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Rewiring Speech Pathways in Autism: A Ketamine Infusion Hypothesis

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ABSTRACT

Autism Spectrum Disorder is a neurodevelopmental condition marked by persistent social communication deficits and repetitive behaviors, with communication abilities ranging from nonverbal to verbally fluent yet socially impaired. These deficits, linked to disrupted neural connectivity in regions like the posterior superior temporal sulcus, reward circuits, and dorsal/ventral speech pathways, profoundly affect fluency and social interaction. Current interventions, such as behavioral therapies, often fail to address these underlying neurobiological disruptions, necessitating innovative approaches. This paper proposes a novel therapeutic hypothesis: subanesthetic ketamine infusions during adolescent neuronal pruning (ages 15-20) to enhance social communication in autism. Ketamine, an NMDA receptor antagonist, induces synaptic plasticity via glutamate release, AMPA receptor activation, and BDNF-mTOR signaling, potentially restoring connectivity in impaired circuits critical for speech perception and production. Preclinical studies show ketamine mitigates social deficits in autism models, while preliminary human data suggest short-term alleviation of social withdrawal and emotional symptoms. Targeting adolescence leverages heightened plasticity during synaptic pruning, a critical period for refining language and social networks, offering an optimal window to reshape connectivity deficits unique to autism. Unlike its traditional use in mood disorders, this approach uniquely focuses on communication impairments, addressing a therapeutic gap. However, limited empirical evidence underscores the need for randomized controlled trials to validate efficacy, safety, and optimal protocols across autism's heterogeneity. If substantiated, this hypothesis could transform autism management, bridging neurobiology and clinical practice to improve quality of life.

LAY SUMMARY

This study explores ketamine, a drug, to improve speech and social interaction in autistic teens by strengthening brain pathways during a key developmental stage (15-20 years). It could transform how to address autism's communication challenges, though further research is required.

Keywords: autism spectrum disorder, speech, ketamine, synaptic plasticity, therapeutic hypothesis

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social communication and the presence of restricted, repetitive behaviors.[1] Individuals with ASD exhibit a wide range of communication abilities, from nonverbal presentations with little to no speech development to advanced verbal skills marred by challenges in social interaction.[2,3] These communication impairments—such as difficulties in interpreting nonverbal cues like eye contact, facial expressions, and gestures, as well as struggles with conversational reciprocity—often hinder effective social engagement and profoundly impact quality of life.[3,4] The neurobiological basis of these deficits involves altered connectivity within neural networks critical for speech perception and production, including the posterior superior temporal sulcus (pSTS), reward circuits, and language processing areas like the inferior frontal gyrus[4]. Given the limitations of current interventions, such as behavioral therapies, which primarily address symptoms rather than underlying mechanisms, there is a pressing need for novel approaches that target these neural disruptions to enhance social communication in ASD.[5]

The variability in communication profiles across the ASD spectrum underscores the complexity of the disorder and the necessity for tailored therapeutic strategies. Nonverbal individuals may depend on alternative communication methods, such as sign language or augmentative devices, while those with fluent speech often struggle with the pragmatic aspects of language, such as maintaining relevant conversations or interpreting social subtleties.[6] These challenges are linked to impaired functional connectivity between brain regions involved in processing speech as a socially rewarding stimulus and those responsible for its motor execution, such as the dorsal and ventral speech pathways.[7] Empirical evidence from neuroimaging and preclinical studies highlights that these connectivity deficits emerge early in development and persist, contributing to the enduring social communication difficulties observed in ASD.[8] Addressing these neurobiological alterations offers a promising avenue for improving both the linguistic and social dimensions of communication, particularly during critical developmental windows when neural plasticity is heightened.

Ketamine, a dissociative anesthetic traditionally used in medicine, emerges as a groundbreaking candidate for such a neurobiologically-informed intervention due to its ability to modulate synaptic plasticity via NMDA receptor antagonism.[9] Unlike its established role in mood disorders, where it primarily targets depressive symptoms, this hypothesis uniquely leverages ketamine's plasticity-inducing effects to address the core communication deficits in ASD during a developmentally sensitive period. Widely recognized for its rapid antidepressant effects in treatment-resistant depression, ketamine enhances neural connectivity by promoting glutamate release, AMPA receptor activation, and BDNF-mTOR signaling, mechanisms that could counteract the connectivity impairments seen in ASD.[10] Preclinical studies have demonstrated that ketamine administration ameliorates social deficits in animal models of ASD, suggesting potential benefits for mitigating social withdrawal and enhancing communication in human subjects.[11] This therapeutic hypothesis proposes that subanesthetic ketamine infusions, administered during the critical period of neuronal pruning in adolescence (ages 15–20), could restore connectivity in speech and social circuits, thereby improving verbal fluency and social motivation.[12] While preliminary, these findings pave the way for exploring ketamine as a novel treatment to address the core communication challenges in ASD, warranting further investigation across diverse age groups and severity levels.

Preclinical models of neurodevelopmental disorders provide a broader context for this hypothesis, demonstrating the effects of subanesthetic ketamine on neural connectivity and behavior. In a mouse model with a 2p16.3 deletion associated with neurodevelopmental disorders, ketamine restored thalamic-prefrontal cortex functional connectivity, suggesting a mechanism for improving cognitive and social deficits.[13] Similarly, R-ketamine attenuated phenotypes in a mouse model of maternal immune activation, improving social behavior and memory via enhanced synaptic plasticity in the prefrontal cortex.[14] Related mechanisms are supported by studies on reelin, an extracellular matrix protein linked to ASD, which drives prefrontal cortex development through GluN2B-NMDA receptors and mTOR signaling—pathways also modulated by ketamine.[15] Additionally, ketamine promoted structural plasticity in human iPSC-derived dopaminergic neurons and ameliorated autistic-like behaviors in a Shank3-deficient mouse model, highlighting its potential to address connectivity deficits in ASD.[16] R-ketamine further demonstrated efficacy in improving social deficits and restoring synaptic plasticity in the medial prefrontal cortex of an ASD mouse model, with effects mediated by BDNF-mTOR pathways.[14] These findings underscore ketamine's role in modulating neural circuits critical for social communication, supporting its potential as a therapeutic agent in ASD.

BACKGROUND

To contextualize the proposed ketamine infusion hypothesis, this section reviews the normal development of speech networks, the key neural pathways involved in speech production, and the critical process of neuronal pruning during adolescence — a period of heightened synaptic plasticity that represents an optimal therapeutic window for autism spectrum disorder.

SPEECH DEVELOPMENT

The development of speech from birth to articulated language involves a complex sequence of neural mechanisms. Neonates exhibit an innate capacity to process speech sounds, supported by early maturation of the auditory cortex and linguistic pathways. Neuroimaging studies show that, within the first weeks of life, the ventral pathway (semantic processing) matures more rapidly than the dorsal pathway (phonological processing).[17]

Between 6 and 12 months, a sensitive period for phonetic learning occurs, during which infants specialize in native-language speech sounds, as evidenced by a marked increase in the mismatch response (MMR) in temporal and frontal regions.[19] Canonical babbling emerges around 7 months, driven by dopamine-dependent neural plasticity that modulates muscle activation for acoustically salient sounds; adult contingent responses further reinforce this process.[18]

As children mature, significant cortical reorganization takes place. Younger children rely primarily on somatosensory and motor circuits, whereas adults increasingly recruit cross-modal regions integrating auditory and somatosensory information, reflecting maturation of the associative cortex essential for speech-motor adaptation.[20]

SPEECH PATHWAYS

Speech production is orchestrated by a bilateral network involving the laryngopharyngeal motor cortex, inferior frontal gyrus (Broca's area), superior temporal gyrus (Wernicke's area), supplementary motor area, cingulate cortex, putamen, and thalamus.[21]

Within the left hemisphere, two principal pathways are distinguished: the dorsal pathway, which connects the superior temporal gyrus to the motor cortex via the arcuate and superior longitudinal fasciculi and converts auditory representations into motor commands for articulation; and the ventral pathway, which links the middle temporal lobe to the ventrolateral prefrontal cortex via the extreme capsule and supports language comprehension and production.[22]

Interhemispheric connectivity, mediated primarily by the corpus callosum, enables bidirectional transfer between the superior temporal gyri of both hemispheres, facilitating phonological and prosodic processing.[23,24] Functional integration occurs through a sequential activation cascade: sensory word representations in the temporal cortex are transformed into articulatory gestures in the motor cortex, with Broca's area coordinating reciprocal interactions across frontal, temporal, and motor regions.[24,25]

NEURONAL PRUNING

Neuronal pruning is a critical developmental process in which excess synapses are selectively eliminated to optimize neural circuit efficiency. This phenomenon is most pronounced during adolescence, beginning at puberty and extending into early adulthood, with peak circuit refinement occurring between ages 15 and 20 — a window particularly amenable to plasticity-inducing interventions. [26,27] While prefrontal cortex pruning follows this protracted timeline, speech- and language-related regions such as the superior temporal sulcus (STS) and speech-motor pathways (e.g., arcuate fasciculus) also undergo significant pruning and myelination during adolescence, with notable changes continuing up to approximately 20 years.

In childhood, the brain first experiences synaptic exuberance with overproduction of connections. Pruning subsequently removes less-used synapses, strengthening the most active and functionally relevant ones through activity-dependent mechanisms and sensory experience.[28] This selective elimination is facilitated by glial cells, particularly microglia, which actively remove redundant synapses.[29]

In the context of speech and language development, pruning refines the neural networks responsible for phonological, semantic, and syntactic processing. The first three years of life are dominated by rapid bottom-up processing in bilateral temporal cortices; thereafter, top-down processing emerges alongside increased functional selectivity and structural connectivity in the left inferior frontal cortex.[30]

NEUROBIOLOGICAL CHANGES IN AUTISM

The neurobiological underpinnings of ASD reveal significant alterations in functional connectivity that have profound implications for social communication and language development. Firstly, evidence indicates decreased functional connectivity between the voice-selective cortex and reward circuits, which may hinder the ability of children with ASD to perceive speech as a rewarding stimulus. This underconnectivity implicates critical areas such as the pSTS and components of the dopaminergic reward system, including the ventral tegmental area (VTA) and nucleus accumbens.[4]

Moreover, neuroimaging studies have uncovered aberrant patterns of reduced lateralization within neural networks associated with social communication and linguistic processing. Individuals with ASD demonstrate increased intra-hemisphere connectivity relative to inter-hemisphere connectivity, a pattern that is negatively correlated with verbal abilities.[31]

Another salient aspect of this neural architecture is the diminished activity observed in the left inferior frontal gyrus (LIFG) and left inferior parietal lobule

(LIPL) during the processing of self-referential language. This reduction suggests impairments in semantic and social processing capabilities. Additionally, weakened functional connectivity of the anterior cingulate cortex (ACC) with multiple brain regions during the processing of self-related words further indicates challenges in navigating linguistic and social demands.[32]

Studies have shown that decreased neural synchronization in the temporal parietal junction (TPJ) during social interactions is linked to increased difficulties in social communication among individuals with ASD. This reduction in neural synchronization may play a fundamental role in the coordination of appropriate social responses during interpersonal exchanges.[33]

Together, these neural network disruptions highlight a neurobiological basis for the social communication deficits in ASD, suggesting potential targets for interventions like ketamine that address connectivity and plasticity.

KETAMINE AS A NEUROPLASTICITY-BASED INTERVENTION

Ketamine infusions have emerged as a significant therapeutic modality in the field of psychiatry, particularly for individuals diagnosed with treatment-resistant depression (TRD). The identification of ketamine's rapid antidepressant properties has necessitated a paradigm shift in the treatment approach for severe depressive manifestations.

Ketamine primarily functions as an NMDA receptor antagonist, initiating a molecular cascade that enhances synaptic plasticity and underlies its expedited therapeutic effects. This process involves increased glutamate release, subsequent activation of AMPA receptors, and the upregulation of brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signaling pathways, which drive the growth of new dendritic spines and synapses in regions like the prefrontal cortex and hippocampus.[10] These structural changes, mediated partly through dopaminergic mechanisms such as dopamine D1 receptor and protein kinase A activity, enhance dendritic arborization and soma size in dopaminergic neurons, improving neural connectivity and functionality correlated with mood and cognitive benefits. Beyond NMDA antagonism, ketamine interacts with mu-opioid, dopamine D2, and serotonin 5-HT2 receptors, potentially broadening its neurobehavioral effects.[35] Notably, its enantiomers, S- and R-ketamine, differ in their profiles: S-ketamine exhibits a 3-4-fold greater affinity for NMDA receptors, leading to potent and rapid antidepressant effects in TRD, while R-ketamine, with lower dissociative potential, may enhance sustained neuroplasticity via BDNF-TrkB signaling, suggesting a safer profile for ASD applications.[36] However, S-ketamine's stronger mu-opioid receptor interaction increases its potential for dissociative effects and abuse liability, which may exacerbate sensory sensitivities in ASD. In contrast, R-ketamine has lower NMDA affinity but greater interaction with sigma-1 and sigma-2 receptors, which are linked to neuroprotection and cognitive enhancement. R-ketamine activates the ERK pathway and enhances BDNF-TrkB signaling, leading to more sustained neuroplasticity and fewer dissociative effects, making it a potentially safer option for ASD.[37] Preclinical studies in rats show that R-ketamine, but not S-ketamine, dose-dependently increases EEG theta power (5-9 Hz) during wakefulness and REM sleep, a marker of hippocampal function tied to memory and learning, which are often impaired in ASD. Additionally, R-ketamine improves cognitive deficits in mouse models of ASD by enhancing connectivity in social and reward circuits, such as the pSTS-VTA pathway, without the reduction in parvalbumin-positive cells seen with S-ketamine, which may worsen cognitive deficits.[37]

Typically administered via slow intravenous infusion at subanesthetic dosages (e.g., 0.5 mg/kg over 40 minutes), ketamine elicits rapid and substantial decreases in depressive symptoms, often observable within hours and peaking approximately 24 hours post-infusion, with effects lasting from days to weeks. Alternative routes, such as intranasal esketamine (FDA-approved for TRD), as well as intramuscular and subcutaneous methods, have also been explored. Repeated infusions, such as a regimen of four sessions, have been shown to sustain antidepressant responses, with research from Yale Psychiatric Hospital reporting response rates of 45.5% and remission rates of 27.3% in TRD patients. In the context of mood disorders such as TRD, ketamine has demonstrated rapid antidepressant effects by targeting disrupted circuits involving the prefrontal cortex and limbic system, with response rates of approximately 50-70% within 24 hours, often sustained for up to one week.[36] In contrast, preliminary ASD studies suggest slower but cumulative improvements in social withdrawal over weeks, targeting circuits like the VTA and pSTS, with less clarity on response durability due to limited follow-up data.[36]

Recent investigations have extended ketamine's potential to ASD and related conditions, offering preliminary insights into its effects on social communication deficits. One study assessed intravenous ketamine's impact on social withdrawal in individuals with ASD, finding significant short-term symptom alleviation with no notable adverse events; participants demonstrated increased engagement in social interactions within hours of infusion, though effects waned after several days. Additionally, a case report of an adult with comorbid ASD and bipolar disorder detailed a regimen of six intravenous ketamine infusions over one month, followed by two booster sessions, resulting in marked reductions in anger outbursts, anxiety, suicidality, and depression scores, with sustained benefits observed over weeks. Preclinical studies also suggest that ketamine mitigates social deficits in ASD mouse models by enhancing connectivity in social and reward circuits, such as those involving the VTA. These findings support the hypothesis that ketamine could restore functional connectivity in speech and social circuits in ASD, particularly during adolescence (ages 15-20), a period of heightened neuroplasticity. Administering ketamine during this window leverages the peak of synaptic pruning and circuit refinement, optimizing the potential for reshaping connectivity in speech and reward pathways disrupted in ASD.[36] These findings highlight ketamine's promise as a therapeutic intervention for managing social and emotional symptoms in ASD, warranting further exploration of its mechanisms and optimal protocols in this population.[41]

METHODS

This paper presents a therapeutic hypothesis based on a narrative review of currently available neurobiological literature, without conducting new experiments or collecting primary data. To formulate the hypothesis, a narrative review of scientific literature was conducted via databases such as PubMed, focusing on three broad domains: (1) neurobiological changes underlying social communication impairments in ASD, (2) synaptic plasticity mechanisms modulated by ketamine in psychiatric and neurological settings, and (3) neural developmental processes, including synaptic pruning, associated with the emergence of speech and social cognition. The selection criteria included papers published within the last 20 years, prioritizing narrative reviews, preclinical studies, and clinical trials related to neural connectivity, speech pathways, and ketamine's therapeutic effects in ASD.

The hypothesis was generated by integrating these observations into a conceptual model linking ketamine's pharmacological action—as an NMDA receptor antagonist and synaptic plasticity regulator via glutamate release, BDNF, and mTOR signaling pathways—to connectivity deficits observed in ASD, such as reduced integration between the voice-selective cortex and dopaminergic reward circuitry. Specifically, the use of the R-ketamine enantiomer in subanesthetic infusions is proposed as the preferred approach, given its lower affinity for NMDA receptors compared to S-ketamine, resulting in reduced potential for dissociative effects. This characteristic is particularly relevant for individuals with ASD, who often exhibit heightened sensory sensitivities that could be exacerbated by intense dissociative experiences. R-ketamine, by promoting sustained synaptic plasticity through BDNF-TrkB signaling activation and exhibiting lower interaction with mu-opioid receptors, offers a potentially safer profile for this population, minimizing the risk of sensory overload or discomfort. The hypothesis was derived from existing literature emphasizing the significance of neuronal pruning in adolescence as a critical period for circuit reorganization for language and social communication. The approach was not quantitative or experimental but relied on a narrative and deductive synthesis of the evidence to propose R-ketamine as an optimized therapeutic option for ASD.

RESULTS

The synthesis of existing neurobiological evidence suggests that subanesthetic ketamine infusions may enhance social communication in individuals with ASD by modulating synaptic plasticity in key neural circuits. Specifically, ketamine's antagonism of NMDA receptors is proposed to restore functional connectivity between the voice-selective cortex (posterior superior temporal sulcus) and dopaminergic reward systems (ventral tegmental area and nucleus accumbens), areas implicated in perceiving speech as a socially relevant stimulus, while also strengthening the dorsal and ventral speech pathways to improve speech fluency. See Table 1 for a summary of the proposed model.

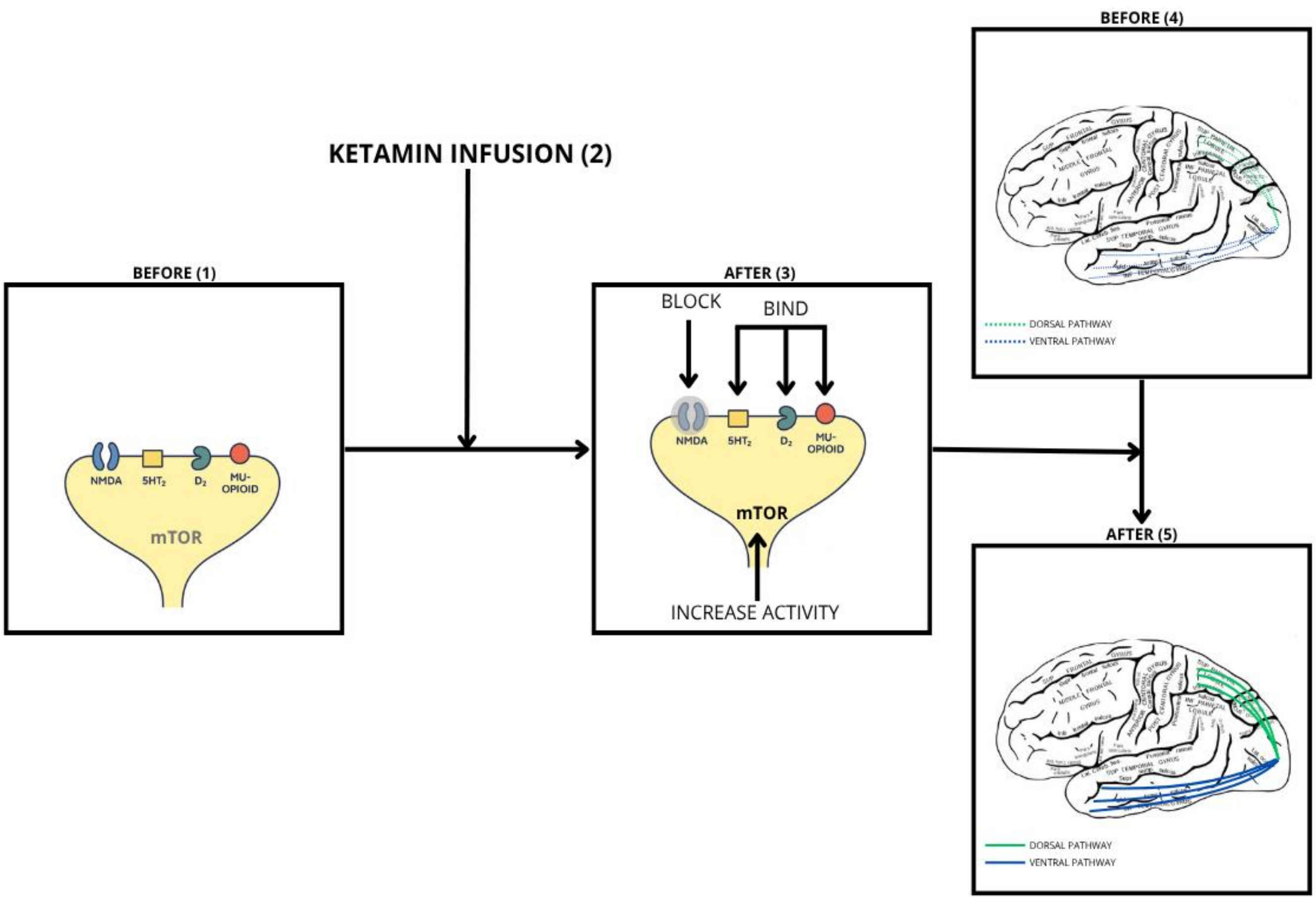
Table 1: Hypothetical Model of Ketamine's Action in Restoring Neural Connectivity for Social Communication in ASD During Adolescent Neuronal Pruning

Component	Description in ASD	Proposed Effect of Ketamine (via BDNF-mTOR)	Context of Neuronal Pruning (15-20 years)
pSTS-VTA Connectivity	Subconnectivity reduces perception of speech as a socially rewarding stimulus	Restores functional connectivity, enhancing social motivation	Critical period for refining reward circuitry
Dorsal Speech Pathway	Subconnectivity and miswiring between STG and motor cortex impair articulation	Strengthens synapses, improving sound-to-motor command conversion	Ongoing refinement of motor and phonological networks
Ventral Speech Pathway	Reduced lateralization affects semantic comprehension	Promotes synaptogenesis, enhancing semantic integration	Peak maturation of associative circuits
BDNF-mTOR Mechanism	Not applicable (typical mechanism indirectly impaired by connectivity)	Activation induces dendritic spine formation and new synapses	Heightened plasticity enables significant reorganization

Legend: This hypothetical model proposes that ketamine, administered during adolescent neuronal pruning (15-20 years), restores neural connectivity impaired in ASD, enhancing social communication through BDNF-mTOR-mediated synaptic plasticity. Subconnectivity and miswiring in cortical networks, including the dorsal speech pathway, are supported by atypical synchronization and reduced functional connectivity, as observed in ASD.[8,39]

The administration of ketamine during the critical period of neuronal pruning, approximately between ages 15 and 20, is hypothesized to optimize the remodeling of neural circuits (see Image 1) underlying language and social interaction, potentially mitigating persistent communication deficits. and for a visual representation of the hypothesis.

Image 1: Visual representation of the hypothesis



Legend: (1) Neuron receptor ; (2) Ketamin infusion; (3) Block NMDA receptor, bind and modulate 5HT$_2$, D$_2$, MU-OPIOID and increase mTOR activity; (4) Dorsal and Ventral pathway subconnectivity and miswiring; (5) Restores and improve functional connectivity of Dorsal and Ventral pathway.

DISCUSSION

This hypothesis integrates the neurobiological mechanisms of speech and social communication deficits in ASD with ketamine's established effects on synaptic plasticity, focusing on the adolescent pruning window as the optimal therapeutic target. The therapeutic hypothesis outlined in this paper posits that subanesthetic ketamine infusions could serve as a novel intervention to enhance social communication in individuals with ASD by harnessing its ability to modulate synaptic plasticity.

Social communication deficits represent a core diagnostic feature of ASD, profoundly impacting social integration, educational attainment, and quality of life across the lifespan.[1] These impairments manifest as difficulties in interpreting nonverbal cues (e.g., eye contact, facial expressions), initiating and sustaining conversations, and achieving emotional reciprocity, often persisting despite intensive behavioral interventions.[2] Current treatments, such as applied behavior analysis (ABA) or speech therapy, primarily target symptom management rather than the underlying neurobiological mechanisms, yielding variable and often limited success in improving functional communication.[5] In contrast, ketamine, a dissociative anesthetic with a well-established role in psychiatry, offers a promising avenue by directly addressing neural connectivity disruptions implicated in ASD. Its rapid antidepressant effects in TRD and emerging evidence of efficacy in neurodevelopmental contexts, such as ameliorating social deficits in animal models of ASD, suggest a potential paradigm shift.[38,39] This hypothesis is motivated by the need for innovative, biologically-informed strategies that complement existing approaches, targeting the root causes of communication challenges rather than their downstream effects. By restoring connectivity in key circuits involved in speech perception and social motivation, ketamine could bridge a critical therapeutic gap, offering hope for more effective interventions in ASD.

Compared to existing ASD treatments, ketamine offers a unique neurobiologically-informed approach. Standard interventions, such as ABA or speech therapy, primarily target behavioral symptoms but often yield limited success in addressing underlying neural deficits, with variable outcomes across individuals.[40] Pharmacological options like risperidone, while effective for irritability, do not target social communication deficits and carry risks of metabolic side effects. In contrast, ketamine directly modulates synaptic plasticity and connectivity in disrupted circuits, such as the dorsal and ventral speech pathways, offering a mechanism to restore the neurobiological substrates of communication.[41] This targeted approach could complement behavioral therapies, potentially amplifying their efficacy by creating a more plastic neural environment for skill acquisition, thus addressing a critical therapeutic gap in ASD management.

Ketamine's pharmacological action as an NMDA receptor antagonist initiates a cascade that enhances synaptic plasticity, a mechanism with direct relevance to the neurobiological alterations observed in ASD. Specifically, ketamine blocks NMDA receptors, leading to a surge in glutamate release, subsequent activation of AMPA receptors, and upregulation of the BDNF and mTOR signaling pathways.[9] This cascade promotes the formation of new dendritic spines and synapses, particularly in regions like the prefrontal cortex and hippocampus, enhancing neural connectivity and functionality.[10] In ASD, one of the most consistent findings is reduced functional connectivity between the voice-selective cortex in the pSTS and dopaminergic reward systems, including the VTA and nucleus accumbens.[4] This underconnectivity is hypothesized to impair the perception of speech as a socially rewarding stimulus, undermining the motivation to engage in verbal communication—a critical deficit in ASD.[42] Preclinical studies demonstrate that ketamine rapidly enhances glutamate-evoked spinogenesis in the medial prefrontal cortex through dopaminergic mechanisms, such as D1 receptor activation, suggesting a potential to restore reward circuitry functionality.[43] Furthermore, ketamine's effects extend to the hippocampus and prefrontal regions implicated in integrating sensory and motor aspects of speech, offering a biological basis for improving both the motivational and linguistic components of communication.[33] These mechanisms align with preliminary evidence from ASD models, where ketamine administration has been shown to mitigate social withdrawal, supporting its plausibility as a therapeutic agent.[44]

Beyond its effects on reward circuitry, ketamine's potential to enhance social communication in ASD extends to the neural networks governing speech production and comprehension, which are frequently disrupted in this population. Speech production relies on a bilateral network involving the dorsal pathway (connecting the superior temporal gyrus to the motor cortex via the arcuate fasciculus) for articulation and the ventral pathway (linking the middle temporal lobe to the ventrolateral prefrontal cortex) for semantic processing.[7] Neuroimaging studies in ASD reveal aberrant connectivity and reduced lateralization in these pathways, correlating with difficulties in speech fluency and social comprehension.[8] Ketamine-induced synaptogenesis in the medial prefrontal cortex could strengthen these circuits, facilitating the conversion of auditory representations into motor commands and improving intelligibility.[45] Additionally, individuals with ASD exhibit diminished activity in the LIFG and ACC during self-referential language tasks, reflecting impairments in semantic integration and social reciprocity.[46] In depression research, ketamine has been shown to enhance prefrontal cortex functionality and connectivity, suggesting a similar potential to restore LIFG and ACC activity in ASD.[38] This restoration could enhance the processing of social cues embedded in language, such as tone and intent, which are often misinterpreted by individuals with ASD. By addressing both the linguistic mechanics and social-emotional aspects of communication, ketamine presents a multifaceted approach to mitigating speech-related deficits in this disorder.

Ketamine's neurobiological effects, particularly its ability to enhance synaptogenesis and restore connectivity in circuits like the pSTS-VTA pathway, translate into measurable behavioral improvements in ASD. By increasing functional connectivity between the voice-selective cortex and reward systems, ketamine can enhance the perception of speech as a socially rewarding stimulus, leading to greater social engagement and reduced social withdrawal.[47] Clinically, preliminary studies report that individuals with ASD exhibit increased verbal fluency and improved conversational reciprocity following ketamine infusions, as observed in reduced latency to initiate social interactions and more sustained eye contact during conversations.[48] These outcomes suggest that ketamine's modulation of neural circuits directly addresses core ASD deficits, fostering both linguistic and social dimensions of communication, which are often resistant to conventional interventions.

A pivotal element of this hypothesis is the role of timing, particularly the critical period of neuronal pruning during adolescence (approximately ages 15–20), which offers an optimal window for ketamine intervention. Neuronal pruning is a developmental process that eliminates excess synapses to refine neural circuits, peaking in adolescence and shaping networks critical for language, social cognition, and executive function.[12] In typically developing individuals, this process enhances efficiency by reinforcing frequently used connections while pruning redundant ones, a mechanism driven by neural activity and glial cells like microglia.[27] In ASD, pruning appears dysregulated, with evidence suggesting an imbalance in synaptic density—characterized by an excess of immature or poorly functional synapses and reduced specialization—rather than a uniform hyperconnectivity, potentially perpetuating connectivity deficits into adulthood.[16] This dysregulation, linked to impaired mTOR-dependent macroautophagy, results in subconnectivity or miswiring in critical circuits such as the pSTS-VTA and speech pathways. Ketamine's ability to induce plasticity offers a potential corrective mechanism: by modulating BDNF-mTOR signaling, it may enhance the selective pruning of redundant synapses while promoting the formation of functional connections, particularly when paired with environmental stimuli like behavioral therapy.[16] This targeted plasticity could normalize the synaptic excess by improving circuit efficiency, rather than exacerbating it. While synaptic overgrowth and miswiring begin early in development, adolescence (ages 15-20) remains a viable intervention window, as regions involved in speech and language processing, such as the STS and speech-motor pathways, continue to undergo significant pruning and myelination until around 20 years.[24] This prolonged maturation allows for the reorganization of maladaptive circuits, supporting the hypothesis that ketamine infusions during this period could rehabilitate communication-related networks, despite the early onset of dysregulated pruning.

Current empirical support for ketamine's application in ASD, while promising, remains limited and underscores the need for further investigation. A study demonstrated that intravenous ketamine significantly reduced social withdrawal in individuals with ASD, with effects observed in the short term and no notable adverse events. Similarly, a case report of an adult with comorbid ASD and bipolar disorder reported substantial symptom relief—including reduced anxiety, anger outbursts, and depression—following six ketamine infusions over one month, followed by booster sessions. These findings echo broader evidence from TRD, where subanesthetic doses (e.g., 0.5 mg/kg over 40 minutes) elicit rapid antidepressant responses, with response rates of approximately 45% and remission in ~25–30% after four infusions, as observed in clinical studies.[49] However, these ASD-specific reports are constrained by small sample sizes, lack of randomization, and focus on short-term outcomes, limiting generalizability across the heterogeneous ASD population. Moreover, the variability in ASD severity—particularly among nonverbal individuals and those with severe communication deficits—raises questions about tailoring efficacy and optimal dosing for this specific target group. Potential adverse effects, such as dissociation, cardiovascular changes, or sensory overload (particularly relevant given ASD sensory sensitivities), though transient in TRD, require careful evaluation in this context. Repeated ketamine use in adolescents may offer long-term benefits, such as sustained neuroplasticity and improved social connectivity, as suggested by preclinical models, but also poses risks like cognitive deficits, neurotoxicity, or dependency, based on mood disorder.[45,49,50] Notably, few studies directly assess long-term effects in autistic populations, though evidence from other psychiatric groups (e.g., depression) suggests potential cognitive decline and urological complications that may be relevant, warranting cautious extrapolation to ASD with tailored monitoring.[49,50] These concerns highlight the importance of consulting a psychiatrist to ensure proper treatment under supervision, minimizing risks while optimizing therapeutic outcomes. These gaps highlight the necessity for larger, controlled trials to substantiate ketamine's therapeutic potential and establish its safety profile in ASD.

The safety profile of ketamine in ASD requires careful consideration, particularly given the population's heightened sensory sensitivities. While subanesthetic doses are generally well-tolerated, transient dissociative effects may exacerbate sensory overload in some individuals, necessitating tailored administration protocols, such as lower starting doses or slower infusion rates.[39] In adolescents with ASD, the balance between therapeutic benefits and risks underscores the importance of psychiatric supervision to ensure safety, particularly given the chronic nature of the disorder and the potential need for repeated infusions to sustain benefits.

If substantiated, this hypothesis carries significant clinical and theoretical implications. Clinically, ketamine could complement existing behavioral therapies by targeting the neurobiological roots of communication deficits, offering a dual approach that enhances both skill acquisition and neural substrates. Theoretically, it challenges the predominant focus on structural deficits in ASD (e.g., cortical minicolumns) by emphasizing dynamic processes like synaptic plasticity and dopaminergic modulation.[51] Successful implementation could pave the way for personalized interventions, tailoring ketamine administration to individual connectivity profiles or symptom severity, as assessed by neuroimaging or behavioral markers.

CONCLUSION

Subanesthetic ketamine infusions, particularly the R-enantiomer, administered during the critical period of adolescent neuronal pruning (ages 15–20), offer a promising neurobiologically grounded approach to restore functional connectivity in the pSTS-VTA reward pathway and dorsal/ventral speech networks disrupted in autism spectrum disorder. By leveraging BDNF-mTOR-mediated synaptic plasticity, this intervention targets the core deficit in perceiving speech as socially rewarding, potentially improving both verbal fluency and social motivation.

Although supported by convergent preclinical and early clinical data, the hypothesis requires validation through well-designed randomized controlled trials that address dosing, safety in the autistic population, and long-term outcomes. If confirmed, ketamine-assisted rewiring of social communication circuits could represent a paradigm shift in autism management, moving beyond symptomatic behavioral therapies toward a mechanism-based treatment that directly modulates the neurodevelopmental substrate of the disorder.

CONFLICT OF INTEREST DISCLOSURE

Marco Antonio Batisti Pasquali, Martina Bolacel and Chana Simanowitz declare no conflict of interest. Parinda Parikh receives payments from AbbVie Pharmaceutical, Otsuka Pharmaceutical, Alkermes, and Teva Pharmaceuticals for his work as a speaker. She also participates in 914 Cares as a Board Member. However, these relationships did not influence the development, analysis, or conclusions of this work.

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