agents are noncompetitive open-channel blockers of NMDARs; memantine possesses a low affinity for the Mg^{2+} binding pocket and is purportedly selective for extrasynaptic receptors (Lipton, 2004). (Fig. 3) These studies are reviewed in Part III – Pharmacologic and ERP Evidence from Clinical Research.

*In practice, eNMDARs possess a tonic and a phasic calcium current. The tonic low-amplitude Ca^{2+} influx current is regulated by glial-dependent modulation and reuptake of ambient extrasynaptic glutamate (Fleming et al., 2011). The phasic slow inward large-amplitude Ca^{2+} current is thought to be induced by vesicular release of glutamate from astrocytes into the extrasynaptic space, possibly mediated by astrocytic metabotropic glutamate receptors (Fellin et al., 2004a). This implies a substantially more complicated role for physiologic firing and regulation of eNMDAR than as an excitotoxic failsafe, and as such is an area of active on-going research, some of which we will touch on in subsequent sections.

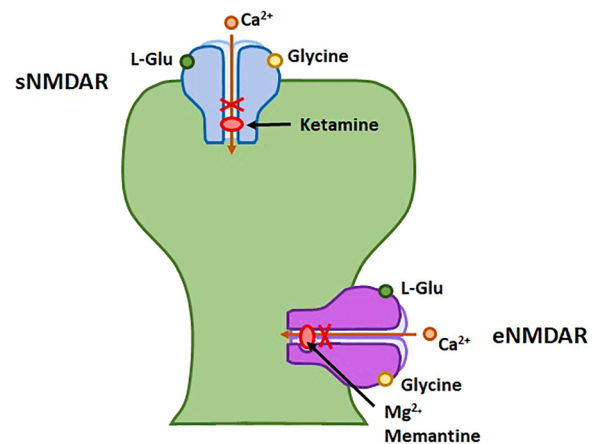


Fig. 3. Binding site of NMDAR antagonists Memantine and Ketamine.

Memantine has a low affinity for the Mg^{2+} binding site and is thought to be relatively selective for extrasynaptic NMDAR receptors.

1.3. Kainate Receptors

Kainate, or Kainic Acid Receptors (KAR) are the third family of ionotropic glutamate receptors, named after the receptor agonist Kainate, a neurotoxin isolated from the red algae *Diogenea simplex* used in epilepsy research (Laycock et al., 1989). Compared to fast excitatory signaling by AMPARs, synaptic KARs' excitatory post-synaptic currents (EPSC) possess slower decay kinetics, which make them especially well-suited for regulation of metaplasticity (via temporal and amplitude modulation of pre- to post-synaptic firing patterns) (Yang et al., 2007; Sachidhanandam et al., 2009; Castillo et al., 1997).

Structurally, KARs are tetramers composed of the subunits GluK1, GluK2, GluK3, GluK4, and GluK5 (previously named GluR5–GluR7 and KA1 and KA2, respectively). (Fig. 1c) Of these subunits, GluK1, GluK2, and GluK3 can form functional homomeric and heteromeric receptors, but GluK4 and GluK5 require one of the other subunits to form functional receptors. Subunit composition and function of receptors are highly location specific and compartmentalized; CA3 and CA1 KARs produce vastly different effects (Carta et al., 2014).

Synaptic KARs at mossy fiber to pyramidal cell synapses in layer CA3 of the hippocampus act as excitatory ionotropic receptors at physiologic levels of glutamate release. However, with higher frequency stimulation, synaptic KARs act metabotopically, potentiating EPSPs by suppressing the inhibitory K⁺ afterhyperpolarization current via a protein kinase C (PKC)-mediated signaling pathway (Ruiz et al., 2005). In this synaptic coupling, KAR's slow decay kinetics allows it to act as a conditional amplifier for inputs to CA3 pyramidal cells, leading to modulation of short-term plasticity in the setting of repetitive stimulation by mossy fibers (Sachidhanandam et al., 2009).

Presynaptic KARs on the other hand, induce γ -aminobutyric acid (GABA) release from CA1 interneurons under physiologic conditions (e.g. ambient glutamate spillover), likely via a metabotropic signaling pathway, producing small inhibitory postsynaptic currents in post-synaptic pyramidal cells (Jiang et al., 2001). Under higher intensity stimulation, KAR activation results in short term facilitation of IPSPs (Lourenço et al., 2010). In this GABAergic synaptic coupling, KAR's slow decay kinetics allows it to reset the phase of spontaneously firing CA1 interneurons (Yang et al., 2007), which may play a critical role in modulating neuronal network oscillations and information transfer (Carta et al., 2014; Goldin et al., 2007).

How KAR regulation at the synaptic level affects the hippocampus, both in physiologic and disease states is an area of active research. Consistent with KAR's role in metaplasticity and fine tuning of synaptic firing patterns, GluK2 knockout mice, with affected CA3 KARs and therefore dentate gyrus to CA3 synapses, have demonstrated moderate memory deficits in pattern completion and spatial tuning of CA1 cells (Nakashiba et al., 2008). CA3 KARs have been implicated in the modulation of cortical gamma oscillations in laboratory conditions and therefore may play a role in modulating and/or propagating thalamic oscillatory activity (Fisahn et al., 2004). The relationship between KARs and language has not been established. However, gamma-range oscillatory activity has been implicated in binding different sensory representations into a cohesive semantic memory, including object-word associations (Hart et al., 2007).

1.4. Metabotropic Glutamate (mGlu) Receptors

Metabotropic glutamate receptors (mGluRs) are dimeric class-C G protein-coupled receptors (GPCR) found throughout the central and peripheral nervous systems and peripheral organs. There are eight receptor subtypes (mGluR1–8) each with its own splice variants, broken into 3 groups based on sequence homology, G-protein coupling, and ligand selectivity (Niswender and Conn, 2010). Here we briefly discuss characteristics of each group and focus on mGluR3, 5, and 7 given their role in synaptic plasticity and neurodegenerative diseases (Fig. 1d).

Group I receptors include mGluR1 and 5, are generally located post-

synaptically, and are linked to the regulation of synaptic plasticity via activation of mammalian target of rapamycin (mTOR) and ERK pathways. (Page et al., 2006) mGluR5 is expressed preferentially in the hippocampus, cortex, and striatum (Romano et al., 1995) and has been shown to be functionally linked to the GluN2 subunit of NMDARs via Homer and PSD proteins (Attucci et al., 2001). Activation of mGluR5 leads to phosphorylation of linked NMDARs and potentiation of Ca²⁺ influx. (Attucci et al., 2001) mGluR5 is also involved in striatal synaptic plasticity underlying habit memory and motor learning (Gubellini et al., 2004) and is linked to increasing NMDAR excitability and conductance in the indirect basal ganglia loop/pathway (Awad et al., 2000). Conversely, Group I mGluR-dependent LTD can be induced by low frequency pair-pulse stimulation, resulting in postsynaptic AMPAR endocytosis via a PKC mediated pathway (Lüscher and Huber, 2010). mGluR-dependent LTD is thought to play a physiologic role in encoding novelty and hippocampal learning (Lüscher and Huber, 2010), but may be pathologically enhanced in Alzheimer's Disease by soluble A β oligomers, leading to shrinkage and loss of dendritic spines (Li et al., 2009).

mGluR5s on astrocytes have been associated with vesicular release of glutamate and regulation of phasic slow inward calcium currents in extrasynaptic NMDARs. There is evidence that this type of channel activation can occur synchronously across multiple neurons in the hippocampus and does so in an oscillatory fashion based on astrocytic intracellular Ca²⁺ concentrations. (Fellin et al., 2004b) mGluR5s may therefore contribute to the propagation of thalamic gamma oscillations in a GABA receptor-independent manner (Whittington et al., 1995), which (as mentioned in the KAR section) may play a role in maintaining the binding of different aspects of semantic memory, including object-word associations (Hart et al., 2007).

Group II receptors, which include mGluR2 and 3, are known to modulate synaptic plasticity by reducing neuronal excitability (Davidson et al., 2016; Hermes and Renaud, 2011). Presynaptic mGluR2/3 generally act as autoreceptors that decrease the probability of glutamate release by inhibiting voltage-gated calcium channels (Nicoletti et al., 2011). Postsynaptic group II mGluRs can inhibit depolarization by activating G protein-coupled inwardly rectifying K⁺ channels (GIRKs) (Knoflach and Kemp, 1998). Glial mGluR3 in particular has been associated with neuroprotection against NMDAR-associated excitotoxicity, possibly through production of pro-survival factors in astrocytes including transforming growth factor- β (TGF- β) (Corti et al., 2007).

Group III receptors include mGluR4, 6, 7, and 8, are localized presynaptically at the active zone of neurotransmitter release, and are involved in autoregulation of synaptic glutamate concentration and release (Nicoletti et al., 2011). mGluR7 is unique due to its comparatively low affinity for glutamate compared to the rest of Group III receptors and has been proposed to serve as a feedforward inhibitor of glutamate overstimulation (Niswender and Conn, 2010). Under high frequency stimulation, mGluR7 interacts with presynaptic GABA and adenosine receptors, suppressing presynaptic Ca²⁺ influx and glutamate-vesicle release, subsequently facilitating LTD in the hippocampus (Pelkey et al., 2005). More recent studies have suggested a positive regulatory role for mGluR7 as well. Under targeted activation, mGluR7 was shown to facilitate presynaptic glutamate release through a separate G-protein coupled mechanism involving phospholipase C (Martín et al., 2010) and may be essential to the induction of LTP at Schaffer collateral-CA1 synapses (Gogliotti et al., 2017). In addition to AD, mGluRs as a class are implicated in various neurologic and psychiatric diseases, including genetic epilepsies, Fragile X Syndrome, Parkinson's Disease, and schizophrenia.

In the broadest terms, AMPARs are essential for fast excitatory transmission and expression of LTP and LTD. NMDARs are responsible for the induction of LTP and LTD, the regulation of neuronal health and apoptosis, and the propagation of excitotoxic damage. KAR and mGluR are associated with the maintenance of synchronous neuronal oscillations and metaplasticity (i.e. the fine tuning of plasticity processes via

timing and amplitude of receptor activation) (Abraham, 2008). In the following section, we build on this foundation to demonstrate the role glutamate receptors may play in the pathogenesis of AD, FXTAS, and ischemic strokes. We posit that receptor dysfunction is associated with the development of language disorders, and that physiologic glutamate transmission through these receptors plays a key role in the regulation and maintenance of language processing.

2. Disorders of Language and Glutamate in Three Conditions (AD, Ischemic Stroke, FXTAS)

In this section, we review the preclinical data for language dysfunction and disorders of glutamate neurotransmission in Alzheimer's disease, Aphasic Stroke Syndromes, and Fragile X-associated tremor/ataxia syndrome (FXTAS). Alzheimer's disease is perhaps the most thoroughly studied of these three and provides a neurodegenerative model of an insidious language decline. Aphasic stroke syndromes have been categorized extensively by their various forms of language dysfunction, but the role of glutamate neurotransmission therein is less well understood. Finally, FXTAS is a relatively newly described disorder. While FXTAS is thought to be a neurodegenerative disorder, synaptic level changes may start early in neurodevelopment. Most studies referenced in this section provide pre-clinical data from in-vitro and animal models; for clinical pharmacologic and ERP studies involving these diseases, please refer to the section titled *Clinical Evidence in Pharmacologic and ERP Studies*.

2.1. Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive disease characterized by prominent memory and learning impairments, generally followed by language, visuospatial, and executive dysfunction (McKhann et al., 2011). Language dysfunction can occur in all stages of AD, although a breakdown in verbal fluency and naming together with normal articulation and syntactic abilities can precede diagnosis by years, manifesting during prodromal AD and perhaps even the preclinical stages (Taler and Phillips, 2008; Auriacombe et al., 2006a).

It is postulated that early language dysfunction in AD is due to semantic memory breakdown, rather than a nonspecific consequence of global cognitive decline (Verma and Howard, 2012), and can occur independently of changes in mini-mental state examination (MMSE) scores (Chan et al., 2001). Naming and comprehension, as demonstrated by decreased performance in object naming (e.g. on Boston Naming Tests (BNT)) and semantic fluency (category fluency) (Henry et al., 2004) decline at a faster rate than phonemic fluency (Clark et al., 2009).

Language degradation in AD occurs in a hierarchical manner; early errors tend to be superordinate replacements (e.g. using the generic “bird” instead of a more specific “dodo”) rather than intrusions (e.g. listing “carpenter” in an animal naming task) or repetitions (e.g. using the word “oyster” twice in the same list). There is a gradual erosion of peripheral followed by core concepts: language forms learned last deteriorate first (e.g. an AD patient may have a harder time articulating or processing the concept of “death and taxes” compared to a more central concept such as “hunger”) (Auriacombe et al., 2006b). Some early AD patients also demonstrate a breakdown of conceptual boundaries leading to a loosening of category associations (e.g. “cafeteria” becomes associated with “noon” because of the association with eating and having lunch.) (Laisney et al., 2011).

The semantic errors in AD likely represent a breakdown in semantic stores and impaired access and search function. (Verma and Howard, 2012). The neuroanatomic distribution for the semantic language network is an area of active research: there is evidence for a left-hemisphere predominant, widely distributed cortical semantic network (Joubert et al., 2010) (more on the distributed model in the thalamic aphasia section), modality specific regions acting in parallel (Binder et al., 2009), and amodal representations localized within

bilateral temporal lobes (Lambon Ralph, 2014). These models are in part supported by functional MRI (fMRI) studies in early AD patients. Olichney et al. reported decreased activation of the left medial (and lateral) temporal lobe in fMRI word repetition/semantic category decision tasks (Olichney et al., 2010a) and Peelle et al. demonstrated reduced activation of bilateral ventral temporal cortices and the left dorsolateral prefrontal cortex in mild AD patients during a fMRI semantic judgment task (Peelle et al., 2014).

2.1.1. NMDAR in Alzheimer's Disease

AD is a disease characterized by the accumulation of extracellular beta-amyloid (A β) plaques and hyperphosphorylated Tau-proteins within the central nervous system. Pathologic changes can occur years to decades before the onset of clinical symptoms. (Danysz and Parsons, 2012).

Oligomeric A β has been shown to interact with GluN2B subunits which are preferentially expressed on extrasynaptic NMDARs (eNMDAR). Activation of extrasynaptic NMDARs inhibits CREB-mediated pro-survival pathways and blocks BDNF gene expression, decreasing cellular resiliency against neurotoxicity. (Hardingham et al., 2002; Li et al., 2011) eNMDAR activation also causes sustained rather than transient mitochondrial calcium (Ca²⁺) elevations, which leads to mitochondrial dysfunction, cytochrome c release, ATP depletion and failure of energy production, and oxidative stress leading to cell death. (Bading, 2017; Zhang et al., 2016) Increased intracellular Ca²⁺ also directly promotes genomic death responses through cytosol to nucleus translocation of Forkhead transcription factor FoxO3a (Dick and Bading, 2010) and promotes beta-secretase activity and cleavage of amyloid precursor protein (APP) into A β , creating a positive feedback loop of runaway glutamate associated excitotoxicity (Ferreira et al., 2012; Rush and Buisson, 2014).

A β oligomers promote LTD via endocytosis and decreased expression of synaptic NMDA receptors through striatal-enriched phosphatase 61 (STEP) (Snyder et al., 2005) and proteasome mediated EphB2 degradation (Hu et al., 2017). This may lead to reduced sNMDAR-associated BDNF activation and downstream delivery of GluA4 subunit containing AMPARs to synapses, and acquisition of classic conditioned responses (Li and Keifer, 2009).

Although the total number of synaptic NMDARs are reduced, A β fibrils may still facilitate excitotoxicity by enhancing the activity and sensitivity of the remaining sNMDARs through β -integrin/Src Kinase activation. (Uhász et al., 2010). Intrasympatic A β fibrils further cause mild membrane depolarization in a receptor independent fashion, which may partially relieve NMDAR from their Mg²⁺ block, resulting in receptor hyperexcitability (and may contribute to the increased incidence of late life-onset seizures in AD patients). (Minkeviciene et al., 2009) In light of this, endocytosis of sNMDAR and associated LTD may serve a physiological rather than pathological role as a limited, last-ditch neuroprotective attempt against A β -mediated excitotoxicity.

Hyperphosphorylated Tau-proteins also may contribute to A β and glutamate-mediated excitotoxicity by stabilizing membrane bound extrasynaptic NMDA receptors. hTau is mistargeted and accumulates in the somatodendritic compartment of neurons and is critical for the localization of tyrosine-kinase Fyn to dendritic spines. Fyn phosphorylates and stabilizes the GluN2B subunit with PSD-95, and further facilitates interaction between A β and GluN2B-containing NMDARs, promoting downstream excitotoxicity (that is rescued by knockout Tau), but without directly affecting synaptic NMDAR-mediated EPSCs.* (Ittner et al., 2010).

*A recent phase 2a clinical trial investigated the effects of the Fyn kinase inhibitor saracatinib (AZD0530) in AD patients with daily treatments for 52 weeks versus a placebo. It failed to detect significant effects on the rate of cerebral glucose metabolism decline in AD-related regions of interest or cognitive decline (as scored by ADAS-Cog, MMSE, etc). However, secondary volumetric MRI analysis did detect a trend toward slowing of hippocampal volume decline in the study group

compared to placebo. (van Dyck et al., 2018).

2.1.2. AMPAR in Alzheimer's Disease

Synaptic AMPAR density and hence AMPA mediated LTP is attenuated by A β . A β protein accumulation has been shown to reduce AMPAR-mediated EPSC and hippocampal dendritic spine density, leading to memory impairments in mice models through direct interaction with GluA1/2 subunit containing AMPAR. (D'Amelio et al., 2011). Some proposed mechanisms underlying these changes include loss of synaptic AMPAR via interference of non-canonical wnt signaling pathways (Cerpa et al., 2010) and clathrin-dependent endocytosis of AMPAR by preferential binding of A β -oligomeric assemblies to the GluA2 (calcium-impermeable) subunit (Zhao et al., 2010).

In contrast, rapid synaptic insertion of CP-AMPA has been found to be induced by intracellular A β oligomers through selective protein kinase A (PKA) phosphorylation of the GluA1 subunit. Increased CP-AMPA density led to increased AMPAR mediated EPSCs, leading to the hypothesis that intracellular A β oligomer neurotoxicity in early stages of AD is in part mediated by AMPAR associated excitotoxicity. (Whitcomb et al., 2015).

A β oligomers may contribute to network-wide hyperexcitability and decreased seizure threshold through a pre-synaptic mechanism. This is thought to be due to A β -induced GABAergic disinhibition at the level of interneurons, leading to increased synchronous firing at excitatory synapses, rather than a direct effect on AMPA or NMDA receptors. (Palop and Mucke, 2010).

AMPA trafficking and anchoring (and synaptic function) may be disrupted by hyperphosphorylated tau (hTau) in dendritic spines, potentially in a PSD-95 associated fashion similar to its effect on NMDARs. (Hoover et al., 2010) A β activation of Caspase-3, and downstream phosphorylation of tau proteins by glycogen synthase kinase-3 β (GSK) have been demonstrated to attenuate AMPA mediated LTP, positing a three-way interaction between A β , hTau, and glutamate receptors (D'Amelio et al., 2011; Jo et al., 2011).

2.1.3. KAR in Alzheimer's Disease

No clear association has been made between KARs and A β or hTau. However, KARs have been shown to modulate EPSPs at CA3 mossy-fiber pyramidal cell synapses, which demonstrate a unique NMDAR-independent form of presynaptic short and long-term potentiation. (Sanz-Clemente et al., 2013). Further understanding of this process may open venues for compensatory therapies to offset the loss of NMDAR-mediated synaptic plasticity.

Alternatively, KAR-mediated LTD via membrane receptor endocytosis (Chamberlain et al., 2013) and transcription level alterations (Evans et al., 2017) have been demonstrated, but how this effect regulates synaptic circuits in the mature hippocampus is not fully understood. If KAR endocytosis can reduce post-synaptic cellular excitability from repeated presynaptic stimulation (Chamberlain et al., 2013), then antagonism at KAR receptors may improve neuronal resiliency against excitotoxicity.

2.1.4. mGluR in Alzheimer's Disease

Migration of postsynaptic mGluR between synaptic and extra-synaptic locations is impaired by A β binding to neuronal membranes, resulting in receptor clustering at excitatory neuronal synapses. Activation of pathologically clustered mGluR5 results in sharp rises of intracellular Ca²⁺, ultimately contributing to synaptic dysfunction and NMDAR dysregulation. (Renner et al., 2010). Activation of presynaptic mGluR2 triggers selective release of highly aggregating A β 42 (but not A β 40) peptides from nerve terminals; and chronic mGluR2 suppression is associated with a reduction in amnesic behavior and decreased levels of brain A β peptides in transgenic mice models (Kim et al., 2014). In contrast, glial mGluR3 activation appears to be neuroprotective by increasing secretion of TGF- β and paracrine-mediated induction of cyclin-dependent kinase inhibitors and anti-apoptotic cascades (Corti et al., 2007; Caraci et al., 2011).

Collectively, interactions between A β and hTau and glutamate receptors can attenuate LTP, increase LTD, destabilize synaptic integrity, and induce neurotoxicity and cell death. (Hu et al., 2012) (Table 1) We

Table 1
Glutamate Neurotransmission in Alzheimer's Disease.

NMDAR	AMPA	KAR	mGluR
Beta Amyloid (Aβ)			
<p>Selective eNMDAR activation through GluN2b interaction.</p> <ul style="list-style-type: none"> Decreased Resilience Against Neurotoxicity by inhibiting CREB and BDNF expression. Enhances NMDAR activity and sensitivity via β-integrin/Src Kinase, promoting excitotoxicity. Promotes Mitochondrial Dysfunction via sustained Mitochondrial Ca²⁺ current. Promotes Genomic Death Responses via FoxO3a. Promotes Cleavage of APP into Aβ. 	<p>Rapid membrane insertion of CP-AMPA via PKA phosphorylation of GluA1.</p> <ul style="list-style-type: none"> Excitotoxicity in early stages of AD. <p>Loss of synaptic AMPAR via interference of non-canonical wnt signaling pathways and clathrin-dependent endocytosis of receptors.</p> <ul style="list-style-type: none"> Reduction of AMPA-mediated EPSC, attenuating LTP. Decrease Dendritic Spine Density Memory Impairments 	<p>No clear association demonstrated but may provide compensatory therapies in the future.</p> <p>NMDAR-independent presynaptic STP and LTP.</p> <p>KAR endocytosis may reduce post-synaptic cellular excitability from repeated presynaptic stimulation.</p>	<p>mGluR5 clustering at excitatory neuronal synapses.</p> <ul style="list-style-type: none"> Rise in intracellular Ca²⁺ and synaptic dysfunction. NMDAR dysregulation. <p>Presynaptic mGluR2 activation</p>
<p>Endocytosis and decreased expression of sNMDAR via STEP and EphB2 degradation.</p> <ul style="list-style-type: none"> Promotes LTD 	<p>Aβ induced Caspase-3 activation leads to downstream phosphorylation of Tau.</p>		
Hyperphosphorylated Tau (hTau)			
<p>Stabilizes membrane bound eNMDAR via Fyn pathway.</p> <p>Facilitates Aβ and NMDAR interactions leading to excitotoxicity.</p>	<p>Disrupts AMPAR trafficking and membrane anchoring.</p> <ul style="list-style-type: none"> Attenuates LTP 		<p>Selective activation of mGluR3 may be neuroprotective against Aβ-driven apoptotic cascade by inducing TGF-β secretion and cyclin-dependent kinase inhibitors.</p>

NMDAR = N-Methyl-D-Aspartate receptors, AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, KAR = Kainate receptors, mGluR = metabotropic glutamate receptors, eNMDAR = extrasynaptic NMDAR, sNMDAR = synaptic NMDAR, CP-AMPA = Calcium Permeable AMPAR, EPSC = Excitatory Post-Synaptic Currents, STP = Short Term Potentiation, LTP = Long Term Potentiation.

postulate that this dysregulation in glutamate receptor homeostasis plays a key role in early semantic dysfunction in AD. Indeed, genome-wide association studies have revealed a link between worsening language performance and GLI3 allelic variants in patients at risk for and with AD (GLI family zinc finger 3, a developmental transcription factor in patterning brain structures), language performance in this population was also found to be associated with in pathways involving glutamate receptor trafficking and function. (Deters et al., 2017).

Some potential mechanisms underlying the semantic dysfunction include disruption of the distributed cortical language network through excitotoxicity and cell death, leading to disrupted synaptic integrity and a failure to access relevant semantic associations — particularly at semantic integration centers with high concentrations of NMDAR and AMPAR (e.g., the hippocampus (Piai et al., 2016a)). In the upcoming sections, we examine the clinical evidence for this glutamate hypothesis in ERP and pharmacologic studies.

Imbalance between glutamate and the inhibitory neurotransmitter GABA also may contribute to semantic dysfunction. Indeed, higher concentrations of GABA in the left anterior temporal lobe (ATL) of healthy subjects have been associated with improved semantic performance (increased accuracy) and efficiency (lower task-induced ATL activity) in a semantic association task. (Jung et al., 2017). Similarly, higher GABA to glutamate concentration ratio in the left lateral pre-frontal cortex was associated with reduced reaction time in a word selection task (de la Vega et al., 2014). Glutamate-GABA (excitatory/inhibitory) imbalance may therefore lead to hindered word selection and semantic processing; it is also possible that impaired GABAergic inhibitory frameworks may lead to the loosening of semantic associations seen in AD (Amieva et al., 2004).

2.2. Aphasic Stroke Syndromes

The classic neuroanatomical models of language are founded on lesion studies of aphasic stroke patients. Compared to neurodegenerative diseases such as AD, acquired language disorders due to ischemic strokes serve as relatively discrete events in time and space, which offer important insights into the effects of glutamatergic neurotransmission on language. Here we focus on Broca's and Wernicke's aphasia as classic examples of expressive and receptive language deficits, respectively, and subcortical aphasia to highlight some aspects of anomic and mixed-transcortical aphasias. The role of glutamate in stroke aphasia has not been studied based on specific aphasia subtypes, therefore, additional aphasia syndromes including global, conduction, and transcortical expressive and receptive aphasias will not be individually discussed.

2.2.1. Broca's Aphasia

In 1861, French surgeon Pierre Paul Broca first noted, "in all probability, both hemispheres collaborated in language and could more or less substitute for each other according to the conditions, although the third frontal convolution of the left hemisphere was the principal site of the function." (Berker et al., 1986). Classic Broca's Aphasia (BA), due to a lesion in Brodmann's Areas 44 and 45, presents as dense expressive aphasia with varying degrees of (less appreciated) language comprehension deficits, such as the processing of syntactic ambiguity. (Kirshner, 2016). "The old man the boat" is an example of a syntactically ambiguous phrase, the word "old" can serve as either an adjective or a noun, and the word "man" can be either a noun or a verb. The 'best' interpretation would read similarly to "the old (people) man the boat; however, patients with BA would have difficulty arriving at such an interpretation, if they succeeded at all.

Wassenaar and Hagoort suggest that these comprehension deficits may arise from an impairment in real time sentence and syntax construction rather than loss of linguistic knowledge. (Wassenaar and Hagoort, 2005). Deriving from a computational lexical-parsing model, syntactic processing can be thought of as the building up of binding links of sufficient strength between competing word forms, until one set of

interpretations prevails ("winning binding frame") (Hagoort, 2003). BA patients are capable of initiating this so-called syntactic unification process. However, when confronted with a syntactically complex or ambiguous sentence, they are unable to create the winning binding link of sufficient strength in an adequate timeframe, because the lexical store, although intact, is not readily available. This can lead to parsing errors and syntactic violations or a complete failure to bind with a lexical frame despite initiation attempts, presenting clinically as delayed and/or erroneous language comprehension of syntactic information (Wassenaar and Hagoort, 2005).

2.2.2. Wernicke's Aphasia

Wernicke's Aphasia (WA) is a predominantly sensory/receptive aphasia characterized by severe deficits in auditory language comprehension and repetition with relatively fluent, albeit largely meaningless, language production. (Hillis, 2007). Comprehension deficits in Wernicke's Aphasia are primarily a combination of acoustic-phonologic and lexical-semantic errors, and can include nonverbal processes such as color-to-picture matching, picture-to-picture matching, and drawing from memory (Robson et al., 2012a).

Lesions in the pSTG and surrounding areas, particularly the superior temporal sulcus, are thought to be responsible for acoustic-phonologic errors (e.g. impaired repetition and auditory discrimination). (Robson et al., 2012a). The level of impaired auditory discrimination in WA patients has been shown to be sensitive to the degree of verbal comprehension impairments, whereas no correlations have been found between nonverbal semantic impairments and auditory comprehension. This suggests that impaired phonologic analysis of speech is likely the primary cause of comprehension deficits and that auditory and non-auditory language comprehension, while often found in conjunction, are to some extent distinct processes in WA (Robson et al., 2012b).

Based on recent studies of chronic WA patients (Ogar et al., 2011), functional neuroimaging (Binder et al., 2009), and diffusion tensor imaging (DTI) (Saur et al., 2010), lesions in the pMTG are now thought to be the primary source of semantic comprehension impairment in WA. Damage to pMTG can lead to a dysregulation of modal percepts (e.g. visual features, olfactory, somatosensory, etc) associated with a concept, resulting in semantically inappropriate responses. For example, a WA patient may say "I forked my hair" instead of "I combed my hair", because of an erroneous association between the visual percept of a fork's tines and the teeth of a comb.

In addition, studies have demonstrated that language performance in WA, which was otherwise insensitive to changes in word familiarity/frequency and naming performance on the Boston Naming Test (BNT), improved considerably with phonemic cues. (Jefferies and Lambon Ralph, 2006). This supports the hypothesis that the core semantic representations in the anterior temporal gyrus, which acts an amodal hub among various cortical association areas, are spared in WA (lesions in the anterior temporal gyrus are primarily associated with semantic dementia) (Ogar et al., 2011; Robson et al., 2014).

Taken together, these findings suggest that language comprehension deficits in WA reflect issues with access at the level of auditory discrimination and to intact modal percepts, and not with semantic knowledge stores, which are preserved. (Thompson et al., 2015).

2.2.3. Subcortical Aphasia

Since the days of Broca and Wernicke, our understanding of language processes has expanded to include a network of cortical and subcortical structures hypothesized to encompass different components of language comprehension and production. In the topographically distributed model of semantic language formation, the thalamus acts as a putative binder of different aspects of semantic information. (Kraut et al., 2003). Bilateral thalamic depth electrode and scalp recordings during a semantic memory recall task demonstrate a decrease in theta range power but an increase in the power of spatially specific, phase-locked gamma oscillations in the thalamus and occipital leads, suggesting that thalamus

may drive the formation of semantic object associations and semantic memory recall (Slotnick et al., 2002a). This finding is consistent with the idea that thalamic relay neurons modulate selective engagement by switching between gamma rhythm-associated active engagement during language processing and a relatively disengaged state that minimizes attention to irrelevant stimuli (Nadeau and Crosson, 1997).

In thalamic aphasia, semantic paraphasias (e.g. substituting the word “cat” with “dog”) and anomia predominate; semantic word-finding can be severely affected such that verbal output deteriorates to jargon similar to the presentation of acute WA, while auditory-verbal comprehension and repetition remain relatively intact. (Crosson, 2013). These thalamic lesions can result in decreased neuronal metabolism and cerebral blood flow in anatomically connected language cortices, *a la* von Monakow’s connectional diaschisis theory, further supporting the thalamus as a hub for cortically-distributed language processes. (Nadeau and Crosson, 1997; Carrera and Tononi, 2014). Furthermore, cortical infarcts due to middle cerebral artery occlusions can result in a reduction of neurons and severe gliosis in ipsilateral, but not contralateral, thalamic nuclei (Qü et al., 1998), suggesting that thalamic disruption or disconnection may play a role in cortical aphasic syndromes as well.

The basal ganglia (BG) is another subcortical structure thought to play a role in language functions, specifically, in fine tuning lexical search and selection from existing lexical stores by modulating a cortico-striatal-pallido-thalamic (CSPT) circuit. (Crosson, 2013). Patients with chronic BG infarcts are not typically impaired on most classical tests of aphasia (e.g. the Western Aphasia Battery (WAB)) but do demonstrate difficulties with more complex language functions such as resolving meanings of semantically ambiguous passages and producing word lists, definitions, synonyms, and antonyms (Copland et al., 2000).

Crosson hypothesizes that the BG modulates signal-to-noise ratios during frontal lobe-mediated word selection tasks, allowing words to be produced more quickly and with fewer errors. (Crosson, 2013). Adapting Nambu’s model of a cortical-BG loop, Crosson describes the frontal lobe-BG interaction as follows: Upon initiation of a new word selection task, the hyperdirect BG loop first suppresses any active thalamic language connections, turning off any primed lexical-semantic networks from prior tasks. The direct BG loop then assists in the selection of a new semantic concept by enhancing the signal-to-noise ratio of the most contextually appropriate lexical item. Finally, the indirect BG loop reduces the activity level of competing semantic alternatives so that only the relevant semantic concept is selected (Nambu, 2004; Bohsali and Crosson, 2016). Thus, damage to the BG may lead to difficulty with complex language tasks that demand high efficiency in lexical selection whereas simple language processes such as those tested by the WAB may be spared.

2.2.4. Receptor Fingerprints, Language Networks, and Stroke

Despite the differences in topography and symptoms of the aphasic stroke syndromes, there may be a common link in the form of glutamate receptor expression and density. Balance between the densities of different neurotransmitter receptors, including the glutamate receptor subtypes and glutamate to GABA receptor ratios, form patterns unique to specific cortical functions which can span discontinuous regions, which Zilles et al. termed “receptor fingerprint”. (Zilles et al., 2002).

Select left hemispheric language regions (including the inferior frontal gyrus and the pars opercularis in Broca’s region and the pSTG in Wernicke’s region) have been shown to have similar receptor fingerprints despite cytoarchitectural differences and topographical distributions. These receptor fingerprints were different from the three primary sensory regions, including at the level of kainite receptor density. In the right hemisphere, structures within Broca’s region demonstrated a cluster of similar receptor densities, including NMDARs, forming a receptor fingerprint that differed from ipsilateral (right hemispheric) motor mouth, prefrontal, and temporal regions. Additional structures involved in language processing, including Brodmann’s areas 7, 9, 46,

and 32 and regions of the fusiform gyrus, also shared receptor fingerprint similarities. (Zilles et al., 2015).

It is conceivable that alterations in a region’s receptor density/fingerprint, also may affect its function. For example, changes in glutamate receptor expression in a language-related structure post stroke, even without gross structural injury, may still affect language processing. In the following sections, we review how glutamate receptor expression is altered in the lesion and perilesional regions during the acute (Qü et al., 1998; Pellegrini-Giampietro et al., 1992; Liu and Zukin, 2007) and chronic phases (López-Valdés et al., 2014) following a stroke. Strokes in or near language processing areas may alter the region’s receptor fingerprint, even in perilesional regions with no neuronal cell death (i.e. the ischemic penumbra). It is also possible that changes in glutamate receptor density in structures involved in distributed language networks such as the temporal-frontal network, may contribute to language processing deficits on a more global scale.

2.2.5. NMDAR in Aphasic Stroke Syndromes

Following an ischemic stroke, NMDARs are upregulated in the cortical rim surrounding the ischemic core (i.e. the penumbra) (along with a down-regulation of GABA receptors). This upregulation of excitatory receptors localizes to the superficial cortical layers II-IV, which include the supragranular layers where NMDAR-associated neurons are preferentially situated. (Qü et al., 1998). Receptor upregulation may acutely contribute to NMDAR-associated excitotoxicity, and administration of NMDAR antagonists (MK-801 and memantine) within 30–45 minutes after a penetrating vessel occlusion significantly reduces microinfarct volumes in acute stroke. (this is also a likely mechanism to explain some therapeutic consequences of NMDAR modulation in vascular dementia (Barbancho et al., 2015)) (Shih et al., 2013).

Abnormal glutamate activity extends beyond the acute phase of ischemic strokes; NMDAR antagonism by memantine for 28 days following cortical middle cerebral artery occlusion has been shown to decrease reactive astrogliosis and increase vascular density around the infarcted cortex. (López-Valdés et al., 2014). In contrast, there is also evidence of increased BDNF pathway signaling in the peri-infarct cortex (likely associated with NMDAR activation). The BDNF pathway has been associated with promoting activity-dependent neuron survival and synaptogenesis and protects against excitotoxicity through downstream activation of antioxidant enzymes such as Mn-SOD and anti-apoptotic proteins such as Bcl-2 (Mattson, 2008).

NMDARs are also implicated in cortico-subthalamic nucleus (STN) transmission, which is likely closely related to a CSPT circuit via a STN to globus pallidus glutamatergic synapse. (Crosson, 2013). Blockade of NMDAR in the STN reduces early excitation of the globus pallidus interna (GPI) and prevents downstream suppression of thalamocortical activity. (Nambu et al., 2000). NMDAR dysregulation in this setting may lead to language dysfunction due to impaired cortico-basal ganglia loops causing increased noise-to-signal during word selection tasks, inadequate suppression of competing semantic alternatives, and/or deficits in set-switching between new words or concepts (Crosson, 2013).

2.2.6. AMPAR in Aphasic Stroke Syndromes

Ischemic injury to neurons induces a change in AMPAR expression at synaptic sites within 24 hours of injury. In the hippocampus, GluA2-containing calcium impermeable AMPARs are dissociated from PSD sites and endocytosed through the physiologic clathrin-mediated pathway. At the same time, CP-AMPA receptors become preferentially expressed at the receptor surface, leading to increased amplitudes of miniature EPSCs. (Liu and Zukin, 2007) Moreover, GluA2 mRNA expression is also preferentially reduced compared to GluA1 and GluA3 within 24 hours of ischemic insult, indicating transcriptional level changes in addition to alterations in receptor trafficking (Pellegrini-Giampietro et al., 1992).

How much of these changes in AMPAR expression is independent of NMDAR dysregulation is unclear. However, studies have demonstrated

that selective blockade of CP-AMPA is neuroprotective in ischemic stroke models (Noh et al., 2005), indicating that direct rescue of AMPAR homeostasis may be beneficial to ameliorating post-stroke excitotoxic injury.

2.2.7. KAR in Aphasic Stroke Syndromes

Kainate receptors have so far not been identified in structures implicated in subcortical aphasic strokes (e.g., the thalamus). However, hippocampal layer-CA3 KARs have been implicated in the modulation of cortical gamma oscillations in laboratory conditions (Fisahn et al., 2004), oscillations which may be associated with subcortical language functions.

As noted in the subcortical aphasia section, spatially specific, phase-locked gamma-range oscillations recorded in the thalamus and occipital leads increase in power during semantic memory tasks; this has led to the hypothesis that the thalamus may bind different aspects of semantic information. (Hart et al., 2007; Slotnick et al., 2002b). Moreover, Nadeau hypothesized that thalamic relay neurons may alternate between selective engagement and a relatively disengaged state by switching between theta and gamma frequency oscillations (Nadeau and Crosson, 1997).

Taken together these findings raise the possibility that hippocampal KARs may act in tandem with thalamus-driven gamma range oscillations, to recruit the hippocampus as a part of a globally distributed language network, and/or to maintain selective engagement of hippocampus during semantic recall/language tasks. KAR dysfunction in the hippocampus also may be associated with language dysfunction in hippocampal sclerosis and medial temporal lobe epilepsy (Hamberger et al., 2007) .

2.2.8. mGluR in Aphasic Stroke Syndromes

mGluR1 mediates post-synaptic activation in thalamic relay neurons and demonstrates high levels of receptor expression in this cell population. Furthermore, cortico-thalamic input may be enhanced by modulating mGluR1 activation; and tonic activation of mGluR1 may potentiate synaptic NMDAR response. (Salt et al., 2012) Although these data are derived from a purely somatosensory model, it is plausible to infer that mGluR may play a similar role in the topographically distributed, cortico-thalamo-cortical model of language processing, and that modulation of mGluR may have an effect in thalamic aphasia syndromes.

Taken together, cortical and subcortical aphasic syndromes are likely linked by a distributed network of semantic and lexical representations. Failure to activate and bind the appropriate lexical-semantic constructs leads to various presentations of aphasia in Broca's, Wernicke's, and Subcortical Aphasic syndromes. NMDAR, CP-AMPA, and mGluR may play a role in modulating language deficits by promoting synaptic signaling and protecting against ischemic excitotoxicity. (Table 2) Seemingly disparate structures involved in language processing also may share a similar receptor fingerprint, including the density of glutamate receptors. (Zilles et al., 2015). Alterations in glutamate receptor expression post-stroke also may change the receptor fingerprint unique to these language processing regions, thereby contributing to both local and global language dysfunction.

2.3. Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS is a neurodegenerative disorder that may affect premutation carriers of the Fragile X Mental Retardation 1 (*FMR1*) gene. *FMR1* premutation, or carrier status, is usually defined by 55-200 CGG repeat nucleotide expansions at the 5' untranslated region of position q27.3 in the X chromosome. (Brouwer et al., 2009). The syndrome affects approximately 40% (Yang et al., 2014a)-80% (Hagerman and Hagerman, 2016) of older male and 8% (Yang et al., 2014a)-20% (Hagerman and Hagerman, 2016) of female *FMR1* premutation carriers, with the females displaying more variable and milder disease phenotypes.

Table 2

Glutamate Neurotransmission in Post-Stroke Aphasia.

NMDAR	AMPA	KAR	mGluR
Post-Stroke Aphasia			
Upregulation in the stroke penumbra following acute ischemic stroke (particularly in cortical layers II-IV) may contribute to post-stroke excitotoxicity. NMDAR antagonists administered within 30-45 minutes of a penetrating vessel occlusion can significantly reduce microinfarct volumes.	AMPA expression at synaptic sites are altered within 24 hours of ischemic injury. • CI-AMPA are endocytosed via a clarithin-mediated pathway. • CP-AMPA are preferentially expressed, leading to increased amplitudes of EPSCs. • GluA2 mRNA expression is also reduced within 24 hours of insult.	Hippocampal KARs modulate cortical gamma oscillations and may act in tandem with the thalamus in modulating language functions. • Thalamus-driven gamma oscillations may be essential for binding different aspects of semantic information and the selective engagement of cortically distributed language components.	mGluR1 mediates post-synaptic activation in thalamic relay neurons. Tonic activation of mGluR1 may potentiate sNMDAR responses in cortico-thalamo-cortical models of language formation. • Modulation of mGluR may have an effect in thalamic aphasia syndromes.
NMDAR are involved in cortico-STN transmission in CSPT circuits. • NMDAR blockade in the STN prevents downstream suppression of thalamocortical activity • Receptor dysregulation may affect subcortical language processing.	Selective blockade of CP-AMPA is neuroprotective in ischemic stroke models.		

NMDAR = N-Methyl-D-Aspartate receptors, AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, KAR = Kainate receptors, mGluR = metabotropic glutamate receptors, CP-AMPA = Calcium Permeable AMPAR, CI-AMPA = Calcium Impermeable AMPAR, STN = Subthalamic Nucleus, CPST = Cortico-Striatal-Pallido-Thalamic

Symptoms of FXTAS may include both Alzheimer's and Parkinson's disease-like phenotypes, with executive impairments usually being most prominent. Attention, memory, and visuospatial deficits are also typically present, in addition to psychiatric symptoms and progressively debilitating intention tremor and ataxia. (Liu et al., 2012). Premutation carriers also may exhibit language (Cornish et al., 2011) disorders such as decreased phonemic fluency on the Controlled Oral Word Association Test (Seritan et al., 2014) and increased pragmatic language violations on the Pragmatic Rating Scale (Losh et al., 2012) .

At the molecular level, FXTAS is characterized by an overexpression of the *FMR1* mRNA (Tassone et al., 2007) and a normal to moderately decreased (36-74%) concentration of the *FMR1* protein (FMRP) product (Tassone et al., 2000; Kenneson, 2001), indicating deficient translation of mRNA into protein. Overexpression of aberrant *FMR1* mRNA leads to a gain of function toxicity, involving sequestration of RNA binding proteins by expanded CGG repeats, production of cytotoxic FMRpolyG peptide products, and direct DNA damage due to formation of co-transcriptional R loops in the non-template DNA strand (Hagerman and Hagerman, 2016).

How these molecular changes lead to the FXTAS phenotype is still an

area of active research; FMRP levels at or below 70% of normal controls (1 standard deviation) demonstrate a linear correlation with reduced global IQ ($R = 0.481$, $p < 0.0001$ (Quillian, 1967a)) for both genders. (Kim et al., 2019). Selective deficits in inhibition (Hayling Sentence Completion Test category B errors) may be seen in male premutation carriers who do not meet the diagnostic criteria for FXTAS (i.e. asymptomatic carriers) and has an dose dependent association with mutation burden (CGG repeat length) and increasing age (Cornish et al., 2008; Hunter et al., 2012). Even non-FXTAS (asymptomatic) adult female carriers of the Fragile X premutation show subtle but significant cognitive impairments in relation to their age and number of CGG repeats (Goodrich-Hunsaker et al., 2011).

Although symptoms typically present late in life (in men older than 50 years of age), young premutation carriers (age 5–23 years) have demonstrated increased prevalence of anxiety disorders (76.9% in males and 50% in females) compared to the general population (9.8%), with higher rates (81.8%) in those with concomitant intellectual disability. (Cordeiro et al., 2015). Boys with the premutation also have a higher incidence of attention deficit-hyperactivity disorder and/or autism spectrum disorder (ASD) (93% and 79%, respectively, in one proband group, compared to 13% and 0%, respectively, in sibling controls) (Farzin et al., 2006), and ASD in boy premutation carriers is associated with increased rates of seizures (28% in probands) (Chonchaiya et al., 2012). All this suggests that molecular changes due to increased CGG repeats in FXTAS may begin during early neuronal development. (Farzin et al., 2006).

2.3.1. Glutamate in FXTAS

Dysfunction of glutamate neurotransmission is thought to play a central role in both FXTAS and Fragile X Syndrome (FXS) despite differences in underlying molecular pathology. (Berman et al., 2014). Glutamate application to FXTAS neurons produce sustained Ca^{2+} currents of higher amplitude compared to wild-type (WT) neurons which suggests altered glutamate signaling in the affected FXTAS population. (Liu et al., 2012). Synaptic glutamate clearance is also affected, as reduced expression of glutamate transporters GLAST and GLT-1 in FXTAS hippocampal astrocytes results in more persistent synaptic glutamate concentrations (Cao et al., 2013).

FXTAS neurons demonstrate decreased dendritic complexity and synaptic architecture, and increased expression of stress proteins alpha B-crystallin, Hsp27 and Hsp70 during early neuronal maturation, thought to be a result of aberrant glutamate neurotransmission. (Chen et al., 2010). In a separate study, hippocampal neurons in FXTAS patients also demonstrated gain-of-function mutations in Group-I-mGluRs and deficiencies in vesicular GABA_A transporters. The imbalance between glutamatergic and GABAergic neurotransmission is thought to lead to excessive clustered burst firing and glutamate activation. (Cao et al., 2012). As discussed for Alzheimer's disease, persistent glutamate activation and increased Ca^{2+} currents have been associated with involution of AMPAR and NMDAR, and may lead to reduced LTP and increased LTD, which likely plays a role in the reported learning and memory deficits. (Hunsaker et al., 2012a) (Table 3).

In the cerebellum, postmortem studies of human male FXTAS patients demonstrate a reduction of both GLAST1 and Group-I-mGluR5. mGluR5 downregulation in this case is thought to be downstream of GLAST1 dysfunction and the resultant pathologic accumulation of glutamate in the synaptic cleft. (Pretto et al., 2014). Given the cerebellum's role in speech production and comprehension, such as semantic processing and verbal working memory, these cerebellar-glutamatergic pathologies could potentially contribute to language and dysexecutive deficits seen in FXTAS (Moberget and Ivry, 2016).

Administration of mGluR1 and mGluR5 antagonists (CPCOOEt and MPEP) or GABA_A receptor modulator (allopregnanolone) have been shown to ameliorate clustered burst firing in FXTAS neurons. (Cao et al., 2012). Similarly, mGluR antagonists in *FMR1* knockout (FXS, rather

Table 3

Glutamate Neurotransmission in Fragile X-Tremor/Ataxia Syndrome.

FXTAS	Aberrant glutamate neurotransmission may be the cause of decreased dendritic complexity and synaptic architecture, and increased expression of stress proteins alpha B-crystallin and Hsp27 and Hsp70 during early neuronal maturation process.	Hippocampal neurons demonstrate gain-of-function mutations in Group-I-mGluRs and deficiencies in vesicular GABA _A transporters.
<p>Involution of synaptic NMDAR and AMPAR due to persistent glutamate activation and increased Ca^{2+} currents may lead to reduced LTP and increased LTD.</p> <ul style="list-style-type: none"> • Glutamate application to FXTAS-phenotype neurons produce sustained Ca^{2+} currents of higher amplitude compared WT. • Reduced expression of glutamate transporters GLAST and GLT-1 in hippocampal astrocytes results in more persistent synaptic glutamate concentrations. 		<ul style="list-style-type: none"> • Imbalanced GABA/Glutamate neurotransmission leads to excessive clustered burst firing and glutamate activation. • Reduced FMRP may lead to increased mGluR5 synthesis, internalization of synaptic AMPAR and increased LTD.

NMDAR = N-Methyl-D-Aspartate receptors, AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, KAR = Kainate receptors, mGluR = metabotropic glutamate receptors, LTP = Long Term Potentiation, LTD = Long Term Depression, GABA = γ -aminobutyric acid, FMRP = Fragile X Mental Retardation Protein.

than FXTAS, phenotype) mice have been shown to reduce socially aberrant and repetitive behavior (Burket et al., 2011), and rescue abnormal dendritic spine density and immature/underdeveloped pyramidal neurons (Su et al., 2011; Michalon et al., 2012). Due to this association between glutamate dysregulation and FXTAS pathogenesis, the NMDAR antagonist memantine has been trialed to decrease or modulate the symptoms of FXTAS.

3. Clinical Evidence from ERP and Pharmacologic Studies

In this section, we review the clinical data on glutamate receptor-modulating drugs on language processing. Specifically, we will discuss these effects in AD, Aphasic Stroke Syndromes, FXTAS – diseases in which we have established a preclinical link between glutamate dysregulation and language dysfunction. We will also briefly evaluate the effect of glutamate modulation in healthy individuals.

To better characterize the (potentially transient) electrophysiologic changes in receptor function, and to capture any subclinical alterations in language processing that may not be reflected in behavioral or language batteries, we focus our review on studies utilizing ERPs to evaluate language-associated changes. As ERP studies are less commonly encountered compared to structural and functional imaging and language batteries, we begin with a brief overview of language-associated ERP components.

3.1. Overview of Selected ERP Components

Event-related brain potentials or ERPs are transient time-locked changes in electrical brain activity reflecting post-synaptic activity during the performance of various mental tasks. ERPs are composed of summed EPSP/IPSPs, instantaneously conducted to the scalp primarily from neocortical and/or deep CNS sources, manifest as a series of voltage deflections in bipolar EEG recordings. (Luck and Steven, 2014). Early deflections (~50–200 ms post-stimulus onset) are associated with sensory processing, selective attention, and gating of information (Näätänen, 1988) and later deflections (> 250 ms post-stimulus onset)

reflect controlled, integrative “cognitive” processes, such as those involved in language processing (Kutas and Federmeier, 2011) and memory (Friedman and Johnson, 2000). Of particular relevance are the ‘N400’, ‘Anterior Negativity (AN)’, and ‘P600’ components which have been linked to semantic and syntactic aspects of the language processing system (see Kappenman and Luck’s ERP Handbook for reviews of other language components (Kappenman and Luck, 2012)).

As ERPs can reflect synaptic or neuronal circuit changes before anatomic, metabolic, or behavioral changes are evident. They can be particularly useful in studying early disease states where clinical changes are subtle, such as mild cognitive impairment (MCI). ERPs have an unsurpassed temporal resolution, superior to functional imaging modalities that rely on changes in blood flow or oxygenation (Duncan et al., 2009) and are not influenced heavily by cultural background or educational level compared to neuropsychological tests (Polich and Corey-Bloom, 2005). Certain ERP effects may have an increased sensitivity to changes in glutamate transmission (and other pharmacologic manipulations), as demonstrated by the significant positive correlation between frontal lobe P3-auditory amplitude and glutamate/glutamine ratios in the anterior cingulate gyrus (Hall et al., 2015). We posit that pharmacologic modulation of glutamate receptors should result in both electrophysiological (e.g. ERP) and behavioral changes.

3.1.1. N400

The N400 is a scalp negativity (relative to a mastoid reference) peaking at approximately 400 ms after stimulus-onset with a posterior (centro-parietal) maximum; alterations in N400 topography have been suggested to be a potential biomarker for detection of early dementia (Olichney et al. (2008); Horvath et al. (2018)) N400 amplitude is a sensitive marker of semantic language processing load, which is dependent on both the complexity of the language task at hand and the cognitive capacity to perform it.

The “N400 congruity effect” is a reduction in N400 amplitude when the eliciting word is a good semantic fit (congruous) to its context (word, sentence, or dialogue) compared to a poor fit (incongruous); the better the fit, the lower the amplitude, and thus the larger the N400 congruity effect. (Kutas and Hillyard, 1984; Berkum et al., 1999). In sentence experiments, there is a high inverse correlation ($r = -0.87$) between N400 amplitude and the Cloze probability of the eliciting word (Kutas and Hillyard, 1984). (Fig. 4) Diseases that affect the availability/access

of stored conceptual information and/or the ability to integrate the meaning of the word and its context accordingly increase the task difficulty and cognitive costs of semantic processing and are reflected as modulations in N400 amplitude. (Kutas and Federmeier, 2011).

The separate but related “N400 repetition effect” is modulated by memory functions. Repetition of semantically incongruous words is associated with a reduction in N400 amplitude. This repetition effect is preserved in chronic amnestics despite poor verbal memory performance, implicating an implicit, rather than declarative memory process. * (Olichney et al., 2000; Olichney et al., 2011) (Fig. 5). The N400 repetition effect highlights the link between memory and language processing, as the implicit memory process likely facilitates language comprehension at the sentence level. (Olichney et al., 2000). Furthermore, repeated exposure to the same word is thought to ease semantic processing load and integration. The resulting decreased N400 amplitude is therefore usually considered a form of semantic priming (Palmer et al., 2007).

*However, in the case of FXTAS, the N400 repetition effect amplitude appears to be reduced in those with relatively worse declarative/explicit memory. (Olichney et al., 2010b).

3.1.2. Anterior Negativity and P600

The Anterior Negativity (AN) and the Syntactic Positive Shift (SPS)/P600 both have been linked to syntactic processing. AN occurs within the same latency (300–500 ms) post-stimulus as the N400 but generally has a more frontal (than the N400) and left hemisphere maximum and is thus sometimes referred to as the lateralized anterior negativity (LAN). (Friederici et al., 1996; Lau et al., 2006). The AN effect is a relative negativity elicited by mismatches in word-category (e.g. a noun used instead of a verb) or morphosyntactic features (number, case, gender, and tense) that result in syntactic anomalies (Friederici, 2002) or violations with no acceptable grammatical reading (Hagoort et al., 2003) (Fig. 6). Diseases that alter AN amplitude or onset latency are presumed to be responsible for initiation of the syntactic structure building process (Friederici, 2002) or increasing the difficulty in binding a word to an appropriate lexical frame (Hagoort et al., 2003).

The SPS/P600 is a positive shift occurring at approximately 600 ms after stimulus onset with a centro-posterior maximum. (Gouvea et al., 2010; Leckey and Federmeier, 2020). The P600, initially referred to as the Syntactic Positive Shift (SPS), is thought by some to be an index of the difficulty of syntactic integration. The SPS/P600 occurs in response to syntactic anomalies, although relative increases in SPS/P600 amplitude can be elicited by complex or ambiguous (but technically correct) syntactic structures as well. (Kaan et al., 2000). (Fig. 6) The more cognitive resources required for structural re-analysis or to resolve competing interpretations of ambiguous clauses, the larger the SPS/P600 amplitude and duration. (Hagoort et al., 2003; Gouvea et al., 2010). In the computational lexical-parsing analogy, diseases that alter the SPS/P600 are thought to be responsible for deficits in the ability to unify/arrange lexical components into syntactically coherent phrases (Hagoort, 2003).

Another late positive component, variously called the P600 or Late Positive Component (LPC), has a similar time course and scalp topography as the SPS/P600 but is observed in different paradigms, where it is correlated with episodic verbal memory abilities and declarative memory. (Gouvea et al., 2010; Regel et al., 2014). Exposure to repeated words in word list experiments has revealed larger LPC/P600 amplitudes successfully recognized compared to unrecognized words, and to recalled words compared to un-recalled words during free recall (Palmer et al., 1987) (Fig. 7). The more intact the source memory (e.g. memory of the original word list), the larger the LPC/P600 amplitude. Thus, the LPC/P600 (sometimes referred to as left parietal P600) is often considered an electrophysiological index of recollection. (Rugg et al., 1998).

In contrast, when words are repeated in predictable linguistic contexts, the LPC/P600 amplitude is typically smaller in response to repetitions, but the absolute voltage change is larger in individuals with

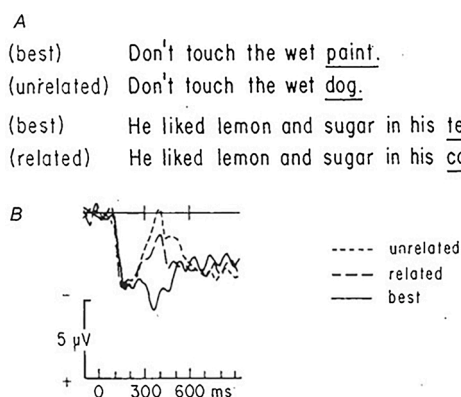


Fig. 4. The N400 Congruity Effect. Adapted from Kutas and Hillyard *Nature* 1984 (Hunsaker et al., 2012a).

A. Two examples of sentences with high contextual constraints completed by low Cloze probability words. Above each experimental sentence is the same sentence terminated by its “best completion”, which was or was not semantically related to the word that was actually presented in the sentence. B. Grand average ERPs for the best completions (solid waveform), the semantically related (large dashed waveform) and the semantically unrelated (small dashed waveform) low Cloze probability words. There is a high inverse correlation between N400 amplitude and the Cloze probability of the eliciting word.

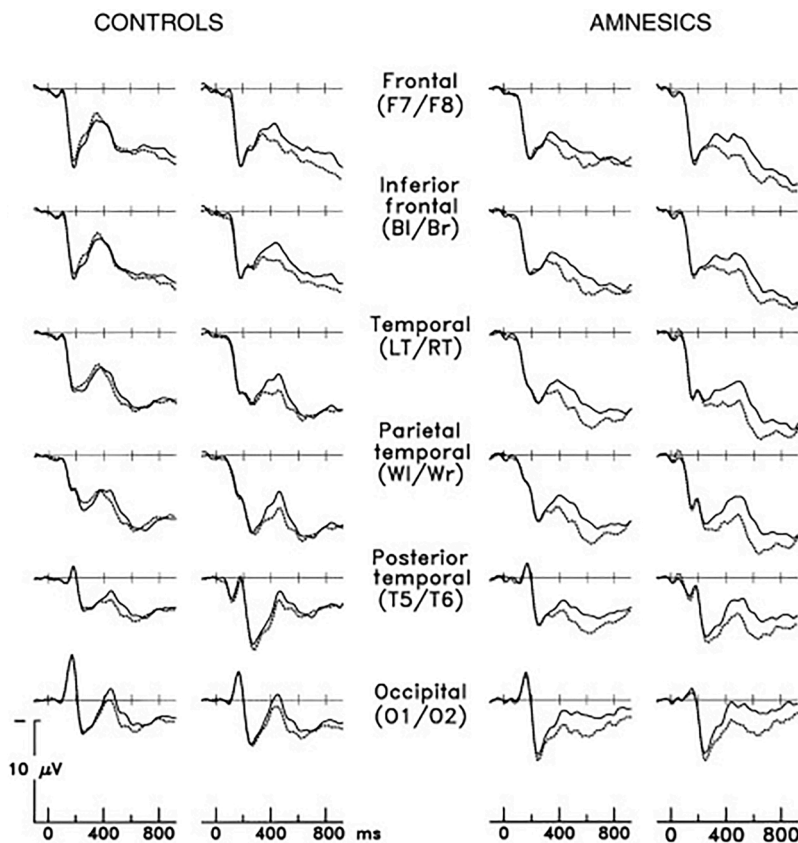


Fig. 5. The N400 Repetition Effect. Adapted from Olichney et al. *Brain* 2000 (Moberget and Ivry, 2016).

Grand Average ERPs from the control and amnesic groups elicited by new (continuous lines) and repeat (dotted lines) words which were semantically incongruous. Negative voltage is plotted in the upward direction. Note the persistent and robust N400 repetition effect in amnesic patients, implicating an implicit, rather than declarative, associated memory process.

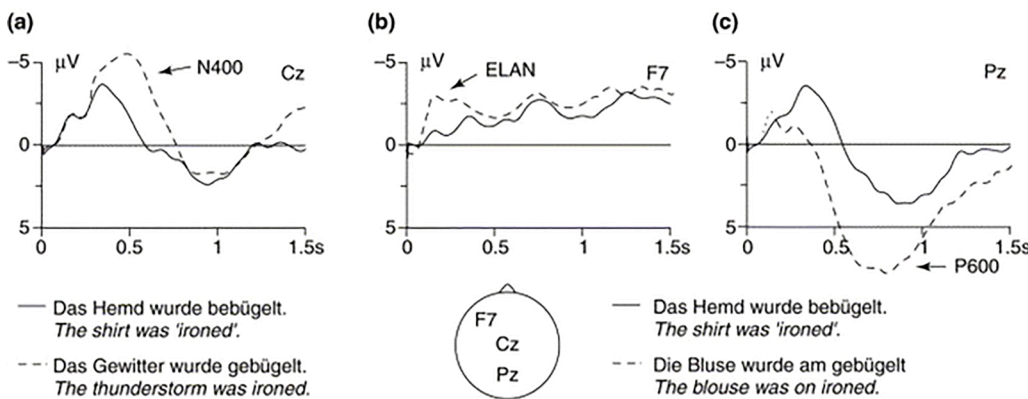


Fig. 6. The Anterior Negativity and SPS/P600 Effects. Adapted from Friederici *Trends in Cognitive Sciences* 2002 (Näätänen, 1988).

A. N400, B. Very Early Left Anterior Negativity (ELAN), C. P600 (Syntactic Positive Shift). Shown are average ERPs for the semantic- and syntactic-violation conditions at selected electrode sites Cz, F7, and Pz. Solid lines represent the correct condition, and dotted lines the incorrect condition. The ELAN and SPS/P600 effects occur in response to syntactic anomalies.

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better memory for the item. This is possibly because a different memory retrieval process is engaged for semantically predictable/congruous words. (Olichney et al., 2008; Olichney et al., 2000; Olichney et al., 2006). The LPC/P600 enhancement can persist ≥ 15 minutes (Friedman and Johnson, 2000; Olichney and Hillert, 2004); active forgetting attenuates the LPC (Paller, 1990), and in general the LPC/P600 may be broadly associated with non-linguistic, learned structures, e.g. musical chord progression and face recognition (Patel et al., 1998).

While the relationship between the SPS/P600 in sentences and the LPC/P600 elicited in memory experiments is unclear (as is the relationship between P600 and P3b more generally) (Leckey and Federmeier, 2020), an association between memory and language processing is implied in Friederici's interpretation of the P600: as a marker for syntactic reanalysis and repair during the resolution of syntactic

processing. On this view, encoding and recall of various syntactic components would be crucial for successful manipulation and resolution of syntactic ambiguities. (Friederici, 2002).

3.2. Alzheimer's Disease

As reviewed by Olichney and Hillert, N400 s in AD generally are smaller in amplitude and delayed in peak latency compared to those in normal elderly persons. (Olichney and Hillert, 2004). A diminished N400 repetition effect in MCI and AD can be rescued (in the MCI group only) by the removal of lexical ambiguity from the task, facilitating semantic priming (Taler et al., 2009). This suggests that A) MCI patients have a preserved semantic store but impaired processing/access compared to AD patients who have impairments in both the semantic

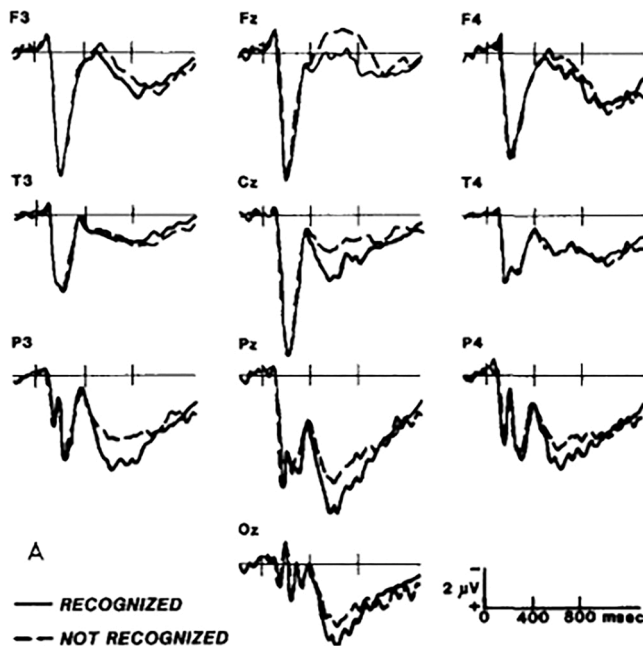


Fig. 7. The LPC/P600 Effect. Adapted from Paller, Kutas, and Mayes *Electroencephalography* 1987 (Polich and Corey-Bloom, 2005).

ERPs averaged based on later recognition performance. Words subsequently recognized elicited greater late positive activity than did words subsequently not recognized.

storage and access processes (Verma and Howard, 2012) and B) pathologic N400 s in the MCI population can be rescued/restored to age-matched normal values. In mild AD and semantic dementia patients, abnormal N400 s are associated with reduced temporal lobe cerebral blood flow, suggesting a close association between the electrophysiological and focal metabolic abnormalities (Grieder et al., 2013).

A longitudinal ERP study of MCI converters to AD demonstrated loss of the N400 congruity effect (and a memory-associated N400 repetition effect (see discussion below)) after a one year of follow-up, prior to most patients' clinical conversion. This led Olichney et al. to conclude that abnormal N400 s in MCI are associated with an increased risk of conversion to AD, with an odds ratio estimated to be in the 4–8 range. (Olichney et al., 2008). The N400 repetition and LPC/P600 effects combined have a high sensitivity (100%) and specificity (80%) to AD dementia, with mild AD patients consistently demonstrating reduced or absent P600 and N400 word repetition effects (Olichney et al., 2006). The N400 is also sensitive to neuronal level changes prior to AD symptom onset. Bobes et al. noted alterations in N400 generator topography and amplitude between healthy controls and pre-symptomatic carriers of the familial AD presenilin-1 mutation, and similar topographic and amplitude distributions between pre-symptomatic and symptomatic presenilin-1 mutation carriers (Bobes et al., 2009). Taken together, these studies demonstrate the utility of ERPs for tracking, quantifying, and possibly predicting language dysfunction in MCI as well as for predicting conversion to AD dementia. (Table 4)

3.2.1. Memantine in Alzheimer's Disease

Memantine is a partial NMDAR antagonist that is currently approved in the U.S., Europe, and Japan for the treatment of AD. (Matsunaga et al., 2015). Memantine is an open-channel blocker of NMDARs, which weakly binds to the Mg^{2+} site and preferentially targets excessively open channels, while interfering only minimally with normal synaptic transmission. (Lipton, 2004). Importantly, memantine purportedly binds preferentially to extrasynaptic over synaptic NMDARs even under pathologic depolarization (Xia et al., 2010) and is able to restore LTP impairment and rescue neurons from pro-apoptotic cascades initiated by

eNMDAR activation (Dau et al., 2014). A meta-analysis by Matsunaga et al. found that memantine monotherapy in AD (9 studies, $n = 2433$) improved cognitive function, AD-associated behavioral disturbances, activities of daily living, global function, and stage of dementia compared to placebo (Matsunaga et al., 2015). These benefits have been consistently shown in moderate to severe stages of AD (Reisberg et al., 2003; Doody et al., 2004), with less consistent, and more controversial effects in mild AD (Peskind et al., 2006; Schneider et al., 2011). Multiple studies have demonstrated that memantine monotherapy (Ferris et al., 2009) or the addition of memantine to chronic donepezil use improve language scores on the severe impairment battery (SIB) language subscale in moderate to severe AD patients. (Ferris et al., 2009; Tariot et al., 2004; Schmitt et al., 2006; Tocco et al., 2014) (Table 5).

Kubova et al. reported on the ERP effects of memantine monotherapy (10 mg twice daily (BID)) for 6 months in mild to moderate AD patients. A significant 20 ms decrease in visual-evoked P300 peak latency was noted in 42% of their cohort ($n = 17$, mini-mental state examination (MMSE) score 12–23); this was thought to be associated with improved allocation of attention and working memory updating. N400 was not measured. (Kubová et al., 2010). To our knowledge, there are no published studies that evaluate the ERP effects of glutamate modulation (antagonist or agonist) on language dysfunction in AD. (Table 6).

3.3. Aphasic Stroke Syndromes

3.3.1. Broca's Aphasia

Broca's Aphasia (BA) patients demonstrated reduced amplitude and significantly delayed onset of SPS/P600 s during word-category violation tests compared to those in healthy controls and non-aphasic stroke patients with right hemisphere lesions. (Wassenaar and Hagoort, 2005). In the same study, BA patients also showed a globally delayed and reduced N400 to semantic violations compared to normal controls; although the effect was less pronounced (i.e. absolute onset delay and amplitude change were lower but still statistically significant) compared to the SPS/P600 changes elicited in the syntactic violation task, consistent with greater impairment in syntactic than semantic processing in BA. AN was not elicited.

3.3.2. Wernicke's Aphasia

Wernicke's Aphasia (WA) patients demonstrated a reduced N400 congruity effect compared to healthy controls in an acoustic word-picture verification test of single word comprehension (Robson et al., 2017). In the same study, WA patients also demonstrated a reduced and inconsistent phonological mismatch negativity, suggesting that the observed comprehension impairment in WA is likely a combination of deficits in phonologic perception and semantic comprehension. Despite the reduced N400 congruity effect, WA patients consistently demonstrate intact N400 semantic priming effects similar to healthy controls, suggesting an intact lexical-semantic store despite semantic comprehension deficits (Hagoort and Kutas, 1995).

There is corroborating ERP and functional imaging evidence that the left posterior STG, which is lesioned in classical WA, is involved in the integration of lexical and syntactic information. Patients with pSTG lesions demonstrate a selective absence of SPS/P600* (Friederici and Kotz, 2003), and this is consistent with functional imaging evidence of pSTG activity during the processing of syntactic structures of verbs (Grodzinsky and Friederici, 2006). (Taken together, these ERP studies suggest that comprehension deficits in WA may be some combination of impairments in sensory/auditory processing, semantic processing, and syntactic integration.

*Further study is needed to establish if AD and MCI patients with reduced or absent P600 effects (Olichney et al., 2006) have significant atrophy in the pSTG region as well; such a finding may further substantiate the link between structure (pSTG), function (language), and electrophysiology (P600).

Table 4
ERP Studies*

	N400 Congruity Effect	N400 Repetition Effect	AN	SPS/P600 Effect	LPC/P600 Effect
Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)					
MCI	Reduced effect precedes clinical conversion to AD by 1 year. (Chen et al., 2010)	Abnormalities increase risk of conversion to AD. Odds Ratio of 4–8. (Chen et al., 2010)			
AD		Reduced or absent in mild AD. Topography changes in pre-symptomatic and symptomatic PSEN-1 mutation carriers. (Paller et al., 2007)			Reduced or absent in mild AD. (Olichney et al., 2008)
Post-Stroke Aphasia					
Broca's Aphasia	Reduced amplitude and increased latency. (Amieva et al., 2004)			Reduced amplitude and increased latency. (Amieva et al., 2004)	
Wernicke's Aphasia	Reduced amplitude. (Olichney and Hillert, 2004)	Intact N400 semantic priming. (Paller, 1990)		Absent in patients with pSTG lesions. (Taler et al., 2009)	
Subcortical Aphasias	In DBS induced functional VIM lesions, reduction in N400 congruity is associated with impaired word-pair lexical decision tasks. (Peskind et al., 2006)		Intact in left BG lesions. (Xia et al., 2010)	Absent in left BG lesions. (Xia et al., 2010)	
Unclassified Aphasias	Reduced in patients with moderate to severe verbal or reading comprehension deficits. (Grieder et al., 2013; Bobes et al., 2009; Matsunaga et al., 2015) Topographic maximum shifts from the right to left hemisphere after 4 weeks of aphasia therapy. (Xia et al., 2010)				
Fragile X Tremor/Ataxia Syndrome (FXTAS)					
FXTAS	Reduced in female FXTAS patients, but with preserved N400 and P600 Repetition Effects. (Shih et al., 2013)	Reduced in patients with poor declarative verbal memory. ¹⁶⁰			Intact in female FXTAS patients (Shih et al., 2013) and most male FXTAS patients (Moberget and Ivry, 2016).
Non-Aphasic Patients					
	Present in thalamic depth recordings. Absent in STN/GPi recordings. (Dau et al., 2014; Reisberg et al.2003; Doody et al., 2004)		Present in thalamic depth recordings. Absent in STN/GPi recordings. (Dau et al., 2014; Reisberg et al.2003; Doody et al., 2004)	Present in thalamic depth recordings. Absent in STN/GPi recordings. (Dau et al., 2014; Reisberg et al.2003; Doody et al., 2004)	

MMN = Mismatch Negativity (another ERP component), pSTG = Posterior Superior Temporal Gyrus, VIM = Ventral Intermediate Nucleus (of the Thalamus), BG = Basal Ganglia, STN = Subthalamic Nucleus, GPI = Globus Pallidus Interna

* Not an Exhaustive List.

3.3.3. Receptive Aphasias

Independent of stroke classification (i.e. Wernicke's, Broca's, Subcortical), aphasic patients with mild comprehension deficits showed an N400 comparable to normal controls while aphasic patients with moderate to severe comprehension deficits had a significant reduction and delay in the N400 to sentence-final semantic anomalies (Swaab et al., 1997) and word-pair associations (Hagoort et al., 1996). Similar patterns of N400 results were found in mild versus severe reading comprehension-impaired aphasia patients (Chang et al., 2016). This seems to suggest that severely impaired comprehension may be independently associated with an impaired ability to integrate lexical-semantic information into higher order representations, regardless of stroke classification.

3.3.4. Subcortical Aphasias

ERP evidence for BG involvement in language processing is mixed. Patients with left basal ganglia lesions and varying degrees of language comprehension impairment demonstrated intact AN (specifically early left anterior negativity (ELAN)) but absent SPS/P600 s compared to healthy controls in a study of verb-specific syntactic violations. The BG lesion group also demonstrated an N400-like negativity with extended duration (300–700 ms) that was absent in healthy controls. Altogether, this was taken to suggest that the BG may be involved in *later stages* of

syntactic processing (hence the affected P600 but not ELAN) and may play a modulatory role in lexical-semantic analysis, perhaps related to the speed of processing. (Kotz et al., 2003).

In contrast, in non-aphasic individuals, depth recordings from the STN in a word-pair task demonstrated an ERP component (~318–362 ms) to prime-words only, suggesting that the STN (and the BG, which is closely interconnected via glutamatergic connections between the STN and globus pallidus) play a role in automatic procedural tasks (e.g. readiness inhibition or warning cues in response to a new word-pair task); although this may not be exclusive to language processing (Tiedt et al., 2017). In other studies, depth recordings from the STN and/or GPI in non-aphasic individuals failed to show sensitivity to semantic (N400) or syntactic violations (P600), leading the authors to conclude that the BG was not involved in essential language processing tasks (Wahl et al., 2008; Krugel et al., 2014a).

A study of functional thalamic lesions induced by deep brain stimulation (DBS) in the ventral intermediate nucleus (VIM) of the thalamus demonstrated reduced N400 congruency amplitudes. This was accompanied by a reduction (slower than normal) response times in a word-pair lexical decision task (Krugel et al., 2014b). Thalamic depth recordings of non-aphasic patients also demonstrated N400 congruency effects to semantic phrase violations, and AN and SPS/P600 to syntactic phrase violations. Taken together, these data suggest that the thalamus

Table 5
Pharmacologic Studies*.

	Therapy	Duration	Effect	Interpretation
Alzheimer's Disease (Moderate to Severe)				
Tariot et al. 2004 (n = 322)	Memantine (10 mg BID) + Stable Dose of Donepezil	24 weeks	Improved SIB, ADCS-ADL19, and CIBIC-Plus.	Addition of Memantine resulted in better outcomes in multiple domains, including language.
Schmitt et al. 2006 (n = 290)	Memantine (10 mg BID) + Stable Dose of Donepezil	24 weeks	Improved SIB Language Domain starting at week 8, Praxis at week 4, and Memory at week 24.	Memantine improves language and memory systems in separate but complementary ways.
Ferris et al. 2009 (n = 801) (Analysis of 4 databases including Tariot et al. 2004)	Memantine (10 mg BID) (+ Stable Dose of Donepezil in 403 patients)	24–28 weeks	More clinically relevant improvement and fewer clinically relevant worsening on SIB-L.	Memantine (with and without donepezil) results in significant benefits for language function for patients with either mild and marked language impairment.
Post-Stroke Aphasia				
Berthier et al. 2009 (n = 27)	Memantine (10 mg BID) + Aphasia Therapy vs. Placebo + Aphasia Therapy	48 weeks	Persistently improved WAB-AQ after drug washout. Improved WAB-AQ with and without aphasia therapy.	Memantine associated language improvement persists after drug cessation.
Kessler et al. 2000 (n = 24)	Piracetam 2400 mg BID + Speech Therapy	6 weeks	Improved Aachen Aphasia Test (Spontaneous Speech, Communicative Verbal Behavior, Semantic and Syntactic Structure)	Piracetam improves language function in post-stroke aphasia.
Güngör et al. 2011 (n = 30)	Piracetam 2400 mg BID	6 months	Improved auditory comprehension on the Gülhane Aphasia Test	Long-term Piracetam use improves auditory comprehension in post-stroke aphasia.

BID = Twice Daily, SIB = Severe Impairment Battery, ADCS-ADL19 = 19-item AD Cooperative Study–Activities of Daily Living Inventory, CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input, SIB-L = Severe Impairment Battery - Language Scale, WAB-AQ = Western Aphasia Battery - Aphasia Quotient.

* Not an Exhaustive List.

may gate the flow of language information between cortically distributed language networks and can be involved in both semantic and syntactic processing tasks ([Tiedt et al., 2017](#); [Wahl et al., 2008](#)). To our knowledge, there are no published studies evaluating the language-related ERP components in thalamic aphasia patients ([Table 4](#)).

3.3.5. Memantine in Aphasic Stroke Syndromes

Barbancho et al. evaluated the ERP effect of memantine monotherapy in a double-blind study involving patients with chronic (> 1-year duration) post-stroke aphasia from left peri-sylvian lesions but heterogeneous presentations of aphasic stroke syndromes. Patients were randomized to treatment with memantine 10 mg BID (n = 14) vs placebo (n = 14) for a total of 20 weeks, with two weeks of constraint-induced aphasia therapy during weeks 16–18. For the ERP recording phase, participants were asked to silently read words presented on a computer screen, selected from a bank of 300 frequently encountered words ([Barbancho et al., 2015](#)).

At baseline evaluation, healthy controls (n = 15) demonstrated lower (early sensory) P100 and N400 amplitudes compared to aphasic stroke patients in both the memantine and placebo groups. By week 16, the memantine group demonstrated a larger decrease in P100 and N400 amplitudes (closer to the healthy controls) and a correlated improvement in their Western Aphasia Battery-Aphasia Quotient (WAB-AQ) scores compared to the aphasic stroke patients in the placebo group. The healthy control group did not show a reduction in ERP amplitudes at 16 weeks.

The addition of two weeks of constraint-induced aphasia therapy (CIAT) in conjunction with memantine saw a continued increase in WAB-AQ scores but no subsequent change in the N400. ERP changes were noted over both hemispheres, although treatment with memantine/CIAT resulted in a significant increase in left hemispheric activity compared to the placebo/CIAT group ([Barbancho et al., 2015](#)).

This improvement in the N400 was thought to be due to memantine's effect in normalizing chronic, aberrant glutamate neurotransmission in the perilesional space and in contralateral hemispheric regions deprived of excitatory glutamatergic neuronal input ([Barbancho et al., 2015](#)). Based on preclinical data, we would also venture a guess that memantine likely normalized aberrant NMDAR activity *downstream* of the

peri-sylvian lesions, in glutamate-regulated synapses in CSPT circuits, and improved the signal-to-noise ratio in set switching between new words or concepts ([Crosson, 2013](#)). It is also possible that memantine increased synaptogenesis in compensatory language circuits, as the data in mice of models of FXS suggest that memantine may enhance excitatory synapse formation and rescue delayed dendritic spine maturation ([Wei et al., 2012](#)).

The silent reading task used for the ERP recording raises two points of note. One, the test minimizes the effects of working memory and short-term recall, suggesting that the changes in N400 amplitude may be strictly language related. Two, the test lacks the specificity to differentiate between semantic and syntactic associated ERPs. However, the increase in the dominant left hemisphere N400 after memantine therapy is consistent with Wilson et al.'s findings, suggesting that memantine-associated glutamate regulation may be involved in, or trigger, a compensatory change, reflected in N400 topography ([Table 6](#)).

An extension of this study also evaluated the effect of memantine on WAB-AQ scores at 24 and 48 weeks (without additional ERP testing). Weeks 20–24 were a memantine washout phase, and weeks 24–48 were an open label phase in which both groups received memantine 20 mg BID. The study group (memantine-memantine) consistently outperformed the control group (placebo-memantine) at both time points whereas both groups demonstrated significant improvements in WAB-AQ scores during the open label phase ([Berthier et al., 2009](#)). The fact that improvements in language performance persisted after the drug washout phase suggests that NMDAR modulation may be associated with long-term remodeling of language networks after stroke, perhaps by altering the local receptor fingerprint (i.e. glutamate receptor density) to better match associated language processing structures. Also, the results of the open label phase demonstrate that memantine can improve language performance in post-stroke aphasia without additional aphasia therapy, although combined therapy leads to better outcomes ([Table 5](#)).

In a study of aphasic stroke patients with heterogeneous lesion sites, an N400 “mismatch effect” was recorded before and after four weeks of non-pharmacologic speech-language therapy ([Wilson et al., 2012](#)). Patients were asked to determine if a spoken word was congruent (match) or not congruent (mismatch) with a picture. In the control group, the N400 was maximal over the central-posterior region (with a significant linear trend toward the right hemisphere (likely due to a false localizing

Table 6

Combined Pharmacologic and ERP Studies*.

	Therapy	Duration	Effect	Interpretation
Alzheimer's Disease				
Kubová et al. 2010 (n = 17)	Memantine (10 mg BID)	6 months	Reduced P300 Peak Latency.	Memantine improved allocation of attention and working memory updating.
Post-Stroke Aphasia				
Barbancho et al. 2015 (n = 27)	Memantine (10 mg BID) + Aphasia Therapy vs. Placebo + Aphasia Therapy	20 weeks	Reduced N400 amplitude (closer to healthy controls); Increased N400 in the Left Hemisphere	Memantine normalized aberrant glutamate neurotransmission. ERP changes correlated with improved WAB-AQ scores.
FXTAS				
Ortigas et al. 2010 (n = 1)	Memantine (10 mg BID)	9 months	Improved N400 congruity + word repetition effect. Improved P600 word repetition effect.	Memantine improved language function.
Yang et al. 2014a, 2014b, 2014c (n = 41)	Memantine (10 mg BID) vs. Placebo	12 months	Improved N400 repetition effect amplitude and latency.	Improved verbal memory based on cued recall.
Non-Aphasic Patients				
Grunwald et al. 1999 (n = 39)	Ketamine (0.5 mg/kg)	Once	Attenuated N400 repetition effect. No change in LPC/P600 repetition effect.	Ketamine affects language but not memory predominant systems, which are separate but complementary.

BID = Twice Daily, WAB-AQ = Western Aphasia Battery-Aphasia Quotient, LPC = Late Positive Component

* To the best of our knowledge, an exhaustive list of current studies.

dipole (Kutas and Federmeier, 2011)) pre- and post-therapy. In the stroke patients, four weeks of therapy led to a topographic migration of the maximal N400 amplitude from the right to the left hemisphere. Compared to the combined memantine and language therapy study, this hemispheric shift due to language therapy alone was thought to be a compensatory response (possibly from a right hemisphere source), rather than a “normalization” of the N400 toward the language dominant hemisphere, as the control group had a persistent right-hemispheric N400 bias. (Alternatively, the left hemisphere signal could also be due to a false localizing dipole from a right medial temporal source.) Altogether, these studies demonstrate that the N400 is sensitive to interventions in chronic stroke patients, while the different effects on N400 between the two studies suggest that glutamate modulation may play a separate but complementary role to non-pharmacologic language therapy in restoring semantic language processing.

3.3.6. Piracetam in Aphasic Stroke Syndromes

Piracetam and piracetam-related compounds are GABA-derivatives with mixed activity at glutamate receptors, nicotinic-Acetylcholine receptors (nAChR), and GABA receptors. (Berthier et al., 2011). Group 1 agents increase AMPA-mediated Ca^{2+} currents by increasing the receptor binding site density for AMPAR and are considered nootropic drugs due to their potential efficacy in cognitive rehabilitation, including for post-stroke aphasia (Malykh and Sadaie, 2010).

One double-blind, placebo-controlled study of 24 patients with post-stroke aphasia combined 2400 mg of piracetam twice daily and intensive speech therapy for 6 weeks. At the end of the study, the piracetam group demonstrated significant improvements in the Aachen Aphasia Test in the subfields of spontaneous speech, especially in communicative verbal behavior, and in the semantic and syntactic structure of their speech compared to the control group. The piracetam-arm also demonstrated increased blood flow in the left transverse temporal gyrus, left triangular part of inferior frontal gyrus, and left posterior superior temporal gyrus on a positron emission tomography (PET) scan during word repetition compared to the control group, although this was thought to be due the drug's nAChR interactions (Kessler et al., 2000). A 6-month, double blind and placebo-controlled study of 30 patients with post-stroke aphasia on 2400 mg of piracetam twice daily demonstrated significant improvement only in auditory comprehension on the Gülhane Aphasia Test compared to the control group (Güngör et al., 2011), suggesting that piracetam may exert a (minor) long-term beneficial effect in post-stroke aphasia. (Table 5)

Currently there are no ERP studies evaluating the effect of piracetam-related drugs on language disorders. It is possible that ERP studies may reveal significant long-term changes with piracetam in control groups that are not readily evident with neuropsychologic testing. However, due to piracetam's mixed mechanisms of action, it is difficult based on clinical evidence alone to determine which effect on language dysfunction can be attributed to its ability to regulate glutamate transmission. Future studies could include evaluation of changes in synaptic AMPAR distribution and density, AMPA-mediated LTP and LTD, and glutamate to GABA receptor ratios particularly in known language-associated brain structures, such as the anterior temporal lobe, in conjunction with ERP measurements in known tasks.

3.4. Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

A significantly reduced N400 word repetition effect was found in FXTAS patients with poor declarative verbal memory (based on California Verbal Learning Test or CVLT delayed recall and discriminability scores) compared to normal controls, suggesting impaired implicit memory and semantic language processing in the FXTAS group (Olichney et al., 2010b). A separate study of exclusively female FXTAS patients demonstrated a reduced N400 congruity effect, but preserved N400 and P600 repetition effects (Yang et al., 2014a). This was again suggestive of abnormal semantic processing; the relatively preserved implicit and verbal memory may be due to a less severe phenotype given the female-only study population, who generally have one normal copy of the fragile X gene on their unaffected X chromosome. It is possible that these deficits in semantic processing noted on the N400 congruity task may be related to category B errors on the Hayling Sentence Completion Test in asymptomatic premutation carriers (Cornish et al., 2011; Hunter et al., 2012), as the latter requires a semantic judgement in addition to an inhibition task (choose an unrelated word to complete the presented sentence) and are demonstrating similar underlying neural vulnerabilities.

3.4.1. Memantine in FXTAS

Ortigas et al. reported that 9 months of memantine 10 mg BID improved the N400 congruity effect and N400 word repetition effect, and the P600 word repetition effect in a 65-year-old female FXTAS patient. (Ortigas et al., 2010) (Table 4). Yang et al. expanded upon this

observation in a double-blind study of 41 FXTAS patients randomized to treatment with memantine 10 mg BID vs. placebo for one year. The treatment arm ($n = 21$) also demonstrated improvements in the N400 repetition effect amplitude and latency, which correlated with improved verbal memory based on cued recall scores. In contrast, the placebo arm of FXTAS patients had longer N400 latencies compared to their baseline ERP one year earlier. (Fig. 8) Although the amplitudes of the P600 word repetition effect correlated well with memory and recall scores, there were no significant changes in the P600 over the course of the study (Yang et al., 2014b).

Memantine-induced clinical and ERP improvements in these patients underscore the role of defective glutamatergic signaling in memory and language dysfunction in FXTAS. It is likely that NMDAR modulation, particularly antagonism at extrasynaptic NMDARs, rescued at-risk neurons from tonic activation and excitotoxicity and may have fostered recovery of NMDAR-mediated LTP (Hunsaker et al., 2012b). Such a mechanism would be in line with findings of sustained Ca^{2+} currents inducing excitotoxic cell death in FXTAS neurons (Cao et al., 2013). Determining whether NMDAR level dysfunction is downstream of mGluR dysfunction (as in FXS (Pop et al., 2014)) will require further study.

Finally, in contrast to MCI and AD data, Yang et al. found that the N400 repetition effect rather than P600 repetition effect was the stronger correlate of verbal memory ability in FXTAS (Yang et al., 2014c). This re-enforces the idea that despite similar patterns in cognitive deficits (Seritan et al., 2008), different physiological mechanisms lead to the cognitive dysfunction and pathogenesis of FXTAS and AD. (Table 6)

The consistent reduction in the N400 repetition effect across multiple studies suggests that abnormalities in implicit memory and semantic priming are the cause of verbal learning and memory dysfunction in FXTAS. More broadly, these findings support the role of glutamatergic signaling in language processing; the ERP data, in particular, highlight the multiple electrophysiological mechanisms and current disruptions that can produce language and memory dysfunction. In summary, the

aforementioned patient studies demonstrate the heterogeneous role of glutamate transmission in the language (and memory) disorders reviewed here.

3.5. Non-Aphasic Patients

We conclude this section with data linking glutamate neurotransmission and language via pharmacological and ERP studies in patients with no language disorders.

Smith et al. demonstrated a clear left lateralized medial temporal lobe (MTL) generator for the N400 repetition effect in depth recording studies of epilepsy patients. The MTL-N400 represented excitation of hippocampal synapses in response to convergent activation from cortical and subcortical projections, and the N400 repetition effect was thought to be associated with synaptic level changes (i.e. LTP induction) from repetitive stimulation of the MTL and the enhanced feedback loop between the MTL and the association cortex. (Smith et al., 1986) By virtue of regulating LTP and therefore the N400, NMDAR and AMPAR are implicated in language processing.

Smith et al. also considered the MTL to be a converging point for the posterior association cortex, the dominant peri-sylvian cortex, and the limbic neocortical connections (Smith et al., 1986). This view is similar to Teyler and DiScenna's 'hippocampal memory index' theory which suggests that the hippocampus is functionally designed and anatomically situated to act as an indexing mechanism and amodal hub for integrating sensory information from the neocortex (Teyler and Rudy, 2007). Indeed, recent direct hippocampal recordings have demonstrated language-associated changes in increased theta power in response to constrained versus unconstrained phrases (Piai et al., 2016b).

These findings are in keeping with topographically distributed models of semantic language formation; with the MTL, rather than the thalamus, binding different aspects of semantic information.

3.5.1. Ketamine in Non-Aphasic Patients

Finally, we review the ERP effects of ketamine — a voltage-

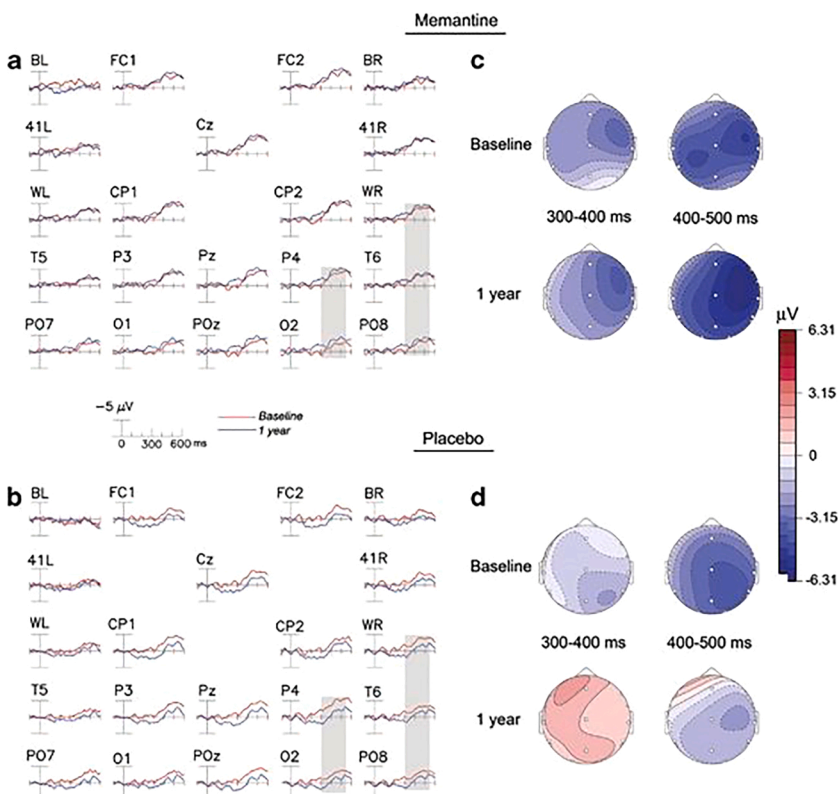


Fig. 8. Memantine Effects on FXTAS. Adapted from Yang et al. *Neuropsychopharmacology* 2014 (Friederici and Kotz, 2003).

A and B: The N400 repetition effects generated by subtracting ERPs to incongruous old target words from ERPs to incongruous new target words, within each group. Robust treatment effects were demonstrated within the shaded right posterior cluster consisting of five electrodes, with significant decreases in the placebo group and an insignificant trend for N400 repetition effect amplitude increases in the memantine group. C and D: Topographic distribution of the N400 repetition effects across the early (300–400 ms) and late (400–500 ms) time windows, plotted by treatment group and visits, within each group.

dependent open-channel blocker of NMDARs. Ketamine has an intra-channel binding site similar to the NMDAR antagonist memantine, which results in occluded current flow, but has a different pharmacokinetic profile and affects both synaptic and extra-synaptic NMDARs (Kotermanski et al., 2013). Ketamine also has a known rapid anti-depressant effect, which may work through downstream targeting of the calcium/calmodulin-dependent eukaryotic elongation factor 2 kinase (eEF-2 K) and psychotropic side effects, as a dissociative anesthetic (Autry et al., 2011).

Grunwald evaluated the effect of ketamine in language processing using a visual word recognition and repetition paradigm and computed ERPs from surface recordings in healthy participants ($n = 16$) and from depth electrodes in temporal lobe epilepsy patients ($n = 25$). A single dose of 0.5 mg/kg IV of ketamine greatly attenuated the N400 repetition effect in both groups, but did not affect the LPC/P600 repetition effect. (Grunwald et al., 1999) (Fig. 9) That NMDAR modulation preferentially affected the N400 but not the P600 suggests distinct neurotransmitter mechanisms at work in language-predominant and memory-predominant systems, which may act in an independent but complementary fashion. (Table 6) This is in line with the observation that the LPC is memory retrieval dependent whereas N400 repetition has

an implicit memory component and is not affected by poor verbal memory recall (i.e. preserved in chronic amnesic patients) (Olichney et al., 2000). Although the ‘classic’ posteriorly distributed N400 has been most closely linked to semantic priming and implicit memory, a frontally-distributed N400, sometimes called the F-N400, has been taken to reflect familiarity-based memory processes in some experimental paradigms (Rugg et al., 1998; Stróżak et al., 2016).

To summarize the clinical data section, there is ample tangential evidence suggesting an association between glutamate neurotransmission and language disorders, but there are no studies directly addressing this relationship. The glutamate-modulating agent memantine has consistently improved language function in moderate to severe AD (Tocco et al., 2014). In the MCI and AD populations, language-related ERP components can be used to evaluate and track language deficits across time. ERP studies have shown sensitivity to effects of memantine on attention in AD patients, suggesting that a language-related ERP study of the effects of memantine in AD could directly address the association between glutamate modulation and language dysfunction.

In stroke patients with cortical or subcortical aphasia, studies using language-related ERP components have been able to parse the language processing deficits into relatively distinct semantic and syntactic components (i.e. N400 and P600, respectively, although there are so-called semantic P600 effects (Leckey and Federmeier, 2020)). Memantine use has resulted in mild improvements in N400 amplitude and improvement in WAB-AQ scores suggesting that glutamate modulation is associated with improved language outcomes in the chronic phase of stroke and that the N400 may provide a valid tracking measure over time. However, given the passive word reading task employed by Barbancho et al., it is unclear whether this relation holds for any or all N400 s, regardless of task. Finally, in FXTAS, glutamate modulation by memantine was associated with improvements in N400 repetition effect and some measures of verbal memory.

As evidenced by these studies, direct clinical data combining language disorders, ERPs, and glutamate pharmacology are scarce, but the existing literature suggests that they may be interrelated and that glutamate is involved in language processing and performance. This is not surprising, considering that glutamate is the most ubiquitous excitatory neurotransmitter in the cortex, and many aphasias are considered classical examples of disrupted higher cortical function. Cortical structures involved in language processing, despite being topographically distributed, seem to share a similar receptor fingerprint, including a unique density of kainite and NMDA receptors (Zilles et al., 2015).

Moreover, models of widely-distributed functional language networks, such as Quillian’s spreading cortical activation of semantic search (Collins and Loftus, 1975; Quillian, 1967b) might well be explained by glutamatergic stimulation of neighboring cortical neurons. Further evaluation of language-associated ERPs, particularly N400 congruency and SPS/P600 effects (which are relatively independent of memory function) would help to verify whether these ERP effects are reliable indicators of treatment response. Once the ERP effects have been validated in that setting, we would hope to see more studies aimed at optimizing language processing by modulating glutamate neurotransmission.

4. Discussion

4.1. On Disease Models

All three language disease models discussed in this article are associated with some degree of glutamate dysregulation. We chose AD and FXTAS to represent different neurodegenerative pathologies and Aphasic Stroke Syndromes to represent acquired language disorders. Other promising disease models for studying the association between glutamate and language disorders include developmental disorders such as fragile X-syndrome and autism spectrum disorder. Here we briefly

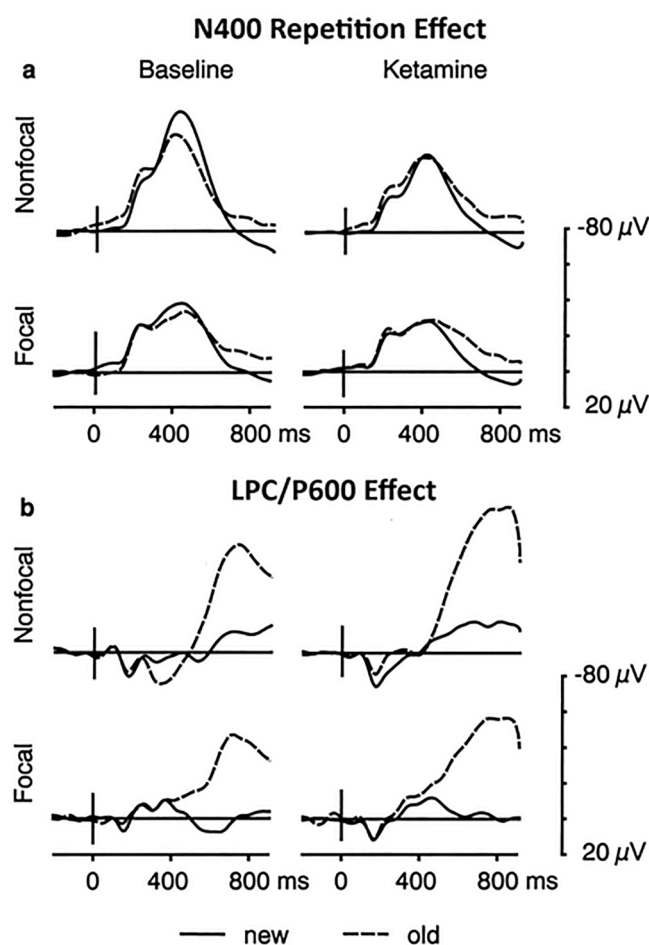


Fig. 9. Ketamine effects on N400. Adapted from Grunwald et al. *Proc. Natl. Acad. Sci. U. S. A* 1999 (Krugel et al., 2014b).

ERPs averaged across patients. (a) Anterior Medial Temporal Lobe-N400 s were significantly affected by ketamine. Recognition effects were significant only without ketamine, not after intravenous administration of this NMDA-receptor antagonist. (b) Ketamine did not affect P600 and LPC/P600 effects.

Focal: recordings from the epileptogenic temporal lobe; Nonfocal: recordings from the contralateral side. Solid line: initial presentations; Dashed line: repetition.

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discuss these models as they can provide important insights into the role of glutamate receptors in language development.

The mGluR5 theory of FXS posits that mGluR5 expression is increased in the hippocampus due to loss of translational regulation by FMRP. Increased mGluR5 leads to decreased AMPAR expression, increased LTD, and decreased dendritic and synaptic strength (Pop et al., 2014). Chronic treatment with long-acting mGluR5 antagonist CTEP in mice of FXS restored cognitive deficits, aberrant dendritic spine density, and overactive ERK and mTOR signaling (Michalon et al., 2012). In a clinical study, a subset of FXS patients with full methylation at the *FMR1* promoter site reported significant improvements in aberrant social behavior (i.e. stereotypic behavior, hyperactivity, and inappropriate speech) in response to the selective mGluR5 antagonist mavoglurant (Jacquemont et al., 2011). Currently there is a clinical study underway at our institution to determine if metformin, which may inhibit glutamate induced excitotoxicity in neurons (Zhou et al., 2016), improves language outcomes in FXS patients (Hagerman, 2018).

Autism spectrum disorder is often co-morbid with FXS, and milder social deficits occasionally occur in FXTAS patients (Hagerman and Hagerman, 2013), and also is associated with glutamate dysregulation (Rojas, 2014) and language processing deficits (Lewis et al., 2006). FMRP levels are reduced in the cerebellar vermis of ASD patients and is associated with increased mGluR5 and reduced GABA_A receptor beta 3 expression in the same region (Fatemi et al., 2011). AMPAR receptor density are also reduced in the cerebellum of ASD patients (Purcell et al., 2001), whereas NMDAR receptor subunits GluN2A and GluN2B have been shown to be increased in rodent ASD models (Rinaldi et al., 2007). Mutations in the *GRIN2B* gene which encodes for the GluN2B subunit of NMDAR are associated with autism, intellectual disability (Endele et al., 2010; Talkowski et al., 2012), and developmental language disorders (Ocklenburg et al., 2011; Hu et al., 2016). Ocklenburg et al postulate that variations in NMDAR efficiency could modulate interhemispheric transfer via the corpus callosum (transmission over the corpus callosum is predominantly glutamatergic (Kumar and Huguenard, 2001)), subsequently influencing language lateralization during development (Ocklenburg et al., 2011). Based on this, interhemispheric communication mediated by glutamate signaling may play a role in the normal development of language. Glutamate dysregulation during development may lead to the onset of language disorders early in life, such as in FXS, or contribute to early language regression as in ASD (or late life regression in FXTAS).

A trial of memantine treatment for 21 months in ASD demonstrated improvements in language function on the Clinical Global Impression Improvement scale (Chez et al., 2007). Studies involving other NMDAR modulators such as acamprosate, amantadine, and minocycline and mGluR5 antagonist AFQ056 are currently underway (Rojas, 2014). Combining studies evaluating the efficacy of glutamate modulators with neuropsychological testing and/or language-related ERP studies, could contribute to our understanding of the role of glutamate neurotransmission in language processing and language development.

4.2. On Pharmacologic Models

As new pharmacologic agents increasingly target specific glutamate receptor subclasses, more options will become available for clinical studies in diseases of glutamate dysregulation. mGluR positive and negative allosteric modulators in particular have shown promise in reversing cognitive impairment, suppressing neuroinflammation, and promoting neuronal survival, possibly independently and via modulation of NMDAR function (Bruno et al., 2017). New AMPAR modulators are also undergoing clinical study and may be beneficial in improving memory and attention via upregulation of BDNF and rescue of dysfunctional synaptic plasticity/LTP (Partin, 2015).

It is also possible that targeted therapy at GABA receptors may in part rescue the excitatory-inhibitory imbalance caused by glutamate dysregulation. The effects of piracetam in stroke aphasia patients may in part

be due to GABA modulation (Kessler et al., 2000; Güngör et al., 2011). There is at least one case report of the GABA-transaminase agonist imipramine improving verbal/language skills in infantile autism, possibly by increasing neuron-to-oligodendrocyte signaling in the corpus callosum (Cohen, 2002). Evaluating the efficacy of these agents on language performance would contribute to the further elucidation of the role of glutamate (and GABA) neurotransmission in language disorders.

4.3. On Testing Instruments

As demonstrated in the ERP and Pharmacology section above, there is some variability in ERP results that may lead to seemingly contradictory conclusions. Some possible reasons for this variability include: variability in experimental designs and data recording procedures, artifact rejection or correction, and the highly technical and challenging nature of ERP data interpretation. Inferences and conclusions drawn from ERP experiments require understanding of the paradigms being used: for example, a common ERP paradigm measures the N400 congruity effect to the ERPs to the final word in a sentence or phrase. However, as Hagoort et al. point out, placing the critical word in sentence-final positions results in activation of other global processing factors, and unacceptable completions seem to elicit enhanced N400-like potentials whether the unacceptability is semantic or syntactic in nature; both of which can confound the study interpretation (Hagoort et al., 2003).

In addition to ERP studies, proton spectroscopy, spectral EEG analysis, and transcranial magnetic stimulation (TMS) may be useful in evaluating the association between language and glutamate. Olson et al. serially measured CNS metabolite concentrations in the posterior cingulate gyrus over 12 months in MCI patients using proton spectroscopy and found an association between glutamate/glutamine concentration and declining performance in Boston Naming Tests in a population subset (Bartnik Olson et al., 2008). Spectral analysis of EEG signals revealed a diffuse slowing in AD but conflicting results in gamma band oscillations (Horvath et al., 2018). As for TMS, Bracco et al. demonstrated that execution of linguistic tasks modified the excitability of the dominant primary motor cortex to TMS in healthy controls but not in patients with amnesic MCI, suggesting alterations in functional connectivity between language-related brain regions and the motor cortex (Bracco et al., 2009).

Finally, deviations from the normal oscillatory pattern of neuronal networks and the functional connectivity between language and motor brain regions support the idea that amnesic MCI, AD, and vascular aphasia each may represent disorders of cognitive networks, either via a network disconnection (Hyman et al., 1984) or an “oscillopathy” with abnormal signaling between connected nodes (Horvath et al., 2018). The fact that mGluR and KAR are involved in maintaining normal neuronal oscillatory synchronization, again implicates their dysregulation in the pathogenesis of language and cognitive dysfunction. Nevertheless, despite similarities in clinical presentation of vascular dementia and AD, there are significant topographical and oscillatory differences between the two diseases (Neto et al., 2015).

5. Conclusion

In this article, we have proposed that glutamate neurotransmission may play a key role in normal physiological processing of language and in the pathogenesis of several language disorders. We reviewed the mechanisms of action of NMDAR, AMPAR, KAR, and mGluR and the role these glutamate receptors and subtypes may play in semantic and lexical processing and in maintaining widely-distributed functional language comprehension and production networks. We evaluated the preclinical data that glutamate dysregulation contributes to the pathogenesis in three disorders of language processing (AD, FXTAS, and Aphasic Stroke Syndromes). The likely importance of GABA-glutamate balance for

normal language processing was also discussed. Finally, we presented clinical ERP and pharmacologic evidence demonstrating improvements in language function in all three as a result of glutamate modulation.

Given the ubiquity of glutamate in the CNS, its role in language processing is likely heterogeneous with overlapping functions of the four receptor subclasses. Maintenance of synaptic plasticity and normal neuronal oscillations appears to be crucial in the access and retrieval of semantic information and the processing and evaluation of syntactically anomalous or ambiguous sentences.

Early language deficits in the neurodegenerative diseases AD and FXTAS may be associated with deficits in implicit and/or explicit memory function(s), whereas the conceptual and lexical stores are relatively unaffected. The NMDAR antagonist memantine appears to improve memory and language dysfunction in these diseases, suggesting that

NMDAR dysregulation may be a part of the disease mechanism. Modulation of NMDAR activity also may improve chronic language deficits in acquired aphasia due to stroke, suggesting continued dysregulation in glutamate transmission one year after the ischemic insult. Based on associated ERP studies, the electrophysiological drivers and the language processing component affected are likely different between the two neurodegenerative disorders, and language deficits in aphasic stroke patients are likely associated with both reduced access to conceptual/semantic information and difficulty achieving syntactic integration.

The extant literature is skewed towards NMDAR function given the limited number of non-NMDA glutamate modulators in clinical and preclinical studies. Preclinical data suggest that AMPAR and mGluR also participate in regulation of synaptic plasticity and neuronal health, while mGluR and KAR may be associated with metaplasticity and maintenance of synchronous neuronal oscillations and distributed language networks. Glutamate to GABA ratios, as well as receptor fingerprints unique to language processing structures, likely also contribute to glutamate's role in language. The data presented here provide an initial framework for the glutamate-language hypothesis; the advent of novel pharmacologic agents and standardization of language-associated test paradigms (including ERP, spectral EEG, and proton spectroscopy) arguably can help validate the role of glutamate neurotransmission in normal language function and deepen our understanding of how glutamate dysregulation impacts specific language disorders.

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