Joint Interventions in Autism Spectrum Disorder: Relating Oscillopathies and Syntactic Deficits*

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Abstract

We put forward a dual clinical intervention strategy for people exhibiting language deficits in autism. This combines an emerging understanding of the ‘oscillopathic’ brain – how an abnormal profile of neural oscillations can give rise to syntactic and semantic deficits – with a more traditional approach centred on a course of speech therapy targeting specific linguistic deficits. It is our intention that a joint intervention focusing on abnormal oscillations alongside deficient language comprehension will also serve to re-align the general focus of inquiry away from cartographic neuroimaging issues and towards dynamic, oscillation-based analyses.

Keywords: Autism spectrum disorder, TMS/tDCS, SLT, neural oscillations, syntax, semantics

1 Introduction

Autism spectrum disorders (ASD) are typically defined as neurodevelopmental disorders involving a number of cognitive, social and communicative deficits. People with ASD exhibit repetitive behaviour alongside communicative problems such as a lack of eye contact and an inability to read paralinguistic cues (Bailey, Phillips, & Rutter, 1996). Systematic causal connections have been drawn between ASD and particular linguistic deficits (Crespi & Badcock, 2008), developments which we would here like to relate in an explicitly programmatic fashion to recent work suggesting that such deficits arise from an abnormally synchronised brain (Benítez-Burraco & Murphy, 2016; Murphy & Benítez-Buraco, 2016a).

We believe that our developing understanding of syntactic and semantic deficits in ASD can complement these investigations into the neural oscillations putatively responsible for them. We will propose a joint intervention strategy through which a therapeutic course targeting syntactic deficits in ASD will be delivered alongside a series of repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) interventions used to modulate the oscillations responsible for the abnormal linguistic ASD profile. Similar approaches have already been taken to improve performance on visual tasks in patients with schizophrenia (Farzan, Barr, Sun, Fitzgerald, & Daskalakis, 2012; Barr, Farzan, Rajji, Voineskos, Blumberger, & Arenovich, 2013), and we hope that the evidence presented here will convince researchers and therapists to consider the viability of a dual syntactic-oscillatory intervention in the ASD population.

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2 Language Deficits in ASD

Emerging research indicates that at the neurological level ASD is primarily characterised by asynchronous neural oscillations (Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). Because children can progress from one disorder sub-type to another during development, we believe that a longitudinal approach to research regarding children with ASD involving perennial ‘oscillopathic’ monitoring and manipulation/stimulation could generate a more robust diagnosis and prognosis. But in order to decide which brain regions and rhythms should be targeted, an understanding of what the precise language-related deficits in ASD are is needed.

Language deficits in ASD are no longer seen as being confined to pragmatic or world knowledge impairments, which are also widely compromised amongst other cognitively impaired children (Abbeduto & Hesketh, 1997). Indeed, ASD is often comorbid with language disorders such as Specific Language Impairment (Tager-Flusberg, 2006). While a core language deficit may exist in ASD, this is hard to pinpoint empirically due to variability in the ASD linguistic phenotype and concomitant linguistic profiles. Nevertheless, it is by now clear that certain linguistic constructions are generally difficult for ASD individuals to interpret.

It has been shown, for instance, that individuals with ASD integrate semantic information differently when interpreting phrases (Eigsti, Bennetto, & Dadlani, 2007) and that semantic knowledge is consolidated differently, being less primed by semantically-related words. Language delay also occurs with syntactic knowledge (Geurts & Embrechts, 2008; Philofsky & Fidler, 2007; Saldaña & Frith, 2007). Relatedly, problems with syntax suggest an impairment of procedural memory.

Language impairments in ASD involve difficulties with comprehending relative clauses, *wh*-questions, raising and passives (Perovic & Janke, 2013; Perovic, Modyanova, & Wexler, 2007; Wada, 2015). Children with autism also exhibit markedly degraded performance when interpreting reflexive pronouns (Fortunato-Tavares, Andrade, Befi-Lopes, Limongi, Fernandes, & Schwartz, 2015; Perovic, Modyanova, & Wexler, 2013). When presented with a battery of dative expressions exhibiting either syntactic alternations or restrictions (either in syntactic constructions or in marked semantic differences) and asked to identify the indirect object of the verb, children with autism performed worse than typically developing controls when the dative could syntactically alternate compared to when it was restricted (Stockbridge, Happé, & White, 2014). Children with autism consequently exhibit severe limitations in their ability to interpret alternating syntactic constructions, and we would like to suggest that this lack of flexibility may emerge from restrictions in oscillatory interactions. Since syntactic capacities directly impact cognition (albeit in ways which are still under debate) the neural basis of these linguistic deficits may shed some light on the biological basis of ASD more broadly.

3 Oscillopathies in ASD

Many of the nerve tracks and regions which differ in the ASD brain from neurotypical individuals are also implicated in language comprehension (Benítez-Burraco & Murphy, 2016), but the idiosyncratic nature of these regional differences (as documented in Hahamy, Behrmann, & Malach (2015)) leads us to suggest that neural oscillations provide a more robust scale of neurolinguistic analysis – in particular given that oscillations are increasingly being shown to be responsible for a number of higher cognitive capacities. For instance, brain dynamics can provide plausible candidates for linguistic computation. Following the model outlined in Murphy (2015, 2016), we will assume that set-formation (the taking of two objects,
X and Y, and forming the set \([X, Y]\)) is implemented via inhibition ‘shielding’ the embedding of a series of cross-cortical \(\gamma\) rhythms within parahippocampal \(\theta\), and that maintaining these sets in memory (creating linguistic phrases) requires the slowing down of certain \(\gamma\) clusters to \(\beta\). The \(\beta\) band has independently been shown to be implicated in maintaining mentally constructed objects in memory (Engel & Fries, 2010). Finally, we will assume that agreement relations are implemented via cross-cortical evoked \(\gamma\), with this rhythm being involved in attention and perceptual ‘feature binding’ (Sohal, Zhang, Yizhar, & Deisseroth, 2009).

With this background, we can turn to the oscillopathic ASD brain and use it as a way to approach possible electromagnetic remedial interventions. Early models of the neurobiological foundations of ASD placed much emphasis on anatomical abnormalities, in particular the volume of certain regions like the amygdala and cerebellum (Amaral, Schumann, & Nordahl, 2008). However, the varying neuropathology of the condition points to more global systematic differences (Murphy & Benítez-Burraco, 2016a).

While studies of the linguistic ASD ‘oscillome’ (neural oscillations ascribed particular computational properties) remain in their infancy, we believe enough has been learned to be able to construct a model of intervention targets. Kikuchi, Shitamichi, Yoshimura, Ueno, Hiraishi, Hiroswa, Munesue, Nakatani, Tsubokawa, Haruta et al. (2013) and Rojas, Maharajh, Teale, and Rogers (2008) reported significantly increased \(\gamma\) power for ASD individuals, with Kikuchi et al. finding in addition reduced cross-cortical \(\alpha\) and \(\beta\). Even slight modulations in the phase of these slower rhythms could lead to the inability of external memory and interpretive systems to ‘read off’ the content of the feature-sets constructed by the above process of cross-cortical \(\gamma\) nesting within \(\theta\). Indeed, we believe that the notion of weak central coherence used by Happé and Frith (2006) to account for language deficits in autism (a reduced ability to distil generalizable information from diverse input) is a direct consequence of disturbed lower-level oscillatory coherence; see, for instance, the communication-through-coherence hypothesis in Fries (2005, 2015) which claims that oscillatory synchronisation modulates the efficacy of anatomical connections.

Inhibiting \(\gamma\)-oscillating regions and stimulating sub-cortical structures oscillating at the slower \(\theta\)–\(\beta\) ranges during these and similar semantic memory tasks would likely prove conducive to increased syntactic and semantic competence. Bangel, Batty, Ye, Meaux, Taylor, and Doesburg (2014) found reduced \(\beta\) during a number estimation task in ASD, and broader disruptions in rhythmic coordination have been frequently documented (Benítez-Burraco and Murphy, 2016). The ASD brain also appears to involve reduced \(\theta\) during tasks necessitating inter-regional synchronisation (Doesburg, Vidal, & Taylor, 2013). If parahippocampal \(\theta\) is a major site of such inter-regional synchronisation (as argued by Fernández-Ruiz and Oliva (2016)) with respect to varying representational properties of language (i.e. semantic, phonological and syntactic representations), then this finding would contribute to an explanation for why people with ASD often have difficulties with this cross-modular feature of language.

Unusually long-lasting prefrontal and central \(\gamma\) has also been documented in ASD individuals during the interpretation of semantic incongruity (Braeutigam, Swithenby, & Bailey, 2008), possibly indicating the recruitment of a general search mechanism (fast \(\gamma\)) to replace the normal rhythmic processes (slow \(\gamma\)) responsible for retrieving and comparing semantic representations. This speaks to the legitimacy of an rTMS or tDCS intervention, as do the findings that picture-naming tasks result in reduced \(\gamma\) and \(\beta\) in the left inferior frontal gyrus in ASD participants (Buard, Rogers, Hepbum, Kronberg, & Rojas, 2013). In addition, abnormal \(\gamma\) oscillations may play a role in the pathogenesis of the inability to properly interpret reflexive pronouns, discussed above. Jochaut, Lehongre, Saitovitch, Devauchelle, Olasagasti, Chabane, Zilbovicius, and Giraud (2015) also found altered oscillatory connectivity between auditory and language cortices in ASD subjects, but the precise phasal properties of this
oscillopathy – and how these properties could relate to and inform an oscillopathic model of language deficits in autism – remains an open topic.

Finally, in a recent MEG study of ASD subjects, Ghuman, van den Honert, Huppert, Wallace, and Martin (2016) found local hypersynchrony in lateral occipitotemporal θ, and long-range hyposynchrony in the α band that was most severe in circuits implicated in social processing. This α hyposynchrony correlated with social symptom severity, and we can infer from this that linguistic competence would also likely be impaired due to the strong relation between these two faculties. These findings point us in a very clear direction for targeted interventions.

4 Therapeutic Interventions in ASD

Focusing rTMS/tDCS interventions on the oscillations responsible for syntactic deficits in ASD brings with it much promise, with TMS recently being used to relieve ASD symptoms such as irritability and repetitive behaviours while enhancing hand-eye coordination, information processing and social skills (Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Oberman, Enticott, Casanova, Rotenberg, Pascual-Leone, & McCracken, 2016; Casanova, Hensley, Sokhadze, El-Baz, Wang, Li, & Sears, 2014). Moreover, Oberman et al. (2016, p. 184) claim that rTMS ‘may represent a novel treatment strategy for reducing some of the core and associated ASD symptoms’. This suggests that rTMS interventions targeting the presently discussed regions would likely contribute to the improvement of linguistic processing.

ASD is a spectral disorder, and so an individual’s linguistic abilities are naturally idiosyncratic. The specific type of speech and language therapy (SLT) intervention, to be delivered alongside any rTMS/tDCS interventions, which would be most efficacious consequently depends upon particular deficits and the targets set by the patient and their SLT practitioner after initial evaluation. As noted above, there is an emerging consensus regarding the syntactic and semantic deficits exhibited by individuals with autism (e.g. difficulties with reflexive pronouns, wh-questions and certain dative expressions). Crucially, Perovic et al. (2013) present reasons to believe that such deficits arise directly from grammatical competence, and are not the consequence of pragmatic deficiencies. Our present joint intervention proposal is thereby granted a strong degree of alignment between phenotypic syntactic deficits and the oscillatory abnormalities claimed here to be responsible for them. As a result, we are confident that any rTMS/tDCS intervention will produce the desired remedial outcomes and will not simply increase performance on ancillary, language-external processes which happen to be tied, on way or another, to the core linguistic deficits.

Typically, SLT targets communication, social interaction and life skills (Bartlett, Gharani, Millonig, & Brzustowicz, 2005; for a systematic overview see Goldstein (2002)). Any intervention would be dependent on the individual consistently demonstrating competent verbal communication; severely delayed speech onset and/or mutism has long been observed in ASD (Kanner, 1943; Lovaas, 1977). For younger patients, SLT approaches similar to the Early Start Denver Model (Dawson, Rogers, Munson, Smith, Winter, Greenson, Donaldson, & Varley, 2010) or pre-school Autism Communication Therapy (Green, Green, Charman, McConachie, Aldred, Slonims, Howlin, Couteur, Leadbitter, Hudry, Byford et al., 2010) would be appropriate, and it would be essential for practitioners to find novel ways of integrating the training of syntactic competence with more traditional developmental pragmatic approaches which involve naturalistic interactions and collaborative work. Most of the therapeutic interventions developed in recent years have focused specifically on pragmatic impairments, and we leave it to future work to develop robust interventions for syntactic and semantic deficits.
Some developmental concerns naturally arise at this point. As Goswami (2016) points out, the oscillatory profile responsible for language comprehension appears to go through a number of stages throughout childhood and into young adulthood, and so a more careful and considered analysis of the oscillatory basis of language deficits in children and young adults with autism would be needed before a joint intervention of the kind proposed here can reasonably be expected to yield remedial outcomes.

Independently, both rTMS/tDCS and SLT interventions have provided positive results for individuals with ASD, and we believe that a combination of these techniques will result in boosted outcomes, with long-lasting effects. Since the noted linguistic deficits in ASD all require the recruitment of procedural and semantic memory resources, we believe that rTMS/tDCS stimulation/inhibition (depending on the oscillopathy) of the presently documented rhythmic sources will lead to a significant improvement in the language capacities of individuals with ASD. Recently, Iaccarino, Singer, Martorell, Rudenko, Gao, Gillingham, Mathys, Seo, Kritskiy, Abdurrob et al. (2016) restored defective γ waves in mice with Alzheimer’s disease, which resulted in remedial effects through microglia modifications, and this approach could easily be applied to people with autism.

In addition, since ASD patients have clear language-related difficulties with working memory, which ultimately impede language processing, it is sensible to ask how the brain performs working memory tasks, and use this knowledge to construct a model of the rhythms and regions which should be attended to during rTMS/tDCS intervention. Lisman and Jensen (2013), for instance, argue that coupled γ and θ oscillations form a code for representing multiple, sequenced items in memory. These rhythms are generated in the cortex (particularly occipital regions) and hippocampus, pointing ASD interventions in a clear direction.

5 Conclusion

To conclude, we believe that not only do oscillatory signatures yield new endophenotypes of ASD, but they can also point therapists and clinicians towards a clear set of task-dependent electrophysiological interventions. We have suggested that this program should be linked to more traditional speech therapy interventions, targeting (i) the oscillopathic signatures implicated in linguistic – and, more specifically, syntactic – deficits in ASD via transcranial magnetic stimulation and transcranial direct-current stimulation, and (ii) the specific syntactic difficulties documented in ASD (e.g. the interpretation of reflexive pronouns, as in Fortunato-Tavares et al., 2015). A course of speech therapy targeting these linguistic structures, alongside the more direct oscillopathic intervention, would be a novel joint program in its comprehensiveness and intensity, particularly if as little as one hour a week of SLT can make a significant difference (Vismara, Colombi, & Rogers, 2009). Finally, given the identification of similar oscillopathies in schizophrenia (Murphy & Benítez-Burraco, 2016b), rTMS could also be used as a therapeutic intervention to modulate the oscillations responsible for the abnormal linguistic profile documented in the brains of individuals with schizophrenia – a topic for future, and promising, research.

References


