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Treating autism by targeting the temporal lobes

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ABSTRACT

Compelling new findings suggest that an early core signature of autism is a deficient left anterior temporal lobe response to language and an atypical over-activation of the right anterior temporal lobe. Intriguingly, our recent results from an entirely different line of reasoning and experiments also show that applying cathodal stimulation (suppressing) at the left anterior temporal lobe together with anodal stimulation (facilitating) at the right anterior temporal lobe, by transcranial direct current stimulation (tDCS), can induce some autistic-like cognitive abilities in otherwise normal adults. If we could briefly induce autistic like cognitive abilities in healthy individuals, it follows that we might be able to mitigate some autistic traits by reversing the above stimulation protocol, in an attempt to restore the typical dominance of the left anterior temporal lobe. Accordingly, we hypothesize that at least some autistic traits can be mitigated, by applying anodal stimulation (facilitating) at the left anterior temporal lobe together with cathodal stimulation (suppressing) at the right anterior temporal lobe. Our hypothesis is supported by strong convergent evidence that autistic symptoms can emerge and later reverse due to the onset and subsequent recovery of various temporal lobe (predominantly the left) pathologies. It is also consistent with evidence that the temporal lobes (especially the left) are a conceptual hub, critical for extracting meaning from lower level sensory information to form a coherent representation, and that a deficit in the temporal lobes underlies autistic traits.

Introduction

Autism spectrum disorder is a complex neurodevelopmental condition that is estimated to affect 1 in 68 children in the United States [1]. It is theorized to have multiple etiologies, "an emergent property of developmental interactions between many brain regions and functions" [2]. However, based on convergent evidence that autistic symptoms can emerge and later reverse due to changes in temporal lobe physiology (e.g. caused by pathologies [3–10] or temporarily induced by brain stimulation [11]), here we hypothesize a possibility for an early intervention.

Compelling new findings in infants show that a core signature of autism is a deficient left anterior temporal cortex response to language and "a reversed or absent laterality patterns" [12]. This signature grows more pronounced with age in toddlers at risk for autism, whereas typically developing children show opposite developmental trajectories [12,13]. Indeed, there has been extensive evidence implicating the temporal lobes with autism. For example, in young children, autistic traits have been associated with deficit in the left temporal lobe [3,4,6,14–18], enlargement of the right temporal lobe [19,20] and atypical hemispheric lateralization [21,22], especially for language related areas in the temporal lobes [13,23–27].

Intriguingly, such evidence fits nicely with results from an entirely different line of reasoning and associated experiments. We have observed that some autistic-like cognitive abilities can be induced to a degree in otherwise healthy adults by suppressing the left anterior temporal lobe while simultaneously facilitating the contralateral right anterior temporal lobe [11] using transcranial direct current stimulation (tDCS). Specifically, Chi and colleagues [11] showed that applying cathodal stimulation (decreasing excitability) at the left anterior temporal lobe together with anodal stimulation (increasing excitability) at the right anterior temporal lobe enabled a superior visual memory, an advantage similar to those with high functioning autism on an identical memory task [28].

If autistic traits in children are associated with a deficit in the left temporal lobe as discussed above, and if we could temporarily induce autistic like cognitive abilities in healthy people by suppressing left temporal lobe dominance with tDCS [11], then it follows that there is a possibility we could mitigate autistic traits by using a reverse stimulation procedure, in an attempt to restore normal functioning and lateralization of the left temporal lobe.

This possibility is consistent with intriguing cases where autistic traits can emerge in previous healthy people as a result

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of temporal lobe pathologies (predominantly the left temporal lobe) [3–8] and spontaneously disappear upon temporal lobes recovery [5,6,9,10]. For example, DeLong and colleagues observed a 14 year old girl where autistic traits, emerged due to predominantly left temporal lobe pathology caused by acute encephalitis, later spontaneously reversed following temporal lobe recovery [5]. Similarly, Hoon and Reiss observed that a constellation of autistic features emerged in a 2 year old boy as a result of a left medial temporal lobe tumour, including the amygdala [6]. But after the tumour was removed, much of the autistic symptoms spontaneously disappeared. More directly, Deonna and colleagues found that anti-epileptic medication, carbamazepine, resulted in a complete reversal of autistic symptoms in a 2 year old child with predominantly left frontotemporal lobe pathology and epileptiform discharges [9]. While pathologies in such cases are not exclusively confined to the left anterior temporal lobe, they raise the possibility that there is a direct intervention targeting the temporal cortex that can reverse some autistic traits early in their developmental trajectories.

Importantly, while the majority of studies implicate the bilateral temporal lobe abnormalities with the emergence and manifestation of autistic traits [29–35], evidence suggests that, in children, autism is especially associated with deficit in the left temporal lobe [7,8,12–14,16–18,36–38], the hemisphere that is typically dominant for language. For example, Hauser and colleagues observed that 15 out of 18 autistic children in their study showed abnormality at the left temporal lobe and argued that temporal lobe dysfunction "may be a major factor in the pathogenesis of the syndrome of infantile autism" [14]. Similarly, White and Rosenbloom reported a case of a 2-year-old autistic boy who had a partial absence of the left temporal lobe. They suggested that "malfunction or malformation of temporal-lobe structures, especially when they occur in early development and in the dominant hemisphere, may be correlated with the development of autistic behaviours" [18]. From the above, there is extensive evidence that the emergence and manifestation of autistic traits are associated with atypical functioning and lateralization of the left temporal lobe, whether due to suppression of the left temporal lobe or due to bilateral temporal lobe pathologies. Our stimulation protocol aims to mitigate autistic traits by correcting such temporal lobe abnormalities.

Hypothesis

Accordingly, we hypothesize that at least some autistic traits can be mitigated by restoring normal functioning and lateralization of the left temporal lobe. Specifically, we propose to do this with transcranial direct current stimulation (tDCS) by applying anodal stimulation (facilitating) at the left anterior temporal lobe and cathodal stimulation (suppressing) at the right anterior temporal lobe.

Importantly and contrary to extensive evidence noted above that implicates different areas of the temporal lobes, our stimulation protocol specifically targets the anterior region of the temporal lobes. This is because we have had success in modulating autistic like cognitive ability in healthy people with tDCS by placing the electrodes (5 cm × 7 cm) at the anterior temporal lobes [11]. One reason [39] that the anterior temporal lobes are not more often implicated for autism is that, until 2011, functional magnetic resonance imaging (fMRI) was known to produce distortion and signal drop out at this area [40,41]. However a definitive recent study by Eyler and colleagues shows that deficit and atypical lateralization of the left anterior temporal lobe is a core early signature of autism, before such deficit disrupts developmental trajectories downstream [12]. This view is consistent with evidence that the anterior temporal lobes (especially the left), in particular, are theorized to be the conceptual hub. This region is critical for extracting meaning from lower level sensory information to form a coherent representation [42–44], a process that is impaired in those with autism [37,45] (see the Discussion).

Non-invasive stimulation technique

Transcranial direct current stimulation (tDCS) consists of applying weak electrical constant currents to the scalp, via two saline-soaked sponge electrodes, thereby polarizing the underlying brain tissue with electrical fields [46]. Physiologically, anodal tDCS is theorized to induce membrane depolarization (increasing excitability) whereas cathodal stimulation is thought to cause hyper-polarization (decreasing excitability) [47]. Our stimulation protocol is predicated upon evidence that tDCS can suppress or facilitate a brain region and modulate hemispheric rivalry (e.g. increasing a left hemisphere bias) to enable a beneficial cognitive [11,48–50] or clinical outcome [51–54].

Testing the hypothesis

A starting point in testing our hypothesis would be to employ the same tDCS setup as used in the study by Chi and colleagues. Specifically, the anodal sponge electrode (5 cm × 7 cm) should be placed approximately half way between T7 and FT7 on the International 10–20 System (the left anterior temporal area) and the cathodal sponge electrode (5 cm × 7 cm) approximately half way between T8 and FT8 on the same 10–20 System (the right anterior temporal area). Nevertheless, given that the electrodes we used are 5 cm × 7 cm, it is possible that the entire temporal lobes could be affected by our stimulation protocol.

Importantly, while our proposed stimulation could well be most effective for arresting autistic traits early in their development (e.g. in toddlers), there should be caution and qualified supervision in any attempt to apply brain stimulation on children. Because there are only very few studies that have applied brain stimulation on underage subjects to date, it is uncertain what effects tDCS have on the developing mind of children, who have smaller skulls (and thus different distribution of current density) and higher plasticity [55,56].

Accordingly, in testing our hypothesis, the first experiment might involve applying tDCS on young autistic adults (who are otherwise healthy) rather than in toddlers. For additional margin of safety, it would be sensible to increase the stimulation intensity and dosage progressively; beginning with low intensity (1 mA) for 10 min a session and increase, gradually, to up to 2 mA for 30 min.

Furthermore, we do not suggest that our proposed stimulation method is the optimal protocol for treating autism. While there is evidence that tDCS can modulate neuronal excitability and cerebral blood flow at the region under the electrodes [57,58], we cannot exclude the possibility that areas adjacent to the electrodes (5 cm × 7 cm) such as the inferior frontal gyri would be affected by our stimulation protocol. Moreover, bearing in mind that the effects of tDCS are known to be mental state dependent [59] and variable across individuals [60], future studies should explore the use of other neuromodulation methods to restore abnormal functioning and lateralization of the left temporal lobe.

Discussion

How does a left anterior temporal lobe deficit contribute to autistic traits?

Because autism is a highly complex developmental disorder, it is difficult to have a definitive explanation for how autistic traits can emerge as a result of abnormal physiology in the temporal

lobes. However, one possible mechanism is that the temporal lobes (especially the left) are critical for extracting meaning from lower level sensory information [37,45,61–63]. In particular, the anterior temporal lobes have been theorized to be a conceptual hub [42,63,64], a convergence zone where information is rapidly processed and integrated into a coherent representation [42,65], whether the information is auditory language related stimuli or visual socially related facial expressions [66,67]. For example, evidence demonstrates that the superior temporal sulcus shows a hierarchy of activation, with the greatest response to meaningful information of communicative significance and the lowest response to meaningless, non-socially relevant stimuli [37].

More specifically, the left anterior temporal lobe is especially implicated for conceptual combination with the role of binding an ensemble of meaningful features into one coherent representation [43,44,68]. Consistent with this view, this area shows a greater response to meaningful speech (sentences) than unintelligible speech (e.g. reversed sentences) [68,69] and a greater response to familiar than novel faces [70].

Accordingly, in this oversimplified model, the core symptoms of autism arise from a deficit of the temporal lobes (especially the left anterior temporal area) to extract meaning from lower level information to form a coherent representation [12,37,45]. This view is consistent with Snyder's characterization that infantile autism is a failure in the process of concept formation, with a privileged access to lower level raw sensory information before it is packaged into a meaningful whole [45,71,72].

We believe that a deficit in sensory processing, especially when occurring during the critical period [73], would have cascading effects on the development and the appropriate execution of higher cognitive processes [2]. For instance, Eyler and colleagues argues that in infants, deficit in the left anterior temporal lobe response to speech, not only could delay normal language development, but may also 'crowd out' the development of social perception mediated in the right temporal lobe, as the right temporal lobe compensate for ineffectual processing of language in the left temporal lobe [12]. That is, a deficit in sensory processing can result in a spectrum of secondary dysfunctions such as language, social abnormalities seen in autism, depending on genetic predispositions and developmental interaction with the environment [2,37,73–75]. More concretely, without the ability to extract meaning from sensory information to form a coherent concept, it would be difficult to develop language and analyze social cues. This view might also explain why autistic individuals often rely on routines, perhaps as a compensatory mechanism for navigating the world [72]. Consistent with this view, there is evidence that anterior temporal lobe atrophy can increase reliance on superficial similarities (e.g. repetitive behaviour [76], a core symptom of autism) rather than conceptual similarities [64].

Finally, the perspective that failure of the temporal lobes (especially the left) to extract meaning from sensory information is a cause of autistic traits is consistent with evidence that atypical sensory-based behaviors are ubiquitous in autism [2,37,45,74,77–79]. For example, there is a highly significant positive correlation (0.775, $P < 0.01$) between the number of autistic traits and the frequency of sensory processing problems [79]. In fact, "more than 96% of children with ASD report hyper- and hyposensitivities in multiple domains", suggesting that abnormal sensory processing is a unifying phenotype of autism [74].

Earlier ideas for treating autism by non-invasive brain stimulation

The possibility of using brain stimulation to treat autism was foreshadowed earlier by Snyder, in an address to the Nancy Lurie Marks Autism foundation, 'A Possible Push Pull Transcranial Magnetic Stimulation Therapy for Autism' [80]. Specifically, Snyder conjectured, "if we can artificially induce certain core features of autism in perfectly normal people, then we might gain insight into how to reverse the procedure and possibly treat autism itself". More concretely, Snyder suggested the use of brain stimulation to "reinforce concept formation" in those with autism, by stimulating the left anterior temporal lobe while simultaneously depressing the right anterior temporal lobe.

Subsequently, various alternative paradigms that use brain stimulation to treat autism have been suggested [81–87]. In particular, Fecteau and colleagues applied low frequency inhibitory transcranial magnetic stimulation to Broca's area and found that all 10 individuals with ASD showed a reduced latency in a naming task [86]. In addition, Schneider and Hopp applied anodal tDCS at the left dorsal lateral prefrontal cortex to 10 children with autism, and found a modest facilitation in syntactic acquisition [87]. Nevertheless, to date, there has yet to be strong experimental results demonstrating that brain stimulation can treat, diagnose or prevent autism [85].

Caveats of our simplified model of autism

We recognize that autism is a heterogeneous, highly complex neurodevelopmental disorder with no definitive explanation for its etiologies [88]. Furthermore, as Belmonte et al. noted, "primary dysfunctions can be masked by the evolution of compensatory processing strategies which normalize behaviour, and also by the induction of activity-dependent secondary dysfunctions that disrupt behaviour in new ways" [2].

Therefore, we emphasize that our model of autism is oversimplified, in an attempt to connect the dots based on our preconceptions. Accordingly, we have ignored much of the evidence drawn from autistic adults. For example, evidence by Harris and colleagues and Just and colleagues who reported that autistic adults show a reduced activation in Broca's area with corresponding increased activation in Wernicke's area (left posterior temporal area) [89,90]. Instead, we have focused on evidence that is at the onset of autism, most closely identified with Kanner's infantile autism – a preconceptual mind that lacks the ability to make sense of the world [91].

Our hypothesized intervention presupposes that autism is manifested by an early deficit of the left anterior temporal lobe resulting an atypical lateralization [12]. However, there may be additional manifestations of autism, as several papers implicated the medial temporal lobes with autism [6,14,92]. This is not necessarily inconsistent with our hypothesis because it is likely that physiological changes in the medial temporal lobe have ramifications with the functioning of the anterior temporal lobes or even the entire temporal cortex.

Furthermore, because autism is a complex developmental syndrome, it is inherently difficult to determine what our intervention will do to its developmental trajectories. There may well be various genetic factors and environmental influences that play an even greater role on the development of autistic traits. That is, a deficit in the temporal lobes may only be one of the multiple predisposing factors for the emergence of autistic traits. For example, abnormalities in the frontal lobes such as early brain overgrowth [93].

In addition, because autism is multifaceted with diagnostic criteria that go through ongoing change, it would be naive to assume that one method can treat all facets of autism [94]. It is possible that our suggested protocol is only effective for some particular autistic symptoms. It is also possible that our proposed treatment for autism is only effective for a subset of autistic individuals, perhaps those more closely identified with Kanner's criteria for infantile autism [91]. This, in part, could be due to the fact that the diagnostic criteria for autism have been greatly relaxed over the last 30 years [94]. It would be worthwhile to investigate whether

age, gender, handedness, and severity of autistic symptoms play a role on the effectiveness of our proposed intervention.

Conclusion

Recent findings demonstrate that an early emerging signature of autism is a deficit and atypical lateralization of the left anterior temporal lobe, an area critical for extracting meaning from sensory information. Accordingly, we hypothesize that at least some autistic traits can be mitigated, if not arrested early in their development, by restoring normal functioning and lateralization of the left temporal lobe (especially the anterior region). Specifically, we hypothesize that autism can be treated with tDCS, by applying anodal stimulation (facilitating) of the left anterior temporal lobe together with cathodal stimulation (suppressing) of the right anterior temporal lobe. This possibility is consistent with evidence that autistic traits can emerge and spontaneously reverse due to changes in temporal lobe physiology in general. Given how debilitating, costly and prevalent autism is, it is prudent to investigate whether our intervention could provide clinical benefits.

Conflict of interest

The authors declare no conflict of interest.

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