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Speech Motor Function and Auditory Perception in Succinic Semialdehyde Dehydrogenase Deficiency: Toward Pre–Supplementary Motor Area (SMA) and SMA-Proper Dysfunctions

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Abstract

This study reviews the fundamental roles of pre–supplementary motor area (SMA) and SMA-proper responsible for speech-motor functions and auditory perception in succinic semialdehyde dehydrogenase (SSADH) deficiency. We comprehensively searched the databases of PubMed, Google Scholar, and the electronic journals Springer, PreQuest, and Science Direct associated with keywords *SSADHD*, *SMA*, *auditory perception*, *speech*, and *motor* with AND operator. Transcranial magnetic stimulation emerged for assessing excitability/inhibitory M1 functions, but its role in pre-SMA and SMA proper dysfunction remains unknown. There was a lack of data on resting-state and task-based functional magnetic resonance imaging (MRI), with a focus on passive and active tasks for both speech and music, in terms of analysis of SMA-related cortex and its connections. Children with SSADH deficiency likely experience a dysfunction in connectivity between SMA portions with cortical and subcortical areas contributing to disabilities in speech-motor functions and auditory perception. Early diagnosis of auditory-motor disabilities in children with SSADH deficiency by neuroimaging techniques invites opportunities for utilizing sensory-motor integration as future interventional strategies.

Keywords

SSADH deficiency, supplementary motor area, auditory perception, speech, motor

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Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal recessive neurologic disorder that interferes with catabolism of the major inhibitory neurotransmitter γ-amino butyric acid (GABA).[1,2] The diagnosis is mostly established by the identification of biallelic pathogenic variants in *ALDH5A1*.[2,3] The neurotransmitter GABA has an inhibitory role in the mature central nervous system and yet an excitatory role, associated with membrane depolarization, in the developing brain.[4] The enzymatic deficit in SSADH deficiency has often been associated with early life developmental delay with cognitive deficiency, and severe limitation in expressive language, which remains throughout the life span.[5-8] Thus, there are potentially significant implications to understanding the outcomes of functional deficits of GABA in more prevalent neurodevelopmental disorders such as attention-deficit hyperactivity disorders (ADHDs), autism spectrum disorders, and epilepsy.[9]

A further question is whether the symptoms of SSADH deficiency may be amenable to early intervention. SSADH deficiency is generally characterized in early childhood by hyperkinetic behavior, hypotonia, altered sleep, anxiety, and delayed acquisition of motor and language developmental milestones.[6-8] In addition, seizures are observed in approximately half of patients, especially the population aged 12 years and older, which may benefit from intervention in early stages to prevent later negative outcomes. Imaging abnormalities are most consistent in the basal ganglia, specifically the globus pallidi and subthalamic nuclei, in addition to the cerebellar dentate nuclei and, in some cases, subcortical white matter.[10]

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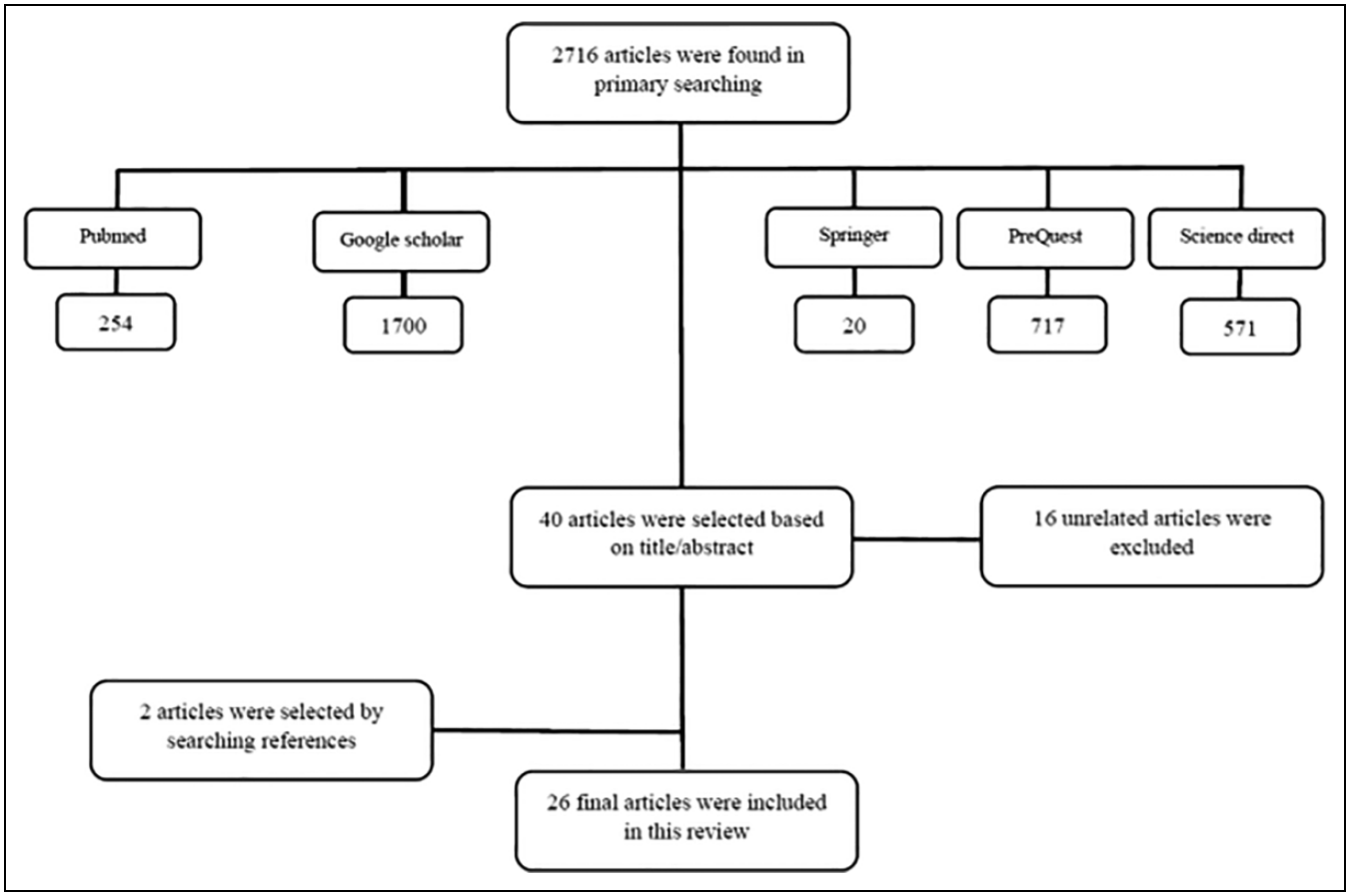

Figure 1. Diagram of the literature search process.

Also, current studies using transcranial magnetic stimulation[10,11] demonstrated abnormalities in primary motor area (M1) in SSADH deficiency. However, there is no strong evidence regarding abnormal connectivity of supplementary motor area (SMA) and M1 or lack of interaction within the motor system in this population. The permeating and persistent language dysfunction is an intriguing deficit, although potentially overshadowed by the early hypotonia, motor delays, and epilepsy. Furthermore, the functional connectivity of cortical and subcortical structures and central motor pathways responsible for speech motor control and auditory perception using resting-state and task-based functional magnetic resonance imaging (MRI) remains unknown in this clinical population. Investigations of cognitive and language dysfunction in the SSADH deficiency population using objective measures are a goal, given the lifelong nature of the language manifestations. This review focuses on the potential role of pre-SMA and SMA proper in auditory processing and motor dysfunction in SSADH deficiency, and the importance of objective measures in early diagnosis of lingual and cognitive disabilities in the clinical population.

Methods

A literature search was conducted using the electronic databases of PubMed, Google Scholar, and electronic journals of Springer, PreQuest, and Science direct. Key words included were *SSADHD*, *SMA*, *auditory perception*, *speech*, and *motor* with AND operator. We focused on English-language journals published from 1990 to 2020. We manually investigated the reference list of all the relevant articles, and reviewed for inclusivity. In primary searching, we found 2716 articles in total databases and e-journals. The articles that had insufficient information about the subject of our review were excluded. After removing duplicates and unrelated articles, we included 26 articles most related to SSADH deficiency (Figure 1).

Results

Dysfunction of Primary Motor Cortex (M1) in SSADH deficiency

Abnormal excitatory and inhibitory balance of M1 in SSADH deficiency is demonstrated in literature.[10,11] A main hypothesis was whether the GABAergic deficit introduces dysfunction in M1 using transcranial magnetic stimulation. M1 may have important functional relationships to subcortical areas (eg, the basal ganglia). For instance, patients with SSADH deficiency had alterations of motor cortical excitability, specifically reductions in the cortical silent period and long-interval intracortical inhibition, suggestive of deficits in GABA(B)-receptor mediated neurotransmission in motor cortex.[10]

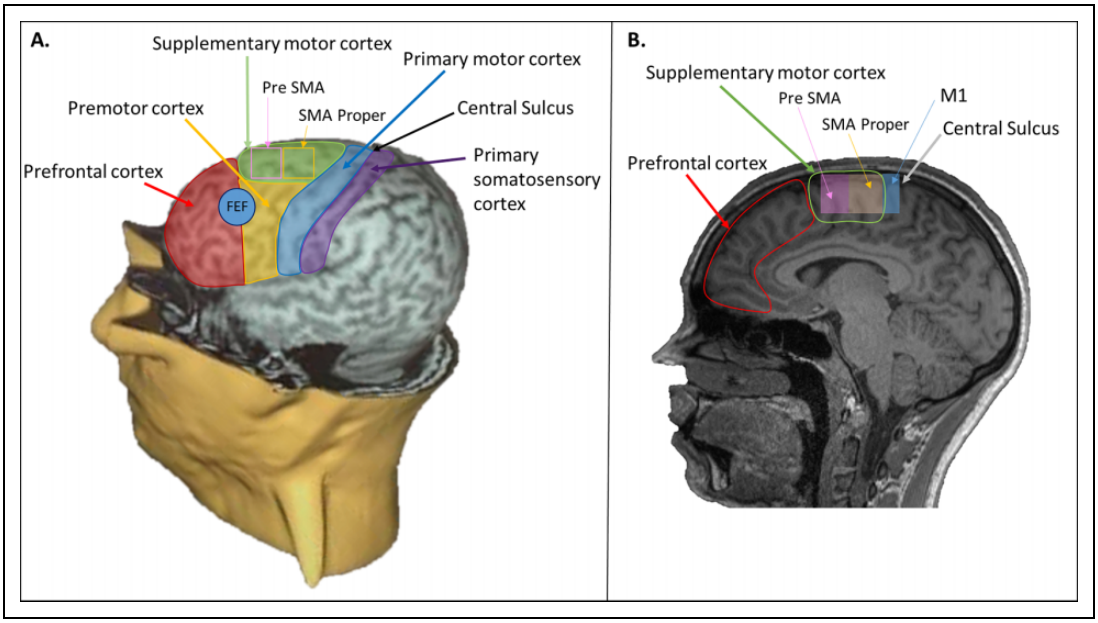

Figure 2. (A) Lateral view of cerebral hemisphere. Image created from an affected subject in the SSADHD Natural History Study. (B) Medial view of cerebral hemisphere showing SMA proper anterior (orange) to the primary motor cortex (M1), and Pre-SMA further anterior (pink). Image from a control subject in the Natural History Study. FEF = Frontal Eye Field. SMA = Supplementary motor area

On the other hand, there is additional evidence for functional connectivity of M1 and the supplementary motor area (SMA) generally. M1 excitability depends on the timing of the SMA proper/M1 stimulation within a temporal domain of 15 milliseconds (ms) with no relationship to pre-SMA stimulation.[12] SMA proper is also directly connected to M1 cortex and the spinal cord,[13] and is thought to function either in parallel with or hierarchically superior to M1. Although motoric speech dysfunction, such as speech dyspraxia, is well reported in SSADH deficiency,[6-9,14] there is no evidence on the functional connectivity of M1, basal ganglia, frontal language areas, pre-SMA, and SMA-proper, which are responsible for speech motor control and auditory perception, in children with SSADH deficiency. Therefore, the hypothesis of connectivity of M1/SMA and SMA dysfunction in SSADH deficiency is based on previous reports of SMA mapping in healthy control volunteers and patients with focal brain lesions.[12,15]

Supplementary Motor Area Dysfunction in SSADH Deficiency

Children with SSADH deficiency likely experience dysfunction in SMA portions reflecting disability in auditory-sensory-motor activities. Nevertheless, functional roles of SMA auditory-sensory-motor functions are parcellated between 2 cytoarchitectonically distinct regions, the SMA proper and more rostral pre-SMA (Figure 2).[16-18] Whereas the SMA proper is comprised of a complete somatotopic representation of body movement, the more anterior pre-SMA has a cognitive or abstract role in the performance of complex tasks, including preparation for movement, new motor skills, and also higher-order aspects of speech.[19] Pre-SMA has been documented as having a main inhibitory role in repetition of speech stimuli (eg, pseudowords or phonemes)[20-22] and in word response selection.[23] As pre-SMA plays a fundamental role in the preparation of speech and initiation of vocalization, this area may be considered as fundamental to initiating the speech process.[20,24,25] It is also involved in finger tapping tasks,[26] memory, decision-making tasks,[27] speech comprehension, and speech intelligibility in specific conditions such as poor signal quality, cognitive load, and time-critical conditions.[28] In contrast, the SMA proper is believed to play a stronger role in motor planning and movement execution.[29] If we consider speech as a fine motor function, the SMA-proper should be responsible for the initiation of planned speech motor codes and the temporal control of motor commands.[30] In general, SMA portions are commonly activated in auditory perceptual and auditory imaginary studies as well. These include imaginary speech, syllables, and words,[31,32] imaginary music,[33] and even uncontrollable perceptions such as auditory verbal hallucinations. However, the role of SMA in auditory function remains relatively unknown, possibly because SMA portions are traditionally conceptualized as being linked to action-related processes, unrelated to audition per se.[34] Considering the critical roles of pre-SMA and SMA-proper in both speech planning, auditory processing, and execution, and their connections with basal ganglia and other cortical areas, we hypothesize that dysfunction of speech motor and auditory processing in SSADH deficiency result at least partially from dysfunction of SMA and pre-SMA cortex.

Connectivity of SMA with Subcortical Areas in SSADH Deficiency

Concerning the connectivity of subcortical areas and SMA, it is mostly cited that the anterior regions of the SMA are strongly connected to the caudate,[35] which is involved in cognitive processes[36,37] and phonological segmentation.[38] In contrast, the posterior regions of SMA are strongly connected to the thalamus and putamen,[17] which are involved in motor processes.[36,39] The SMA proper and pre-SMA receive relatively more basal ganglia input than cerebellar input.[40] Functionally, these signals seem to serve mostly inhibitory mechanisms within the language and speech network. Furthermore, the connectivity of pre-SMA and basal ganglia seems to play an important role for voluntary action control regarding the predicted probability for the need of inhibitory mechanisms.[41,42] For example, connectivity is reported between basal ganglia and cortical regions during the performance of speech tasks, and the subthalamic nucleus (STN) is predominantly linked to regions involved in cognitive linguistic processes (pre-SMA, dorsal anterior insula, and inferior frontal gyrus).[43] Globus pallidus pars interna (GPi) shows stronger connectivity to regions involved in motor control (middle insula, SMA proper, premotor cortex).[43] In the absence of working connected pathways, speech might become dysfluent as observed in SSADH deficiency. Moreover, concerning the cerebellum, it has been shown that pre-SMA and SMA proper are connected to different regions of the dentate nucleus.[44] A study on cerebellar contributions to lexical learning has shown that pre-SMA activity correlates with consolidation of lexical knowledge.[45] Thus, it can be hypothesized that the SMA serves as a coordinator between phonological-phonetic sequencing in dominant language hemisphere and prosodic event timing in the nondominant hemisphere.[40] Although various speech disorders in basal ganglia diseases, such as Huntington disease,[46,47] Parkinson disease,[48,49] and Tourette syndrome,[50,51] may be due to deficient cortical-subcortical loop mechanisms[52] involving SMA and pre-SMA, study of pre-SMA and SMA proper dysfunction in connection with frontal and subcortical areas in children with neurodevelopmental disorders remains challenging.

Connectivity of SMA With Cortical Areas in SSADH Deficiency

In addition to connectivity of SMA with subcortical structures, there is a proposed role of SMA portions with frontal and temporal areas responsible for speech production and auditory perception. Is there a significant relationship between SMA and cortical areas representing some clinical symptoms in SSADH deficiency? Whereas the pre-SMA receives strong input from the prefrontal cortex and projects to the somatotopic representation of upper limb in the SMA proper without direct connection to M1 and the spinal cord,[53] the SMA-proper is highly connected to the premotor and somatosensory cortices and M1.[17] Pre-SMA is also linked to regions in prefrontal cortex, inferior frontal gyrus (IFG), angular gyrus, and anterior cingulate cortex whereas the cluster of the SMA proper comprises connections to premotor, primary motor, somatosensory, and the middle cingulate cortex.[54] There is evidence for a neural pathway connecting pre-SMA and SMA proper with the Broca area, especially the more posterior pars opercularis.[55-57] Increased resting state connectivity between the SMA and the Broca area was observed in auditory verbal hallucinations.[58] Perhaps auditory verbal hallucinations and speech production dysfunctions are related to disrupted connectivity between SMA portions and Broca area.

Objective-Diagnostic Measures of Auditory-Motor Functions in SSADH deficiency

We identified 1 electrophysiologic survey focusing on delayed latencies of visual evoked related potentials (P100) in 2 children with SSADH deficiency.[59] Other electrophysiologic studies focused on absence and vibrissal seizures in mutant mice with SSADH deficiency,[60] epilepsy,[61] and sleep disorders along with polysomnographic abnormalities in patients with SSADH deficiency.[62,63] Positron emission tomography (PET) is mostly used clinically in children to assess for local interictal changes in glucose metabolism, for example, during evaluations for a potential epilepsy focus for surgical therapy.[64] Fluorodeoxyglucose PET (^{18}FDG-PET) has revealed hypometabolism of the cerebellum in patients with SSADH deficiency.[65] Additionally, there was reduced activity in amygdala, hippocampus, cerebellar vermis, frontal, parietal, and occipital cortex in patients with SSADH deficiency using the ligand flumazenil (FMZ), which binds to the benzodiazepine-binding site of the neuronal GABA(A) receptor.[65] Single-photon emission computed tomography (SPECT) is usually utilized to assess the perfusion of epileptogenic foci,[66] but uses radioactivity and does not provide dynamic signal changes. Transcranial magnetic stimulation (TMS), discussed previously, is a safe and tolerated technique in children with developmental delay or epilepsy.[67] Transcranial magnetic stimulation of the motor cortex coupled with electromyography (EMG) enables biomarkers that provide measures of cortical excitation and inhibition that are particularly relevant to epilepsy and related disorders, and for that reason is applicable in SSADH deficiency.[11,68] Although motor thresholds and intracortical inhibition using paired-pulse stimulation have been reported to show altered GABAergic neurotransmission in SSADH deficiency, and furthermore serve as a biomarker for clinical trials,[11] their link to pre-SMA and SMA-proper remain future areas of research.

Functional MRI, Resting-State and Task-Based, for SSADH Deficiency

Resting-state functional MRI has been widely used in clinical studies including epilepsy, depression, Alzheimer disease, and ADHD.[69-72] It investigates synchronous brain activity in a variety of functional systems, such as the visual,[73] auditory,[74] emotional,[73] attentional,[75] language,[51] reading,[76] and memory systems.[77] Resting-state functional MRI is dramatically increasing our understanding of neural development, including the

sequence of development and the extent of neural system connectivity in normally and abnormally developing infants, children, and adolescents.[78,79] Thus, due to a lack of requirement for a child to demonstrate a task-specific response, resting-state functional MRI is suitable for assessing lingual and cognitive characteristics of children with neurodevelopmental disorders such as SSADH deficiency. While task-based functional MRI may have a relatively high demand for children to comply, it is able to evaluate pre-SMA and SMA-proper functions using pseudo-word repetition tasks, rhythmic finger tapping tasks, action observations, and rhythm perception tasks in speech (rhythmic pseudo-words) and music (beat perception) in children and adults with SSADH deficiency compared with typically developing children.

Overall, applying neurophysiological or neuroimaging techniques for early diagnosis of lingual and cognitive disabilities could potentially contribute to prediction of later treatment outcomes. For assessment of pre-SMA and SMA-proper functions, simple perceptional tasks would be employed for young children with SSADH deficiency, such as auditory and automatic detection tasks and passive music listening followed by more complex inhibitory tasks such as GO/NO-GO tasks or rhythmic finger tapping for older patients. With the convergence of aforementioned evidence from multiple imaging modalities suggesting auditory, motor, and lingual roles for the pre-SMA and SMA proper, one may consider that the SMA portions may have significant resting state or task-based altered connectivity to primary and secondary brain speech and language regions and subcortical structures, especially basal ganglia, in SSADH deficiency.

Discussion

Studies to date demonstrate altered GABAergic functioning, with reduced GABA(A) receptor binding on flumazenil-PET, and reduced cortical silent period and long interval intracortical inhibition using paired-pulse transcranial magnetic stimulation implying reduced GABA(B) receptor activity, in SSADH deficiency. These reductions are hypothesized as related to use-dependent downregulation of GABA receptors in this disorder of GABA catabolism. Given the prominence of dysfunction in expressive language, this study reviewed the potential for altered connectivity in pathways implied in speech production and subcortical anatomic abnormalities. Although there are limited data available, studies are in progress in these areas, including transcranial magnetic stimulation, high-density EEG, magnetoencephalography, and MRI/MR spectroscopy. Our focus is on hypothesis generation involving speech-related cortical areas, connectivity studies, and potential for guidance of rehabilitation strategies in SSADH deficiency.

The pre-SMA and SMA-proper play a major role in speech motor control, speech production, and auditory perception. Although SMA portions are mostly responsible for motor functions, future studies can hypothetically provide evidence concerning the engagement of SMA cortex in auditory responsiveness as well. Further, it is proposed that there is a functional connectivity between pre-SMA and SMA-proper with Broca area and the basal ganglia. It is suspected that the functional connectivity of SMA portions is increased in frontal and basal ganglia areas compared to temporal areas, for example, the Wernicke area. Children with SSADH deficiency likely experience dysfunction in connectivity between SMA portions with cortical and subcortical areas, and auditory-speech-motor dysfunction and impaired sensory integration likely ensue. Thus, comparing SMA resting state and task-based networks in SSADH deficiency patients to age-matched controls may provide insight into differences in functional brain activities in speech motor control and auditory processing.

Motor speech difficulties are common in SSADH deficiency, with multiple lines of research indicating excitatory/inhibitory imbalance in M1. We suggest that this may be related to abnormal functional connectivity between M1 and SMA. Given the high penetrance of this phenotype, future studies directly accessing connectivity between these 2 regions, as well as from these regions to the basal ganglia and cerebellum, may identify biomarkers that could be useful for early detection and/or treatment monitoring.

Finally, extension of this work leads to consideration of potential rehabilitation strategies. For instance, there is a hypothesis about the response of SMA during musical perception and music production.[80] Rhythmic stimuli, for example, activate responses of the SMA and basal ganglia.[81] Musical speech training with auditory rhythmic cueing, for example, pseudo-word musical repetitions with finger tapping, may improve auditory-motor integration. This strategy may have advantages compared with other techniques that depend on semantic understanding.[82-85] Studies have further shown differing roles for the SMA regions, that is, imitative role of SMA proper and evaluative role of pre-SMA in active observation.[86] Taken together, these findings highlight potential for action observation and music and speech training based on an integrative strategy (auditory-sensory-motor) for patients with SSADH deficiency.

Conclusions

Supplementary motor area and associated cortices, especially pre-SMA region, may have a fundamental role in cognitive problems observed in SSADH deficiency. There is a high probability of abnormal connectivity between SMA and M1. Multimodal tasks evaluating the connectivity and functionality of these areas, linked with related cortical and subcortical areas, using motor, speech, and auditory functions may lead to novel sensory-integrative interventional approaches for this clinical group. Future directions would focus on using objective diagnostic measurements and rehabilitative and interventional strategies to target clinical symptoms in SSADH deficiency.

Author Contributions

ZZA drafted the manuscript. MLD and PLP revised the manuscript for content, including scientific writing.

Declaration of Conflicting Interests

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