Spring 4-24-2020

Treatment Intervention for Social Functioning and Social Cognition in Adults with Autism Spectrum Disorder (ASD): Utilizing Transcranial Direct Current Stimulation (tDCS) at the Right Temporoparietal Junction (rTPJ)

Joan Esse Wilson
University of New Mexico - Main Campus

Approval Page

Joan Esse Wilson
Candidate

Department of Linguistics
Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Sherman Wilcox, Co-Chairperson

Barbara Rodriguez, Co-Chairperson

Jill Morford

Claudia Tesche

Dina Hill

Title Page

Treatment Intervention for Social Functioning and Social Cognition in Adults with Autism Spectrum Disorder (ASD): Utilizing Transcranial Direct Current Stimulation (tDCS) at the Right Temporoparietal Junction (rTPJ)

by

Joan Esse Wilson

B.A., Accounting, University of Minnesota Duluth

M.S., Speech and Hearing Sciences, University of New Mexico

Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

in

Linguistics

The University of New Mexico

Albuquerque, New Mexico

May 2020

Dedication Page

Dedicated to my brilliant, inspiring, and beautiful daughters, Clarice, Collette, and Jacqui. Success in life, for me, is seeing you incredibly happy and productive.

Acknowledgments

My father worked as a teacher all day in northern Minnesota then drove 140 miles round trip to take night classes for his master's degree. My mother taught me the value of social communication, which is key to my research now (she could also figure out how to fix almost anything through sheer intelligence and problem solving). I want to acknowledge my parents, John and Dorothy Esse, for being excellent examples in life.

To Barbara Rodriguez, my Speech and Hearing Sciences advisor and committee co-chair: We met when I was a new master's student, you were an assistant professor, and our department was still housed in portables. Things have changed on all fronts since then, but your support and encouragement have remained consistent, as well as your incredible insightfulness and sense of humor.

To Sherman Wilcox, my Linguistics advisor and committee co-chair, I recall the day we met. I asked if you'd consider taking me as your student, and you responded, "Absolutely!" I appreciate your passion and willingness to let me explore my research.

To Claudia Tesche, my research mentor, collaborator, and committee member: My research literally would not have been possible without your help and support. You welcomed me with open arms, patiently sat with me through participant sessions, gave me impeccable advice, and made all things complex appear easy.

To Jill Morford, my Linguistics committee member and professor: I was told before we met that you were "brilliant and kind". These descriptions have proven to be true repeatedly in my interactions with you - during dissertation planning, working to fund the graduate student research lab, and offering your clarity of thought as I navigated my doctoral program and academic job search.

To Dina Hill, my committee member and autism spectrum disorder advisor: I am so thankful for your ASD assessment knowledge, as well as for the perspective you bring from your years of working with individuals with ASD and their families.

To Smith Frederick, my supervisor in the College of Education Center for Student Success: You have always followed through on everything you've ever told me. This is quite rare, and I genuinely want to acknowledge and thank you. You've boosted my confidence, given me spot-on advice, and generally been right about most things.

To Kristen Fedesco, my professional colleague, muse, and collaborator: I hope we continue to work together on projects that help people with disabilities, not only because it's such necessary work, but also because we have so much fun while doing it!

Last, but certainly not least, to my husband, Kevin: I did not think I would return to school for a doctoral degree, but you inspired me. You brainstormed ideas with me, stayed up late talking about journal articles, listened to me practicing my presentations over and over, and told me not to worry so much. Like everything else in my life, this wouldn't have been any fun without you.

Also, thank you to these three individuals who provided their expertise and support for research and publications:

Davin K. Quinn, M.D., Department of Psychiatry and Behavioral Sciences, University of New Mexico School of Medicine

Michael C. Trumbo, Ph.D., Cognitive Science and Applications, Sandia National Laboratory

Christopher M. Garcia, M.S., Department of Psychology, University of New Mexico

Treatment Intervention for Social Functioning and Social Cognition in Adults with Autism Spectrum Disorder (ASD): Utilizing Transcranial Direct Current Stimulation (tDCS) at the Right Temporoparietal Junction (rTPJ)

Joan Esse Wilson

B.A., Accounting, University of Minnesota Duluth
M.S., Speech and Hearing Sciences, University of New Mexico
Ph.D., Linguistics, University of New Mexico

ABSTRACT

Social deficits are a key diagnostic feature for autism spectrum disorder (ASD). Transcranial direct current stimulation (tDCS) may be a promising treatment modality to enhance interventions that are currently extremely time- and labor-intensive. This three-article dissertation investigates tDCS applied over the right temporoparietal junction (rTPJ) paired with social functioning and social cognition interventions with adults with ASD, examining measures of social functioning, verbal fluency, social skills, empathy, and facial emotion recognition and processing. Results of these studies show significant differences in performance on several measures after receipt of verum, anodal tDCS over the rTPJ. Theoretical implications are examined within a Language in Motion Framework that discusses perceptible signals, usage-based events, and skilled actions whose implementation in the brain can be explained by neuroscience. This research advances our understanding of how social functioning and social cognition are modulated utilizing tDCS applied over the rTPJ for individuals with ASD.

Table of Contents

Dissertation Introduction

Autism spectrum disorder (ASD) is the fastest growing neurodevelopmental disorder in the United States (U.S.) with 1 in 68 children identified as having ASD (Center for Disease Control, 2016), and a recent study indicating a prevalence as high as 1 in 40 (Zablotsky et al., 2019). This number was 1 in 125 just 14 years ago, an increase that represents a substantial personal and public burden estimated to be as high as $60.9 billion per year in the U.S. for costs such as medical care, intensive behavioral interventions, special education, and lost wages for parents.

Social deficits are core to ASD with specific challenges found in social skills knowledge and use (Laugeson, Ellingsen, Sanderson, Tucci, & Bates, 2014), identification of communicative cues (Zürcher et al., 2013). empathy (Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003), processing of emotion words (Lartseva, Dijkstra, Kan, & Buitelaar, 2014), and theory of mind (ToM) (ability to infer feelings, mental states, and/or intentions of others) (Wellman & Liu, 2004). Social deficits resulting in reduced childhood friendships lead to a lack of experience with interactions that later impacts the development of romantic relationships in adulthood, with only 16% of adults with ASD reporting having been in a long-term relationship (Strunz et al., 2016). Approximately 25% of people with ASD are employed (Holwerda, Van Der Klink, Groothoff, & Brouwer, 2012), with the majority of employment settings offering low pay and limited hours while performing duties below one's education level (Hedley et al., 2016). Even when an individual with ASD is well-qualified for a position, they may require assistance navigating the social demands of the job market while looking for employment, and social deficits make teamwork at the workplace an obstacle to positive employment outcomes (Holwerda et al., 2012). These challenges impact nearly every aspect of an individual's life with ASD, also causing substantial stress and hardship for families and loved ones (Lecavalier, Leone, & Wiltz, 2006).

Social terminology often overlaps or becomes confused: (1) social cognition, (2) social skills, (3) social functioning, and (4) social pragmatic language. The first term, social cognition, refers to mental processes required to complete social tasks, such as attention to information from the sensory environment (Decety & Lamm, 2007), empathy, and ToM (Vangkilde et al., 2016). Second, the term social skills means to utilize social cognition to perform tasks required to participate in social interactions (Reichow & Volkmar, 2010), such as how to initiate or enter a conversation. Third, social functioning considers how one completes daily, social tasks for independent living, such as holding employment or participating in leisure activities with others. Last, social pragmatic language refers to how language is used to accomplish something (e.g., making a request, informing someone), language is adjusted to fit different social contexts (e.g., speaking differently to a teacher than to a friend), and how people follow the rules of conversation (e.g., taking turns, staying on topic, using appropriate facial expressions) (American Speech-Language-Hearing Association, 2016).

The cornerstone of treatment interventions for social functioning deficits for individuals with ASD has centered around forms of behavioral analysis therapy (Myers & Johnson, 2007). Although several of these treatment methods are well-validated, they are extremely time- and labor-intensive to implement. For example, early intensive behavioral interventions can take 20 to 40 hours per week over more than two years to implement (Peters-Scheffer, Didden, Korzilius, & Matson, 2012). Similarly, some adultmediated interventions require attendance to sessions along with the individual with ASD for 90 minutes per week for 16 weeks, with additional homework required outside of sessions (Laugeson, Gantman, Kapp, Orenski, & Ellingsen, 2015). It is clear that a need exists for more accessible, efficient, and effective treatments for ASD. A promising treatment modality to address this need is transcranial direct current stimulation (tDCS), which is a lightweight, inexpensive, noninvasive, and safe method of brain stimulation that delivers weak electrical current to the brain using electrodes positioned on the scalp (Nitsche & Paulus, 2000b; Sellaro, Nitsche, & Colzato, 2016). Researchers have been using tDCS to capitalize on the brain's own electrical, neural system and have shown the potential for increasing cortical excitability and brain activity underneath the anode electrode, and for reducing cortical excitability and activity under the cathode electrode (Amatachaya et al., 2015).

An estimated 85 billion neurons in the human brain fire and transmit electrical signals (Azevedo et al., 2009). During a face-to-face, spoken conversation with another individual, our brain is busy sending electrical signals engaging our visual system to watch for communicative cues, our auditory system is listening to what the other person is saying, our working memory to draw upon past events related to the topic of conversation, our attentional system to attend to the speaker, and our motor planning system is organizing speech production and body language (Bögels, Magyari, & Levinson, 2015). Engaging in a simple conversation is anything but simple when considering the complexity of the brain's neural activity.

Figure 1 shows two side-by-side images depicting an example of a two-electrode delivery of tDCS (Annals of Neurology, 2016). The left image shows the delivery of tDCS with the blue and green circular, anodal (excitatory) electrode placed over the brain's right temporal lobe, and the red and green circular cathodal (inhibitory) electrode placed over the brain's left frontal lobe. The right image depicts the corresponding, underlying brain structure, with the dark blue area under the black circle indicating increased neuronal activity at the site of stimulation.

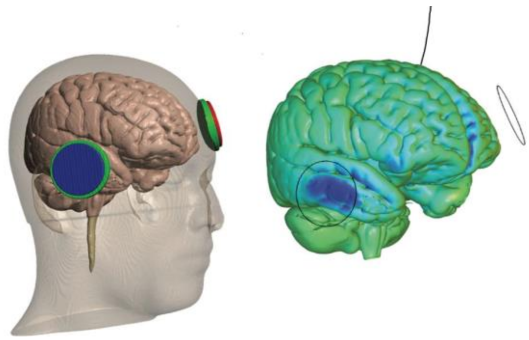


Figure 1. Depiction of cortical excitability found under right-side anodal tDCS electrode site (Annals of Neurology, 2016)

It has been demonstrated that tDCS can safely accelerate and enhance learning (B. a Coffman, Trumbo, & Clark, 2012; Ferrucci et al., 2013), particularly when paired with a task (Gill, Shah-Basak, & Hamilton, 2015), suggesting that pairing tDCS with treatment interventions may be effective for targeting deficits in ASD. Specifically, applying anodal tDCS ("anodal" increases neuronal excitability while "cathodal" decreases it) to the right temporoparietal junction (rTPJ) may capitalize on the critical role the rTPJ plays in social functioning (Krall et al., 2016) as part of a broad, neural network for overall social cognition (Kennedy & Adolphs, 2012). Functional neuroimaging studies have shown the rTPJ plays an important role in higher-level social cognitive processes such as empathy and ToM, as well as during lower-level social cognitive processes, such as evaluating self against others based on sensory information from the environment (Decety & Lamm, 2007). Further, functional neuroimaging has demonstrated that the rTPJ is specifically associated with deficits in social functioning in individuals with ASD (Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011). Importantly, the use of anodal tDCS delivered over the rTPJ has resulted in improvements in social functioning with neurotypical individuals (Santiesteban, Banissy, Catmur, & Bird, 2012). Yet, despite the substantial social functioning and social cognition deficits individuals with ASD face, few studies have investigated the use of tDCS at the rTPJ as a treatment intervention for individuals with ASD.

The objective of this three-article dissertation is to examine the effects of tDCS applied at the rTPJ on social functioning and social cognition measures with individuals with ASD. The central hypothesis is that participants with ASD will show improved performance on social functioning and social cognition measures from verum tDCS ("verum" delivers electrical current that impacts neuronal excitability) compared to sham tDCS ("sham" delivers little or no electrical current and does not impact neuronal excitability). I plan to accomplish the objective of this proposal by pursuing the following three, specific aims across three, separate articles: (1) evaluate the impact on baseline vs. post-tDCS on social functioning measures when tDCS is applied for a total of eight days for eight consecutive sessions over the rTPJ of a high-functioning adult with ASD, (2) determine if tDCS applied over the rTPJ of adults with ASD will result in differences on social skills and/or verbal fluency measures when comparing verum to sham tDCS, and (3) determine if tDCS applied over the rTPJ of adults with ASD will result in differences on empathy and/or facial emotion recognition and processing measures.

These studies are <u>significant</u> because they provide a better understanding of how tDCS applied over the rTPJ impacts social cognition and social functioning in individuals with ASD. Such results have a positive impact because they fundamentally advance our understanding of how social cognition and social functioning is modulated utilizing tDCS. The long-term goal of this research is to identify more accessible, efficient, and effective social functioning and social cognition treatment interventions for individuals with ASD.

Article 1: Transcranial Direct Current Stimulation to Right Temporoparietal Junction for Social Functioning in Autism Spectrum Disorder: Case Report

This is a non-final version of an article published in final form:

Esse Wilson, J,. Quinn, D.K., Wilson, J.K., Garcia, C.M., & Tesche, C.D. (2018). Transcranial direct current stimulation to the right temporoparietal junction for social functioning in autism spectrum disorder. *The Journal of ECT*, *34*(1), e10–e13. https://doi.org/10.1097/YCT.0000000000000445

Link to the publication on the journal's website:
https://journals.lww.com/ectjournal/Abstract/2018/03000/Transcranial_Direct_Current_Stimulation_to_the.20.aspx

Joan Esse Wilson, M.S. University of New Mexico, Department of Linguistics

Davin K. Quinn, M.D. University of New Mexico School of Medicine, Department of Psychiatry and Behavioral Sciences

J. Kevin Wilson, M.S. University of New Mexico, Department of Neurosciences

Christopher M. Garcia, M.S. University of New Mexico, Psychology Department

Claudia D. Tesche, Ph.D. University of New Mexico, Psychology Department

Abstract

Objectives: While there is evidence of improved social functioning after applying transcranial direct current stimulation (tDCS) at the right temporoparietal junction (rTPJ) in individuals who are healthy, no current studies have investigated the use of tDCS at the rTPJ to improve social functioning in individuals with an autism spectrum disorder (ASD). This case investigates the use of tDCS applied to the rTPJ to target social functioning in a high functioning adult with ASD.

Methods: The authors present a case of an 18-year old patient with ASD treated successfully with tDCS. 1.5 mA of tDCS was applied once a day for 30 minutes for 8 consecutive days with the anode electrode over rTPJ (CP6 in the 10/10 EEG system) and the cathode electrode placed on the ipsilateral deltoid. Behavioral outcome was assessed using the Autism Treatment Evaluation Checklist (ATEC) prior to tDCS, after the final tDCS session, and at 2-months post-tDCS. An additional, informal follow-up was also made one year post-tDCS.

Results: ATEC showed substantial improvement in social functioning from baseline to post-tDCS, which was maintained at 2 months. The patient also reported lessened feelings of anger and frustration over social disappointments. Informal follow-up one year after stimulation indicates that the patient continues to maintain many improvements.

Conclusion: Anodal tDCS to the rTPJ may represent an effective treatment for improving social functioning in ASD, with a larger clinical trial needed to validate this effect.

Keywords: autism spectrum disorder; transcranial direct current stimulation; right temporoparietal junction; social functioning

Introduction

Social functioning deficits are a core component of autism spectrum disorder (ASD) with substantial challenges found in empathy (Baron-Cohen, 2009) and theory of mind (Lombardo et al., 2011) (the ability to infer feelings, mental states, and/or intentions of others). These deficits not only represent a quality of life concern for individuals with an ASD, but also for their families and loved ones.

Although the diagnostic term “autism spectrum disorder” currently makes no distinction regarding where an individual with ASD may present along the spectrum in terms of severity (American Psychiatric Association, 2013), conceptualization of a wide range of differing severities of ASD exists (Tebartz van Elst et al., 2014), including for individuals with ASD who may be considered “high functioning” with average or above intelligence (Hofvander et al., 2009). A recent report by the Center for Disease Control and Prevention estimates as many as 46% of individuals with ASD have average or above intelligence (Center for Disease Control and Prevention, 2014). High-functioning individuals with ASD are not typically associated with the severe deficits in verbal communication and behavioral regulation found in “low-functioning” ASD (Maljaars, Noens, Jansen, Scholte, & Berckelaer-onnes, 2011). However, high functioning individuals with ASD are specifically associated with significant psychiatric comorbidities of mood disorders, such as depression (53%), anxiety (50%), attention-deficit/hyperactivity disorder (ADHD) (43%), obsessive–compulsive disorder (24%), chronic tic disorders (20%) and substance related disorders (16%) (Hofvander et al., 2009). Additionally, high functioning adults with ASD display low levels of attainment for meaningful relationships (Hofvander et al., 2009), as well as substantial levels of underemployment, often despite high levels of intelligence and/or education (Hedley et al., 2016).

The cornerstone for treatment of social deficits in ASD has been behavioral analysis therapy (Myers & Johnson, 2007). While this is a well-validated treatment method, it is extremely time- and labor-intensive, highlighting the need for more accessible, efficient and effective treatments for ASD. A promising treatment modality to address this therapeutic gap is transcranial direct current stimulation (tDCS). tDCS is a lightweight, inexpensive, noninvasive and safe method of brain stimulation that delivers weak electrical current to the brain using electrodes positioned on the scalp (Nitsche & Paulus, 2000a; Sellaro et al., 2016). tDCS has shown repeatedly to increase cortical excitability and brain activity underneath the anode electrode, and reduce cortical excitability and brain activity under the cathode electrode (Nitsche & Paulus, 2000a).

The right temporoparietal junction (rTPJ) is identified as playing a critical role in social functioning (Krall et al., 2016). Functional neuroimaging demonstrates that the rTPJ is specifically associated with deficits in social functioning in individuals with ASD (Lombardo et al., 2011). Additionally, anodal tDCS targeting the rTPJ shows improved social functioning in healthy individuals on imitation tasks requiring evaluation of self against others and on perspective taking tasks (Santiesteban et al., 2012). No current studies have investigated rTPJ tDCS in individuals with an ASD. When considering that tDCS has demonstrated an increased effectiveness in individuals with less symptom severity of other disorders, such as depression (Blumberger et al., 2012; Rigonatti S.P., Boggio P.S., Myczkowski M.L., Otta E., Fiquer J.T., Ribeiro R.B., Nitsche M.A., Pascual-Leone A., 2008) and aphasia (Jung et al., 2011), there is indication that tDCS may be particularly well-suited for use with high-functioning individuals displaying less severe traits of ASD. Thus, we present a case of a young, high-functioning adult with an ASD successfully treated with tDCS to the rTPJ to illustrate its potential in improving social functioning.

Materials and Methods

Mr. S is a right-handed, 18-year old male who was diagnosed with high-functioning autism at age 5 years, confirmed by an Autism Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) score of 33 and a Shipley-2 (Shipley, Gruber, Martin, & Klein, 2009) score of 85. The AQ is a reliable instrument that measures the degree adults with normal intelligence display social/behavioral traits associated with ASD (Hoekstra, Bartels, Cath, & Boomsma, 2008; Ruzich et al., 2015), and the Shipley-2 is a standardized measure that provides an overall estimate of cognitive ability. Mr. S lives at home with his parents and siblings, none of whom are diagnosed with an ASD. He has no other medical conditions and was taking no medications at the time of the study. From ages 5-13 years, Mr. S received various interventions privately and at mainstream public schools under an individualized education program, including Applied Behavior Analysis (ABA), Relationship Development Intervention (RDI), speech-language pathology services and occupational therapy services. These therapies were reported as being successful in improving Mr. S's behavior and social functioning, but by adolescence he was no longer responding to these interventions. This, coupled with the pressures of starting high school, increased Mr. S's level of social difficulty, impacting his overall performance at school. His parent also specifically reports increased difficulty for understanding the motivations of others and understanding the rules of conversation (i.e., engaging in frequent interruptions; not maintaining the topic of conversation). These difficulties leave Mr. S feeling socially disappointed, commonly leading to feelings of anger and frustration. During high school Mr. S also began to suffer from depression and anxiety, including suicide ideation, which is consistent with many individuals with high-functioning ASD (Hofvander et al., 2009). His parents sought help for Mr. S through private psychotherapy, but met with limited success. His non-responsiveness to therapies in high school was a concern to him and to his parents as he was approaching adulthood. This concern, as well as a desire to avoid the use of medications, led them to seek out alternative treatments. Through this process, they found out about our team's tDCS research from a posting on a national autism website and contacted us.

Because Mr. S reported a history of depression and anxiety, three measures were utilized to confirm that these conditions were not clinically manifest prior to administration of tDCS: (1) Patient Health Questionnaire-9-Item (PHQ-9) (score of 0), (2) the PTSD Checklist – Civilian (PCL-C) (score of 20), and (3) the Neurobehavioral Symptom Inventory (NSI) (score of 0). tDCS was delivered using an ActivaTek Activadose II (Salt Lake City, UT) iontophoresis device with 25 cm^2 sponge electrodes saturated with electrolyte gel (for improved sensation tolerance). The anode was placed at the rTPJ (CP6 in the 10/10 EEG system). The cathode was placed on the ipsilateral deltoid, with the intention of pulling the current down through the right hemisphere of the brain, thus attempting to avoid deep brain structures. Current was delivered at 1.5 mA for 30 minutes once per day for a total of 8 sessions over 8 days. An initial current target of

2.0 mA was revised to 1.5 mA after the first session when Mr. S reported excessive sensations during stimulation.

Mr. S watched short videos that modeled social behavior[10] during the first two sessions of stimulation. For the remaining six sessions, he engaged in intermittent casual conversations with a psychiatrist. Stimulation was well-tolerated by Mr. S once current levels were adjusted for comfort, with only mild side-effects including redness at the electrode sites and ongoing tingling sensations down his right arm during stimulation.

Results

Parent-reported measures before, during, and after tDCS treatment showed improvement in social functioning, as well as lessened feelings of anger and frustration over social disappointments.

Parent-reported symptoms were assessed using the Autism Treatment Evaluation Checklist (ATEC), a validated rating instrument for tracking changes in ASD symptoms over time(Geier, Kern, & Geier, 2013) that has also been used in previous tDCS ASD studies.(Amatachaya et al., 2014, 2015) The ATEC allows ratings on a total of 77 different items, categorized into four, broad areas: (1) speech/language/communication, (2) sociability, (3) sensory/cognitive awareness, and (4) health/physical/behavior. Ratings from all items were then calculated to provide subscale and total scores, with higher scores associated with higher levels of ASD symptoms. Mr. S's parent completed the ATEC prior to start of tDCS, after the final session of tDCS, and two months later at follow-up. Scores showed a lessening of ASD symptoms over time. Scores from each time point are presented in Table 1.

TABLE 1. Assessment Results with Autism Treatment Evaluation Checklist (ATEC) Before and After tDCS and at 2-Month Follow-Up

	Before tDCS		After tDCS		2-Month Follow-Up	
Scores*	Raw	%ile	Raw	%ile	Raw	%ile
Total:	42	20	20	6	11	3
Subscales:						
Speech	0	0	0	0	0	0
Sociability	7	19	1	2	2	5
Sensory	13	39	8	19	0	0
Behavior	22	50	11	16	9	10

*Higher raw scores and percentiles (%ile) indicate higher levels of ASD symptoms

During the time-frame that Mr. S received tDCS, he and his parent reported an increased interest in social interactions, including engaging in spontaneous, on-topic conversations with sales people while shopping, an activity Mr. S was not previously prone to doing. The parent also reported that Mr. S appeared generally more aware of others' feelings and perspectives and had made improvements with topic maintenance and reducing interruptions during conversations. Additionally, one parent reported at 2-month follow-up that Mr. S had continued improvements with no signs of regression despite starting fall classes. It was also reported that Mr. S experienced lessened episodes of anger and frustration over social disappointments, citing as evidence Mr. S's optimistic response after finding out a classmate could not attend a school dance with him, something that previously would have caused intense feelings of anger and frustration. At informal follow-up one year after stimulation, parent report is that Mr. S is in a job training program and continues to maintain many of the improvements first seen after stimulation sessions, such as considering others' viewpoints and listening and empathizing during conversations, but that he still faces difficulties with maintaining friendships.

Discussion

This is the first case reporting use of anodal tDCS to rTPJ to improve social functioning in an individual with an ASD. Additionally, this is the first case to utilize an anodal and cathodal ipsilateral electrode placement montage in tDCS with ASD.

The vast majority of intervention-based tDCS and TMS studies in ASD employ stimulation to the dorsolateral prefrontal cortex (DLPFC), with a wide range of positive results including decreased levels of irritability (Baruth et al., 2010; Casanova et al., 2012; Sokhadze et al., 2016; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Y. Wang et al., 2016), hyperactivity (D'Urso et al., 2015; Sokhadze et al., 2016; Sokhadze, El-Baz, Tasman, et al., 2014; Y. Wang et al., 2016), and repetitive behaviors (Baruth et al., 2010; Sokhadze et al., 2016; Sokhadze, El-Baz, Tasman, et al., 2014; Y. Wang et al., 2016), as well as interesting findings for increased cardiac vagal control (Y. Wang et al., 2016), increased syntax acquisition (Schneider & Hopp, 2011), minimized responses to irrelevant stimuli (Sokhadze et al., 2010), and improved visual discrimination ability (Baruth et al., 2010). However, tDCS with ASD studies that specifically examine social functioning are limited, with these few studies finding improvements for broad social domains (Amatachaya et al., 2014, 2015) and social withdrawal (D'Urso et al., 2015, 2014) after tDCS stimulation to the DLPFC.

The rTPJ is thought to participate in a broad, neural network for social cognition (Kennedy & Adolphs, 2012). Specifically, functional neuroimaging studies show the rTPJ plays a critical role in higher-level social cognitive processes, such as empathy and theory of mind, as well as during lower-level social cognitive processes, such as evaluating self against others based on sensory information from the environment (Decety & Lamm, 2007). This case supports the rTPJ's role, with participant improvements in areas of higher-order social cognitive processes (e.g., participant showed increased awareness of others' feelings and perspectives) as well as lower-level social cognitive processes (as seen from ATEC score improvements in sociability and sensory/cognitive awareness).

Additionally, tDCS-induced behavioral and physiological effects may depend on choice of electrode montage (Nasseri, Nitsche, & Ekhtiari, 2015; Sellaro et al., 2016). Previous intervention-based tDCS with ASD studies have focused on electrode placements consisting of anodal or cathodal stimulation to the DLPFC with a second electrode placed contralaterally (Amatachaya et al., 2014, 2015; D'Urso et al., 2015; Schneider & Hopp, 2011). In contrast, our case utilizes anodal electrode placement at the rTPJ with the cathodal electrode placed ipsilaterally to pull the current through the right hemisphere of the brain. One possible drawback to this montage may be shunting of the current superficially, potentially causing the participant's tingling sensations in his right arm during stimulation. A future direction for this research might investigate the use of high definition tDCS utilizing electrode placements that could allow shunting across just the scalp, thus avoiding other parts of the body (Richardson et al., 2014).

This is a report of a single case without control participants for use as a comparison. Thus, we are unable to eliminate the possibility that the participant may have improved from factors other than brain stimulation, such as maturation. However, studies have demonstrated that core social impairments of ASD persist over one's lifetime, even in those who are seen to have achieved an optimal outcome (Fein et al., 2013). Additionally, while individuals with ASD might exhibit less overall symptoms as they mature, the consensus in the literature is that most don't achieve optimal outcomes without intervention (Fernell, Eriksson, & Gillberg, 2013), suggesting that substantial improvements in social function in individuals with ASD are not typically seen in the absence of intervention, not even in the presence of maturation. Further research is warranted to confirm this case's findings through a randomized controlled trial. In the case of Mr. S, his social functioning difficulties increased with the onset of adolescence, suggesting that intervention with tDCS during adolescence may have been beneficial. While many factors may influence each individual's treatment outcomes, there is evidence that age of intervention optimizes outcomes for methods such as ABA (Dawson & Rogers, 2010; Harris & Handleman, 2000), suggesting it may also be useful to administer tDCS at earlier ages. Of course, this needs to be balanced against a lack of data regarding short- and long-term consequences of direct current stimulation in the developing brain. A child's developing brain may be more easily influenced by tDCS than an adult's (Krishnan, Santos, Peterson, & Ehinger, 2016; Rubio, Boes, Laganiere, Jeurissen, & Pascual-leone, 2017), offering optimism for tDCS as an innovative future direction for research to determine its safety and efficacy for children with ASD.

It should also be mentioned that there is evidence that the efficacy of tDCS may be enhanced by engaging in task-performance during stimulation (Sokhadze, El-Baz, Sears, et al., 2014). Future studies may find that consistent engagement of individuals with ASD in social training activities, either through videos or interaction with therapists, throughout the stimulation session may enhance the beneficial effects seen following anodal tDCS of rTPJ.

Article 2: Transcranial Direct Current Stimulation (tDCS) Over Right Temporoparietal Junction (rTPJ) for Social Cognition and Social Skills in Adults with Autism Spectrum Disorder (ASD)

This is a non-final version of an article published in final form:

Esse Wilson, J., Trumbo, M. C., Wilson, J. K., & Tesche, C. D. (2018). Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). *Journal of Neural Transmission, 125*(12), 1857–1866. https://doi.org/10.1007/s00702-018-1938-5

Joan Esse Wilson[a], Michael C. Trumbo[b], J. Kevin Wilson[c], & Claudia D. Tesche[c]

[a]Department of Linguistics, MSC03 2130 1 University of New Mexico, Albuquerque, New Mexico, 87131 USA joanwilson@unm.edu

[b]Cognitive Science and Applications, Sandia National Laboratory, 1611 Innovation Pkwy SE, Albuquerque, New Mexico 87123 USA mctrumb@sandia.gov

[c]Department of Psychology, MSC03 2220 1 University of New Mexico, Albuquerque, New Mexico, 87131 USA jkwilson@unm.edu; ctesche@unm.edu

Abbreviations: tDCS, transcranial direct current stimulation; ASD, autism spectrum disorder; rTPJ, right temporoparietal junction; TMS, transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; AQ, Autism Quotient; VF, verbal fluency; ToM, Theory of Mind

Abstract

Social deficits are core to autism spectrum disorder (ASD). Current treatments are extremely time- and labor-intensive. Transcranial direct current stimulation (tDCS) may be a promising treatment modality to safely enhance treatments targeting social cognition and social skills. This pilot study investigates the effectiveness of social skills treatment interventions paired with anodal tDCS for six adults ages 18-58 years with ASD. Differences were predicted on the verbal fluency (VF) test and a test of social skills (TASSK-M) for verum (2.0 mA) vs. sham tDCS, which was randomly assigned in a within-subjects, double-blinded design in adults with ASD with normal or higher cognitive functioning. The anode electrode was placed over right temporoparietal (rTPJ) (CP6) and cathode over ipsilateral deltoid. Wilcoxon signed-rank tests for paired data indicated that participants received a significantly higher score on the VF test after receiving verum tDCS compared to sham tDCS, with no significant differences found on the TASSK-M. *Post hoc* analysis showed that the emotion word portion of the VF test, specifically, indicated significant differences when comparing verum to sham tDCS conditions. These findings provide optimism for the use of tDCS as delivered in the current study paired with social skills treatment interventions for ASD, particularly for improving skills of emotion verbal fluency.

Keywords: transcranial direct current stimulation, autism spectrum disorder, right temporoparietal junction, social cognition, emotion verbal fluency, social skills

Introduction

Autism spectrum disorder (ASD) is now the fastest-growing neurodevelopmental disorder in the United States (Center for Disease Control, 2016). Social cognition and social skills deficits are core to ASD. Social cognition refers to mental processes required to complete social tasks (Decety & Lamm, 2007), while social skills refers to utilizing social cognition to perform tasks required to participate in social interactions (Reichow & Volkmar, 2010). Deficits in these areas impact nearly every aspect of an individual's life with ASD, also causing substantial stress and hardship for their families and loved ones (Lecavalier et al., 2006). Social deficits faced by individuals with ASD represent lifelong barriers to developing and maintaining meaningful relationships (Reichow & Volkmar, 2010), obtaining rewarding employment, and living independently (Hedley et al., 2016). Specific challenges include interactions requiring emotion processing (Lartseva et al., 2014) and identifying and describing emotions verbally, linking directly to ASD difficulties in empathy (Moseley et al., 2015; Wellman & Liu, 2004), which further encompasses the concept of theory of mind (ToM), which is the capacity to take the perspective of another and infer their mental state.

Currently, there is no one, specific treatment for ASD (Myers & Johnson, 2007). Pharmacologic therapies (antidepressants and antipsychotics) are sometimes used in the course of ASD treatment, but these have several adverse side effects such as sleep problems, nausea, and agitation (Oswald & Sonenklar, 2007). Treatment interventions for social cognitive and social skills deficits in ASD have centered around approaches such as behavioral analyses therapies, such as applied behavior analysis (Freitag, Feineis-Matthews, Valerian, Teufel, & Wilker, 2012; Mohammadzaheri, Koegel, Rezaei, &

Bakhshi, 2015; Myers & Johnson, 2007), peer and/or video modeling (Delano, 2007; Watkins et al., 2015), peer-mediated social skills interventions (Wong et al., 2015), teacher-facilitated social skills trainings (Laugeson et al., 2014), and empathy and emotion trainings (Baron-Cohen, 2003). However, these treatment methods are extremely time- and labor-intensive to implement.

There is a need for more effective and efficient treatments for ASD. Noninvasive transcranial stimulation may be a promising treatment modality to safely enhance treatments targeting social cognition and social skills. The vast majority of intervention-based noninvasive transcranial stimulation therapies in ASD have employed Transcranial Magnetic Stimulation (TMS) of the dorsolateral prefrontal cortex (DLPFC). In TMS, current pulses are induced into the brain by a coil held over the scalp. Positive results of TMS include decreased levels of irritability (Baruth et al., 2010; Casanova et al., 2012; Sokhadze et al., 2016; Sokhadze, El-Baz, Sears, et al., 2014; Y. Wang et al., 2016), hyperactivity (D'Urso et al., 2015; Sokhadze et al., 2016; Sokhadze, El-Baz, Tasman, et al., 2014; Y. Wang et al., 2016), and repetitive behaviors (Baruth et al., 2010; Sokhadze et al., 2016; Sokhadze, El-Baz, Tasman, et al., 2014; Y. Wang et al., 2016). Other findings also demonstrate increased cardiac vagal control (Y. Wang et al., 2016), increased syntax acquisition (Schneider & Hopp, 2011), minimized responses to irrelevant stimuli (Sokhadze et al., 2010), and improved visual discrimination ability (Baruth et al., 2010). While these studies indicate that TMS has emerged as a novel tool for the potential treatment of ASD, it is important to note that the findings should be balanced against specific concerns related to ASD, such as developing safety protocols across levels of functioning and age and the need for more large-scale experimental studies to be completed (Oberman et al., 2016).

Transcranial Direct Current Stimulation (tDCS) is a noninvasive method of modulating neuronal activity. In tDCS, a weak electrical current is passed into the brain through one or more electrodes placed on the scalp (Nitsche & Paulus, 2000a). Previous research has demonstrated tDCS-induced improvements in a variety of cognitive domains for both healthy adults and for those with clinical disorders (B. A. Coffman, Trumbo, & Clark, 2012; Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Manenti, Cotelli, Robertson, & Miniussi, 2012). Of particular relevance to the current study, tDCS has increased performance in healthy individuals on skills that are employed during social functioning, such as facial emotion recognition (Boggio, Rocha, da Silva, & Fregni, 2008) and orienting attention to continually changing and sometimes conflicting information (Stone & Tesche, 2009). While TMS has resulted in improvements after stimulation over DLPFC in social relatedness, no improvements were found on tasks of empathy or ToM, such as perspective taking (Enticott et al., 2014). In contrast, tDCS over DLPFC in ASD with findings specific to social cognition or social skills are limited, the few available studies have reported improvements for broad social domains (Amatachaya et al., 2014, 2015) and social withdrawal (D'Urso et al., 2015, 2014) after tDCS stimulation over the DLPFC.

While DLPFC has been a popular stimulation target, both the DLPFC and the right temporoparietal junction (rTPJ) play a role in a broad, neural network for social cognition (Kennedy & Adolphs, 2012; Krall et al., 2016). Functional neuroimaging studies show that the rTPJ plays an important role in social cognitive processes necessary for empathy and ToM (Decety & Lamm, 2007). Further, functional neuroimaging has demonstrated that the rTPJ is specifically associated with ToM deficits in individuals with ASD (Lombardo et al., 2011). Anodal tDCS applied over the rTPJ in healthy individuals shows improved social functioning through tasks for perspective taking and evaluation of self against others (Santiesteban et al., 2012), while cathodal tDCS applied over the rTPJ shows reduced accuracy on ToM and cognitive empathy tasks (Mai et al., 2016). These findings suggest that altering the cortical excitability of the rTPJ may influence performance on tasks used during social functioning in healthy individuals. One case study previously examined using tDCS at the rTPJ with one individual with ASD (Esse Wilson, Quinn, et al., 2018). Our study aims to extend upon this prior case study. There are several advantages of tDCS over TMS. TDCS is portable, inexpensive, and does not require patients to remain motionless for prolonged periods of time – a difficult feat for the low-functioning and hyperactive patients who comprise 75-80% of individuals with autism (D'Urso et al., 2014). These features motivate continued investigation of the potential clinical use of tDCS in ASD.

The objective of the present study was to investigate the effect of combining anodal tDCS at the rTPJ with computer-based social skills treatment interventions. Our hypothesis proposed that anodal, verum tDCS applied at the rTPJ would result in greater, subsequent improvements in performance when comparing anodal, sham tDCS on the verbal fluency (VF) test and on a test of social skills (TASSK-M).

Materials and Methods

Participants

Study procedures were approved by the Office of the Institutional Review Board of the University of New Mexico (UNM). Six right-handed, English-speaking adults mean age of 28.3 years (four males, two females; see Table 1 for complete demographics) identified as having an ASD were recruited by word of mouth and flyer postings at the UNM campus, the UNM Accessibility Resource Center, and through a posting to the Autism Speaks® *Participate in Research* webpage.

Procedure

Participants attended two sessions spaced seven days apart at the Psychology Clinical Neuroscience Center at UNM. In the initial session, informed consent was obtained and participants were screened for ASD with the Autism Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), a reliable instrument that measures the degree to which adults with normal intelligence display social/behavioral traits associated with ASD (Hoekstra et al., 2008; Ruzich et al., 2015). The AQ is one of the most widely used instruments in the world for quantifying autistic traits, with cross-cultural, multiple-language versions existing in Chinese, French, Dutch, Italian, Japanese, Persian, and Polish. It has been found to demonstrate good psychometric properties and to adequately distinguish people with ASD from those without ASD (Lundqvist & Lindner, 2017; Zhang et al., 2016). The AQ has been used successfully for clinical screening, as well as to predict outcomes on topics as diverse as social cognition to spontaneous facial mimicry to auditory speech perception.

Previous research shows that 80% of adults with ASD with normal or above cognitive functioning score a 32 or above on the AQ (Baron-Cohen et al., 2001). Thus, a score of 32 or higher on the AQ was required for study participation. Participants also completed a self-report screening questionnaire on their knowledge of their own ASD. Participants were screened for right-handedness with the Edinburgh Handedness Inventory (Oldfield, 1971) and for cognitive function with the Shipley-2 (Shipley et al., 2009), a standardized measure that provides an overall estimate of cognitive ability. A standard score of 70 or higher was required on the Shipley-2 for study participation.

A timeline summarizing study's pre-stimulation, stimulation, and post-stimulation activities is shown in Figure 1.

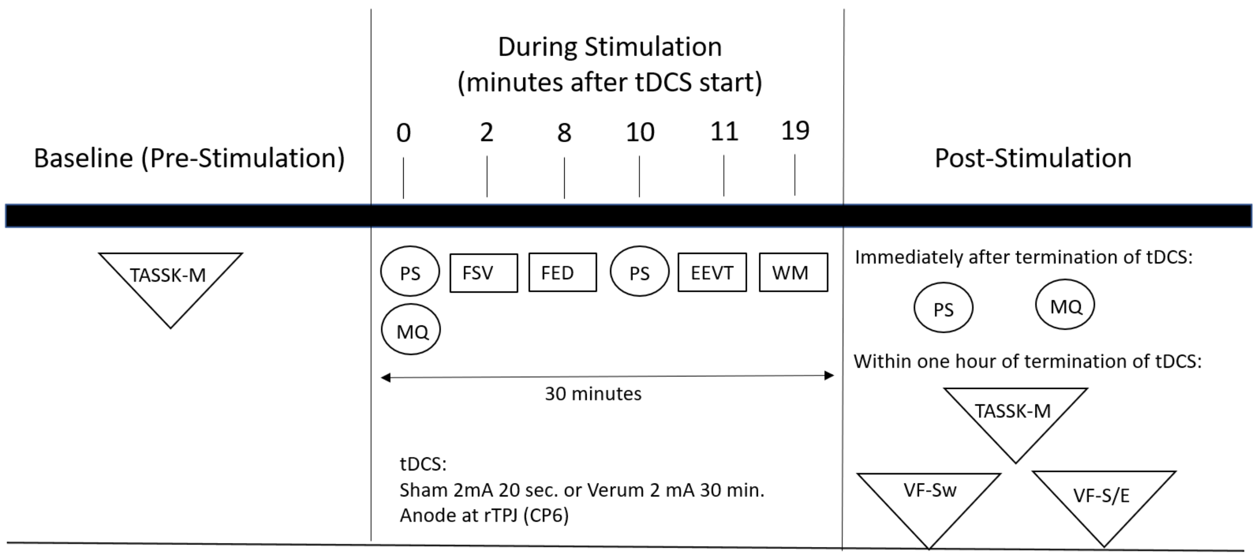


Figure 1. Timeline summarizing study's pre-stimulation, stimulation, and post-stimulation activities where items in triangles are measures where TASSK-M refers to Test of Adolescent Social Skills-Modified, VF-Sw to verbal fluency test for switching, and VF-S/E to verbal fluency test for semantic and emotion categories; items in circles are questionnaire assessments where PS refers to physical sensation questionnaire and MQ to mood questionnaire; and items in rectangles refer to treatment tasks where FSV refers to faces and shapes viewing, FED to facial emotion detection, EEVT to emotion and empathy video treatment interventions, and VM to video modeling.

The Test of Adolescent Social Skills was administered, which is a 26-item test to assess knowledge about specific social skills.(Laugeson, Frankel, Mogil, & Dillon, 2009) modified for adults (TASSK-M) where we revised questions to reflect adult participation, such as changing wording in questions that used terms about being "popular" or "bullying". Next, participants were seated inside an electrically shielded room and prepared for transcranial stimulation. TDCS was delivered through two square 11 cm^2 saline-soaked sponge electrodes (neuroConn DC-STIMULATOR MR). The anode was positioned over the rTPJ (CP6 in the 10-10 EEG system). The cathode was positioned over the ipsilateral deltoid. Previous intervention-based tDCS studies with individuals with ASD have primarily stimulated at the DLPFC with a cathodal electrode placed contralaterally (Amatachaya et al., 2014, 2015; D'Urso et al., 2015; Schneider & Hopp, 2011). Our study placed an anodal electrode at the rTPJ with a cathodal electrode placed ipsilaterally consistent with a previously studied montage (Esse Wilson, Quinn, et al., 2018). Verum tDCS was delivered at 2.0 mA for 30 minutes. Sham tDCS was delivered with a current that increased from 0 to 2.0 mA during 20 seconds, then decreased to 0 mA after 30 seconds. This use of sham tDCS utilizing the delivery of an initial current that then ramps down has been used in previous research (Kessler, Turkeltaub, Benson, & Hamilton, 2013). Participants randomly received either verum or sham tDCS during each of the two experimental sessions. Both the assessing researcher and the participant were blinded as to which condition the participant was in until after the completion of the second visit. During both verum and sham sessions of tDCS, participants were assessed by a mood questionnaire (MQ) twice for mood changes (within first minutes of stimulation and immediately after termination of stimulation), as well as for physical sensations (PS) of itching, heat, and tingling taken at three separate time points (first minutes of stimulation, approximately 10 minutes after start of stimulation, and immediately after termination of stimulation).

After first assessments for mood and physical sensations were completed, approximately two minutes after initiation of stimulation, participants began the faces and shapes viewing task (FSV). Visual stimuli were presented in trials on a 24-inch computer screen. Each trial consisted of the following sequence of stimuli: A white fixation cross appeared against a black background for 2000 ms at the bottom center of the screen. The fixation cross was followed by a black screen for 1000 ms. Next, an image appeared for 4000 ms against a black background. A total of 56 images set against a black background were randomly presented from three, different categories: (1) photos of human faces taken from the NimStim set of normed facial expression (Tottenham, Tanaka, & Leon, 2009), (2) photos of dog faces taken from the internet chosen for compliance to uniform sizing, and (3) photos of shapes. Audio instructions were provided with the onset of each image presentation instructing participants to look at either the person's or the dog's eyes, or to look at the shape. An eye-tracker (SR Research EyeLink 1000) was utilized to track the pupil size and gaze direction during this task. The duration of the presentation of the 56 trials was approximately six minutes.

Following the FSV task, participants viewed three randomly-presented social function treatment intervention videos. These videos provided broad exposure to examples of varied social interactions. The videos were presented with visual and auditory components on a 16-inch laptop screen via Paradigm Stimulus Presentation (www.paradigmexperiments.com). Each of the social function intervention videos were divided into two sections, section A and section B, which were randomly assigned to either the first or second experimental session.

The rationale for choosing the treatment interventions was based on two main considerations: (1) a desire to use evidence-based social skills interventions for individuals with ASD, and (2) the role of the rTPJ (our site for tDCS stimulation) as a neural processing center for empathy and emotion word processing.

The first treatment intervention was a facial emotion detection intervention (FED) that showed male and female human faces taken from the NimStim set of normed facial emotion expressions (Tottenham et al., 2009). Facial emotion recognition training was chosen because this skill is intricately tied to situations where empathy is employed during social interactions, and evidence has demonstrated that individuals with ASD have been able to increase their ability to recognize facial emotion with intervention (Golan et al., 2010). An image of a face appeared displaying one of the six facial expressions of sadness, happiness, fear, surprise, disgust, or anger. Each image was followed by an image of the same face and emotion and was accompanied by a narration describing key facial features, with arrows pointing to these features (Ekman, 2003). For example, key features of sadness were described on a face by pointing out that the corners of the lips are pulled slightly down and the eyebrows are raised. While the image of a face depicting sadness was displayed on the computer screen, the participant heard the description: "The arrows on this sad face show how the lip corners are pulled down slightly and the eyebrows are raised." Arrows appeared on the face pointing to the corresponding corners of the lips and the eyebrows. The facial expression treatment intervention videos comprised approximately two minutes of each session.

The second treatment intervention utilized an emotion and empathy video treatment (EEVT) that showed short videos to teach complex emotions and empathy from *Mind Reading: The Interactive Guide to Emotions* (Baron-Cohen, 2003). We chose the "Mind Reading Interactive Guide to Emotions" as one of our trainings because of its substantial evidence with individuals with ASD (LaCava, Golan, Baron-Cohen, & Smith Myle, 2007; Ramdoss, Machalicek, Rispoli, Mulloy, Lang, & O'Reilly, 2012; Thomeer et al., 2015; Weinger & Depue, 2011). and the specific instruction it provides for emotions tied to empathy using photos and embedded short videos taken from a library of 400 emotions coinciding with faces, voices, and emotion-word descriptions. An emotion word was presented in black text against a white background for 3 seconds, followed by another white background with black text. The text provided a written and narrated description of the emotion word until the participant clicked the space bar to advance to the next screen. Next, a brief, narrated video was shown that described the emotion and showed actors depicting a scenario illustrating the emotional state and how the individuals involved might respond. The narrator of these video examples also drew attention to the actors' facial and body expressions and their emotional states based on the scenario portrayed. A total of 11 different emotion words were presented at each session, with a total duration of eight minutes.

The third treatment intervention used video modeling (VM), which was chosen because of its evidenced use with individuals with ASD (Bellini & Akullian, 2013; Delano, 2007; Sansosti & Powell-Smith, 2008; Thiemann & Goldstein, 2001). VMs were taken from *The Science of Making Friends* (Laugeson, 2013), which were developed in conjunction with the evidence-based Program for the Education and Enrichment of Relational Skills (PEERS®) (Laugeson & Frankel, 2010) to allow participants to witness step-by-step rules for social conversation and how to respond to others across numerous social settings. A total of 24 videos were presented over the two sessions for an approximate total of 11 minutes at each session. Each video contained a brief, verbal introduction discussing a specific social skill, followed by actors demonstrating the social interaction (e.g., models of social interactions for how to enter and leave conversations, deal with arguments, or use eye contact during conversations).

When combining time for initial and mid-point assessments for mood and/or physical sensations along with the time for social treatment intervention tasks, the total time for each participant to complete each session was approximately 30 minutes, allowing for termination of verum tDCS delivery to coincide with the completion of the social treatment intervention tasks.

Within one hour after completion of the transcranial stimulation, including all social treatment interventions, participants completed post-assessment tests, including the TASSK-M and the VF test (Sass, Heim, Fetz, Oetken, & Habel, 2013). Because we felt the VF test could be particularly susceptible to practice effects, it was only administered during post-assessment. The VF test required participants to verbally generate lists of items under time constraint (one minute per category) for two semantic categories (furniture or vegetables) and emotion categories from the six emotions: sadness, happiness, fear, surprise, disgust, and anger. Participants were also given two minutes to provide items one-at-a-time for two emotion categories (fear and disgust) while switching back and forth between the two categories after each item provided. Participants were instructed not to use repetitions of the same word with different endings (e.g. *apple, apple-pear,* etc.) and that different suffixes did not constitute different words (e.g. *carrot, carrots*). If words were repeated during the test or repeated with a differing suffix, these responses were eliminated from the total score. Because of the complexity of verbally generating items for emotion categories, participants were instructed that they could respond using single words or short phrases. Single words or short phrases were both counted as one item for scoring.

Statistical Analysis

There is a substantial amount of heterogeneity in the ASD population (Jeste & Geschwind, 2014), often making it difficult to find suitably matched controls to complete studies. We addressed this difficulty by using a within-subjects, repeated measures design, which allowed participants to act as their own controls over the two randomly assigned (verum or sham), double-blinded sessions. Because of our small sample size, a Wilcoxon signed-rank test model was utilized to examine if group differences existed (sham tDCS, verum tDCS). The Wilcoxon signed-rank test is used with a repeated-measures design where the data is paired, and the test is considered nonparametric, so minimal assumptions need to be made about the data, such as it being normally distributed (Whitley & Ball, 2002). All procedures were two-tailed with an alpha level set at .05. Primary outcome measures considered were (1) scores from the TASSK-M with a total of 26 points possible and (2) VF test score where each item that was accurately provided was scored as one point for the designated semantic or emotion category, as well as for each accurate switch between emotion categories on the switching task. We then conducted a *post hoc* analysis again using the Wilcoxon signed-rank test on five other comparisons, verum vs. sham tDCS on each of the three portions of the VF test (emotion word, semantic, and emotion word switching), and the TASSK-M baseline vs. verum tDCS and baseline vs. sham tDCS. Each of these five comparisons was then analyzed with a Bonferroni correction for multiple comparisons with the statistical significance tested at an alpha level of .007 (.05/7).

Results

Of the six participants who sought to participate in the study, all met screening criteria and completed both visits for the study. No significant changes in mood or pain were reported from either the verum or sham tDCS sessions, with none of the participants reporting more than 25% of their responses on the MQ with negative changes in mood (e.g., moving from "moderately" to "extremely" in response to a question such as "indicate the extent to which you feel irritable"), or reporting a 7 or higher (on a 10-point Likert scale) on any item of the PS questionnaire (assessing sensations of itching, tingling, and heat). Additionally, examination of mean participant rating scores from the PS questionnaire (assessing tingling, burning, and itching sensations) showed no significant differences when comparing verum to sham sessions (p=0.38). Information collected from the self-report screening questionnaire for participant demographics (e.g. age, gender), history (e.g., depression, anxiety, attention deficit), and characteristics (AQ, Shipley-2 scores) is summarized in Table 1.

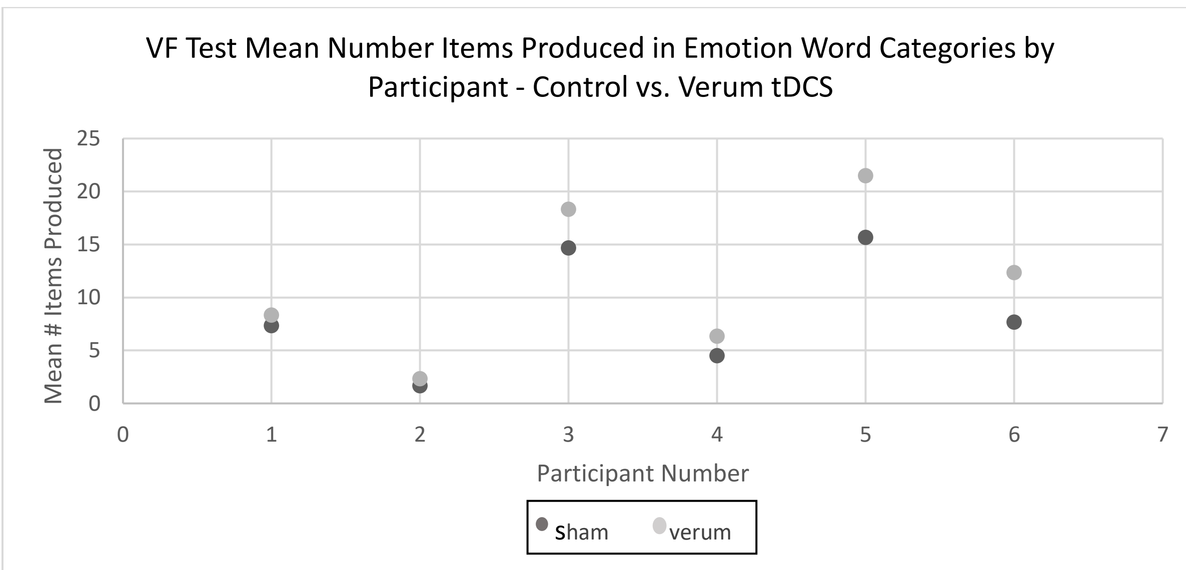
Table 1. Participant demographics, history, and characteristics

DEMOGRAPHICS	
n	6
Gender (M/F)	(4/2)
Age, mean years (SD, range)	28.3 (15.4, 18-58)
HISTORY	
category name	# of participants reporting (% of total)
Depression	4 (67)
Anxiety	4 (67)
Attention deficit	1 (17)
Hospitalization for psychiatric disorder	0 (0)

Current medication use:	
depression	2 (33)
anxiety	0 (0)
Previous use of tDCS	0 (0)
Illicit drug user	0 (0)
Caffeine	
regular user	2 (33)
used during study	2 (33)
Cigarette or other nicotine	
regular user	0 (0)
used during study	0 (0)
Alcohol	
regular user	2 (33)
used during study	0 (0)
CHARACTERISTICS	
AQ score mean (SD)	35.17 (3.19)
Shipley-2 standard score mean (SD)	98 (18.45)

M/F=male/female; SD=standard deviation; tDCS=transcranial direct current stimulation; AQ=Autism Quotient

Wilcoxon signed-rank tests for paired data indicated that participants received a significantly higher score on the VF test Z = -4.47, $p < 0.00$, $r = 1.82$ after receiving verum tDCS compared to sham tDCS, with no significant difference found on the TASSK-M, p =.22. *Post hoc* analysis using Wilcoxon signed-rank tests of the three different portions of the VF test (emotion word, semantic word, and emotion word switching) showed that participants received a significantly higher score on the VF test emotion word portion Z = -4.28, $p < 0.00$, $r = 1.75$, with nearing significance for the VF test emotion word switching portion Z = -1.8998, $p < 0.06$, $r = .77$, after receiving verum tDCS compared to sham tDCS. There was no significant difference when comparing verum to sham tDCS found on the VF test semantic word portion, p = .89. Differences between baseline and verum tDCS on the TASSK-M were nearing significance Z = -1.89, $p < 0.06$, r = .77, with no significant difference on the TASSK-M when comparing baseline to sham tDCS, p = .92. Bonferroni correction for multiple comparisons on all *post hoc* analysis indicated significant differences when comparing verum to sham tDCS conditions on the emotion word portion of the VF test ($p < 0.007$ with the Bonferroni correction). Findings for the emotion word portion of the VF test are depicted in Figure 2.



-

Figure 2. A significant difference was found between verum and sham conditions for mean scores on the verbal fluency (VF) test for emotion word portion ($p < 0.00$). Verum and sham scores are shown for each participant.

Efforts were made to minimize practice effects by spacing sessions seven days apart and randomizing assignment of verum or sham tDCS between visit one and visit two. Nonetheless, to evaluate potential practice effects on the VF task, we compared lists of items provided from visit one and visit two and found that 13% of the items were repeated at the second visit in emotion categories, 24% in semantic categories, and 14% on the emotion category switching task. Additionally, we examined scores to see if they were higher at the second visit, regardless of tDCS condition, to find out if participants were improving from practice. When using a paired-sample t-test, no significant difference was found between first and second visit VF scores in categorizing emotion categories (p = 1.00), semantic categories (p = .890), or the switching task (p = .359).

Discussion

The present study compared the effects of verum (2.0 mA for 30 minutes) to sham tDCS (2.0 mA for 30 seconds) on measures of social cognition and social skills in adults with ASD with normal or higher cognitive functioning. Our pilot findings provide an initial proof-of-concept model for the use of social skills treatment interventions paired with tDCS to the rTJP to improve empathy and emotion-based verbal fluency.

Functional neuroimaging studies have shown the rTPJ plays a critical role in higher-level social cognitive processes, such as empathy and ToM (Sellaro et al., 2016), as well as lower-level social cognitive processes, such as processing of one's own emotional state in reference to others based on sensory information from the environment (Decety & Lamm, 2007; Moseley et al., 2015). Our results are consistent with these findings.

In our study, the Shipley-2 (Shipley et al., 2009) mean score for participants was 98, indicating average or above cognitive functioning, often referred to as "high-functioning" ASD (Hofvander et al., 2009). The majority of individuals with high-functioning ASD also score a 32 or higher on the AQ (Baron-Cohen et al., 2001), which is consistent with participants of the present study who had a mean score of 35.2. Adults with high-functioning ASD display differences in processing during verbal fluency tasks, with difficulty found on verbal fluency tasks involving social/emotional elements (Spek, van Ham, & Nyklíček, 2013), as well as with emotion perception and verbal generativity (Otsuka, Uono, Yoshimura, & Zhao, 2017). Additionally, recent electroencephalographic (EEG) findings show emotion words are processed differently than non-emotion words, pointing to specific contributions of the rTPJ in processing words with emotional content (Rochas, Rihs, Rosenberg, Landis, & Michel, 2014**)**. The VF test measured participants' abilities to quickly generate and categorize items associated with either semantic or emotion categories.

Our study utilized a PS questionnaire at three different points during each session (start, middle, and immediately after tDCS) that provided participant ratings on a Likert scale from 1-10 assessing burning, tingling, and itching. Mean participant rating scores from the PS questionnaire showed no significant differences in physical sensations experienced when comparing verum to sham sessions, indicating that participants were not able to detect whether they were receiving verum or sham stimulation.

Interestingly, while significant differences were found when comparing verum to sham tDCS on the VF test for emotion categories (sadness, happiness, fear, surprise, disgust, and anger), there were no differences in our study for semantic categories (furniture and vegetables), indicating the positive effect of verum tDCS on the rTPJ for specifically generating emotion-based words in high-functioning adults with ASD. One potential explanation is that brain stimulation may correct an excitation/inhibition (E/I) imbalance. Prior research suggests abnormal E/I ratios are present in ASD and this imbalance relates to social dysfunction (Rubenstein & Merzenich, 2003; Yizhar et al., 2011). Regional concentrations of Gamma-aminobutyric acid (GABA) are different in the brains of persons with ASD relative to healthy controls (Coghlan et al., 2012; Gaetz et al., 2014; Mori, Mori, Fujii, Toda, & Miyazaki, 2012; Rojas, Singel, Steinmetz, Hepburn, & Brown, 2014). The same is true for glutamate and glutamine (Glx) (Bernardi et al., 2010; Kubas et al., 2012; Page et al., 2006), with Glx levels correlating to social communication and empathy deficits in ASD (Tebartz van Elst et al., 2014), as well as N-acetylaspartate (NAA) (Chugani, 2012; Endo et al., 2007), a marker of neuronal density and viability (Ebisu, Rooney, Graham, Weiner, & Maudsley, 1994). A meta-analysis of neuroimaging data has identified the TPJ as a region of hypoactivation during social tasks in those with ASD (Martino et al., 2008), suggesting a non-optimal ratio of Glx/GABA in this brain region. TDCS has been found to increase Glx and NAA in brain regions beneath the anode (V. P. Clark, Coffman, Trumbo, & Gasparovic, 2011), and to reduce GABA concentrations (Stagg et al., 2009). Therefore, it is possible that placing the anode over the rTPJ corrected an E/I imbalance, leading to the improvements observed in the current study. This correction of E/I imbalance has previously been suggested as a mechanism by which tDCS induces improvements in a variety of clinical conditions (Krause, Márquez-Ruiz, & Kadosh, 2013).

A limitation of this study is our sample size. It would be worthwhile to complete a larger randomized controlled trial further investigating the use of tDCS paired with social cognition treatment interventions. Additionally, participants in our study self-identified as having ASD, with a score of 32 or higher required on the AQ for participation. Future studies might also confirm diagnosis with a clinical assessment tool. Our study was a pilot to see if combining rTPJ stimulation with social cognition treatment interventions induced benefit. It is important, however, to achieve a stable benefit. Other work indicates this may be possible in the realm of ASD with repeated stimulation sessions (Esse Wilson, Quinn, et al., 2018). Future work may evaluate the impact of repeated sessions on outcome measures and the stability thereof by incorporating a longitudinal component.

Conclusions

Our study investigated the use of anodal tDCS over the rTPJ during social skills treatment interventions with adults with ASD with normal or higher cognitive functioning. Participants completed four computer-based social treatment interventions while verum or sham tDCS was randomly assigned in a within-subjects, double-blinded design over two visits separated by one week. Outcome was assessed using a TASSK-M and a VF test utilizing emotion and semantic categories. Data was analyzed with Wilcoxon signed rank tests to examine if group differences existed. It was predicted there would be differences on these measures when comparing verum tDCS to sham tDCS. Significant differences were found between verum and sham tDCS on the VF test for emotion categories, with approaching significance on the VF test when switching between two emotion categories. There was no significant difference between verum and sham tDCS on the VF test for semantic categories or on the TASSK-M or between verum tDCS and baseline on the TASSK-M. These findings confirm the role for the rTPJ in social cognition and emotion word processing in adults with ASD, and provide optimism for the use of tDCS with treatment interventions for ASD.

Acknowledgments

The authors acknowledge the assistance of Kristen Fedesco and Christopher M. Garcia whose respective assistance with participant recruitment and technology management made this study possible. Funding: This work was supported in part by funding from the University of New Mexico's Graduate Student Professional Association. Sandia National Laboratories is a multi-mission laboratory managed and operated by National Technology and Engineering Solutions of Sandia, LLC., a wholly owned subsidiary of Honeywell International, Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525. Opinions expressed are those of the authors and not necessarily those of the U.S. Government.

Article 3: Improved Performance on the Empathy Quotient (EQ) and Processing of Threatening Facial Emotions in Adults with Autism Spectrum Disorder (ASD) After Transcranial Direct Current Stimulation (tDCS)

(In preparation for submission)

Joan Esse Wilson[a] & Claudia D. Tesche[b]

[a]Department of Linguistics, 1 University of New Mexico, Albuquerque, New Mexico, 87131 USA joanwilson@unm.edu

[b]Department of Psychology, MSC03 2220 1 University of New Mexico, Albuquerque, New Mexico, 87131 USA ctesche@unm.edu

Abbreviations: tDCS, transcranial direct current stimulation; ASD, autism spectrum disorder; rTPJ, right temporoparietal junction; FEP; facial emotion processing

Abstract

Individuals with autism spectrum disorder (ASD) face substantial challenges with empathy (the ability to represent thoughts, desires, beliefs, intentions and knowledge of other individuals) and with recognizing and processing facial emotions. These challenges substantially impact their social interactions with others. Developing skills such as facial emotion recognition and processing (FERP) may be particularly critical for individuals with ASD not only because these skills are considered a first-step towards empathy, but also because of safety concerns specifically stemming from impairments found in ASD for processing threatening facial expressions (e.g., anger, fear). Current treatment interventions for empathy and FERP are extremely time-consuming and laborious to implement, negatively impacting the quality of life of individuals with ASD. Transcranial direct current stimulation (tDCS) may be a promising treatment modality to safely accelerate and/or enhance treatment interventions. This proof-of-concept study investigates the effectiveness of empathy and FERP treatment interventions paired with anodal tDCS for adults with ASD. Differences on the Empathy Quotient (EQ) and on a FERP test were predicted for verum (2.0 mA) vs. sham tDCS. Verum/sham tDCS was randomly assigned in a within-subjects, double-blinded design in adults with ASD with normal or higher cognitive functioning. The anode electrode was placed over right temporoparietal (rTPJ) (CP6) and cathode over ipsilateral deltoid. Data analysis was performed using Wilcoxon signed-rank tests for paired data. Participants received a significantly higher score on the EQ, $Z = -4.47$, $p \leq 0.00$, $r = 1.82$, and had significantly less inaccurate identifications of threatening facial emotion expressions, $Z = -2.37$, $p \leq 0.02$, $r = 0.63$, after receiving verum tDCS compared to sham tDCS. Differences were approaching significance for overall accuracy in identifying the basic six emotions when

comparing verum to sham tDCS, Z = 1.61, $p \leq 0.06$. These results suggest the potential of tDCS paired with treatment interventions for empathy and facial emotion recognition and processing.

Introduction

Autism spectrum disorder (ASD) is now the fastest-growing neurodevelopmental disorder in the United States (Center for Disease Control, 2016), with one recent study showing a prevalence rate as high as 1 in 40 (Zablotsky et al., 2019). Social interaction deficits are a key diagnostic feature for ASD (American Psychiatric Association, 2013). The ability to understand the mental states of others is critical for engaging successfully in social interactions. Immediate communication of mental states is often completed through facial expressions, which are thought to also be a gateway to empathy (Clark, Winkielman, & McIntosh, 2008). Empathy (the ability to represent thoughts, desires, beliefs, intentions and knowledge of other individuals), along with recognizing and processing facial emotions, provide substantial challenges for individuals with autism spectrum disorder (ASD) (Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995). These challenges remain even when controlling for gender, verbal ability, and age, and impact the initiation and maintenance of meaningful relationships (Reichow & Volkmar, 2010), career fulfillment, and factors contributing to isolation, substance use, and depression (Hedley et al., 2016; Hofvander et al., 2009). Individuals with ASD with higher empathy abilities show improved social relationships and overall social functioning (Baron-Cohen & Wheelwright, 2004), thus indicating the importance of developing effective and efficient treatment interventions for improving empathy-related skills.

Developing empathy-related skills, such as facial emotion recognition and processing (FERP), may be particularly critical for individuals with ASD, not only because of the impact these deficits have on quality of life, but also because of safety concerns stemming from specific impairments found in ASD for processing threat-based facial expressions (e.g., anger, fear) compared to other basic emotions (e.g., happy, sad, surprise, disgust) (Ashwin, Chapman, Colle, & Baron-Cohen, 2007; Krysko & Rutherford, 2009). The perception of emotional stimuli that may indicate a threat is thought to be involved with a human biological system for vigilance (Ohrmann et al., 2007). For example, a fearful expression may need to be processed rapidly and efficiently as a threatening warning signal to allow time for humans to modify their actions for self-preservation.

Current, evidence-based treatment interventions that target empathy and FERP abilities include computer-based interactive formats for recognizing complex emotions and mental states (Golan & Baron-Cohen, 2006), teaching empathic communication skills using a visual framework and video-feedback (Kern Koegel, Ashbaugh, Navab, & Koegel, 2016), and using a caregiver-mediated, manualized intervention for improving empathy and social cognition (Laugeson et al., 2015). The number of available interventions with evidence remains scarce, especially for adults with ASD. Additionally, existing interventions are extremely time-consuming and laborious to implement, further highlighting the need to discover ways to improve the delivery of treatments.

One possible way to improve delivery of treatment interventions is to pair them with transcranial direct current stimulation (tDCS) (Gill et al., 2015). Studies utilizing tDCS in neurotypical individuals have demonstrated improvements on empathy-related tasks, such as perspective taking and evaluation of self against others (Santiesteban et al., 2012) and for inferring others' mental states when identifying deception (Sowden, Wright, Banissy, Catmur, & Bird, 2015) or moral judgments (Ye et al., 2015).

Improvements for FERP have been demonstrated after tDCS was applied over the cerebellum (Ferrucci et al., 2012), the right orbital frontal cortex (Willis, Murphy, Ridley, & Vercammen, 2015), and over the superior temporal cortex (Boggio et al., 2008). However, the act of recognizing a facial emotion differs from processing that emotion, with processing requiring the brain to complete more than just a recognition task, but also an in-depth analysis of emotional perceptual stimuli (Adolphs, 2003; Krysko & Rutherford, 2009). The requirements for a multi-level analysis of emotional perceptual stimuli as well as for broad social cognition suggests the usefulness of applying tDCS over the right temporoparietal junction (rTPJ) during treatment interventions for FERP and empathy.

The rTPJ is part of a large-scale neural network for social cognition (Kennedy & Adolphs, 2012). It contributes lower-level processing of environmental sensory-perceptual stimuli, such as discriminating between self and others, as well as higher-level social-cognitive processing, such as perspective-taking, empathy and theory of mind (ToM) (Decety & Lamm, 2007). The rTPJ is also specifically associated with deficits in ToM in individuals with ASD (Lombardo et al., 2011). Anodal tDCS applied over the rTPJ in neurotypical individuals shows improved social functioning on tasks for perspective taking and evaluation of self against others (Santiesteban et al., 2012), These findings suggest that altering the cortical excitability of the rTPJ with tDCS may influence performance on tasks used during social cognition in healthy individuals. There are currently no studies examining the use of tDCS paired with treatment interventions that target FERP for threatening facial expressions or empathy with individuals with ASD.

The objective of the present study is to investigate the effect of combining anodal tDCS over rTPJ paired with computer-based social cognition treatment interventions on measures of the Empathy Quotient (EQ) and FERP test with adults with ASD. We hypothesize that participants will demonstrate (1) higher scores on the EQ, (2) a reduction of inaccurate identifications on a FERP test for threat expressions, and (3) increased accuracy on the FERP test overall, after receiving verum tDCS compared to sham tDCS.

Materials and Methods

Participants

Study procedures were approved by the Human Research Protections Office of the University of New Mexico. Seven right-handed, English-speaking adults (two females) with ASD, mean age of 26.1 years. See Table 1 for complete participant demographics. Participants were recruited by word of mouth and flyer postings at the University of New Mexico (UNM) campus, the UNM Accessibility Resource Center, and through a posting to the Autism Speaks® *Participate in Research* webpage.

Table 1. Participant demographics, history, and characteristics

DEMOGRAPHICS	
n	7
Gender (M/F)	(5/2)
Age, mean years (SD, range)	26.1 (18-58)
HISTORY	
category name	# of participants reporting (% of total)
Depression	4 (57)
Anxiety	4 (57)
Attention deficit	1 (14)
Hospitalization for psychiatric disorder	0 (0)
Current medication use:	
depression	2 (29)
anxiety	0 (0)
Illicit drug user	0 (0)
Caffeine	
regular user	2 (29)

used during study	2 (29)
Cigarette or other nicotine	
regular user	0 (0)
used during study	0 (0)
Alcohol	
regular user	2 (29)
used during study	0 (0)
CHARACTERISTICS	
AQ score mean (SD)	36.14 (3.89)
Shipley-2 standard score mean (SD)	97 (16.95)

M/F=male/female; SD=standard deviation; tDCS=transcranial direct current stimulation; AQ=Autism Quotient

Procedure

Participants attended two sessions spaced seven days apart at the University of New Mexico and followed the procedure of our previous study examining tDCS with social functioning and social cognition (Esse Wilson, Trumbo, et al., 2018). Similar to that study, participants were also screened for ASD with the Autism Quotient (AQ) (Baron-Cohen et al., 2001), a reliable instrument that measures the degree adults with normal intelligence display social/behavioral traits associated with ASD (Hoekstra et al., 2008; Ruzich et al., 2015). The AQ is one of the most widely used instruments in the world for quantifying autistic traits, with cross-cultural, multiple-language versions existing in Chinese, French, Dutch, Italian, Japanese, Persian, and Polish. It has been found to demonstrate good psychometric properties and to adequately distinguish people with ASD from those without ASD (Lundqvist & Lindner, 2017; Zhang et al., 2016). The AQ has been used successfully for clinical screening, as well as to predict outcomes on topics as diverse as social cognition to spontaneous facial mimicry to auditory speech perception. Additionally, based on research demonstrating that 80% of adults with ASD with normal or above cognitive functioning score a 32 or above on the AQ (Baron-Cohen et al., 2001), we required a score of 32 or higher on the AQ for study participation. Last, participants were screened for right-handedness with the Edinburgh Handedness

Inventory (Oldfield, 1971) and for cognitive function with the Shipley-2 (Shipley et al., 2009), a standardized measure where a standard score of 70 or higher was required on the Shipley-2 for study participation.

Two pre-treatment-intervention tests were administered in randomized order: (1) The Empathy Quotient (EQ) (Baron-Cohen & Wheelwright, 2004), and (2) a FERP test.

The EQ is a 60-item measure for global empathy (Baron-Cohen & Wheelwright, 2004; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004) consisting of statements about empathic skills which are rated on a 4-point Likert scale (strongly agree, slightly agree, slightly disagree, and strongly disagree). It has shown validity and reliability for measuring cognitive empathy, emotional reactivity, and social skills (Lawrence et al., 2004), both trait and state components of empathy (Baron-Cohen & Wheelwright, 2004), processes of empathy (Reniers et al., 2012), and an individual's beliefs about their own empathy (Baron-Cohen & Wheelwright, 2004). The EQ also encompasses differing aspects of empathy, such as empathic concern and perspective taking. Additionally, the EQ has been validated cross-culturally and cross-linguistically in Brazil (Gouveia, Milfont, Gouveia, Neto, & Galvão, 2012), Serbia (Dimitrijević, Hanak, Vukosavljević-Gvozden, & Opačić, 2012), the Netherlands (Groen, Fuermaier, Den Heijer, Tucha, & Althaus, 2015), France (Berthoz, Wessa, Kedia, Wicker, & Grèzes, 2008), the French-speaking part of Canada (Lepage, Lortie, Taschereau-Dumouchel, & Théoret, 2009), Japan (Wakabayashi et al., 2007), Korea (Kim & Lee, 2010), and Italy (Preti et al., 2011).

The FERP test consists of 48 trials where participants view neutral and emotional photographic images taken from the NimStim set of normed, multi-cultural male and female facial emotion expressions (Tottenham et al., 2009). We designed the FERP test using a neutral-emotion-neutral presentation of faces (Matsumoto & Hwang, 2011) with each trial first presenting a face showing a neutral expression for 1000 milliseconds (ms), followed by an emotional image of the same face presented for 1000 ms showing one of the six facial emotion expressions of sadness, happiness, fear, surprise, disgust, or anger (Ekman, 2003), followed by another 1000 ms of the same face in a neutral expression. The participant was then asked to identify from a multiple-choice list which of the six emotions had been presented. The goal of the FERP test was to access participants' higher-level, emotion-based cognitive processes, rather than measuring participants' abilities to identify 'micro expressions' (facial emotions presented for < 250 ms) or participants' ability to use compensatory strategies for facial emotion recognition (Harms, Martin, & Wallace, 2010).

After pre-treatment-intervention tests were completed, we followed the same procedures for administration of tDCS paired with social functioning and social cognition treatment interventions as in (Esse Wilson, Trumbo, et al., 2018). This included the administration of two questionnaires during both verum and sham tDCS: (1) a mood questionnaire (MQ) administered twice to detect any mood changes (given within first minutes of stimulation and immediately after termination of stimulation), and (2) a physical sensations (PS) questionnaire to detect levels of itching, heat, and tingling (taken at three separate time points - first minutes of stimulation, approximately 10 minutes after start of stimulation, and immediately after termination of stimulation). Receipt of tDCS and treatment interventions was followed by administrations of the EQ and FERP test. A timeline summarizing study's pre-stimulation, stimulation, and post-stimulation activities is depicted in Figure 1.

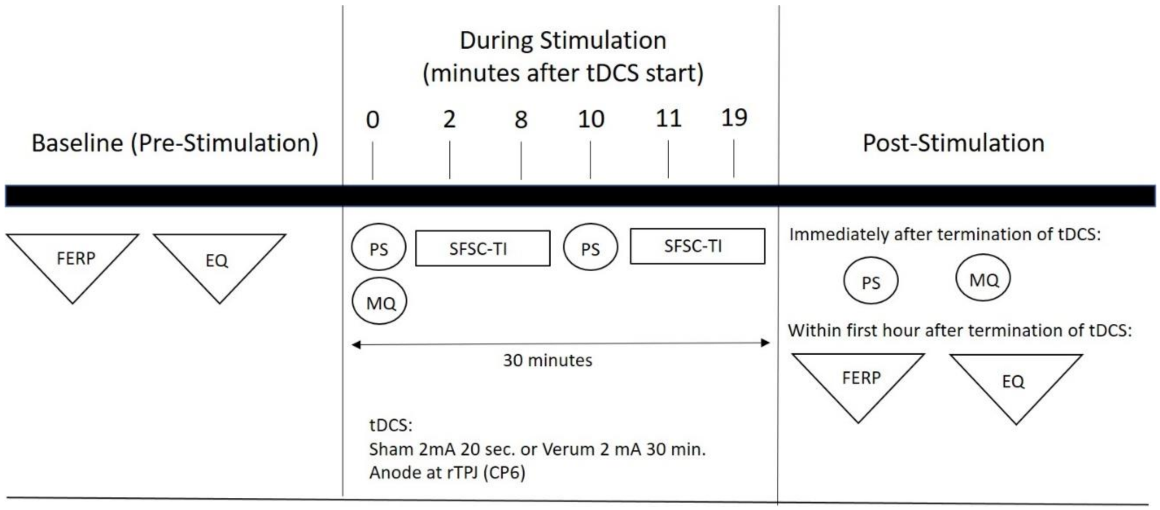


Fig. 1 Timeline summarizing study's pre-stimulation, stimulation, and post-stimulation activities where items in triangles are measures where FERP = Facial Emotion and Recognition and Processing test, and EQ = Empathy Quotient; items in circles are questionnaire assessments where PS refers to physical sensation questionnaire and MQ to mood questionnaire; and items in rectangles refer to treatment tasks where SFSC-TI = social functioning and social cognition treatment interventions.

Statistical Analysis

Due to the high level of heterogeneity in the ASD population (Jeste & Geschwind, 2014), we used a within-subjects, repeated-measures design, which allowed participants to act as their own controls over the two randomly assigned (verum or sham), double-blinded sessions. A Wilcoxon signed-rank test was utilized to examine if group differences existed (verum tDCS, sham tDCS). This test is considered nonparametric, so minimal assumptions needed to be made about the data, such as it being normally distributed, and it is well-suited for repeated-measures with paired data (Whitley & Ball, 2002). Analyses were two-tailed with an alpha level set at 0.05.

Results

Of the seven participants who participated in the study, all met screening criteria and completed both visits for the study. No significant changes in mood from the MQ or pain from the PS questionnaires were reported from either the verum or sham tDCS sessions. Additionally, examination of mean participant rating scores from the physical sensation questionnaire (PS) assessing tingling, burning, and itching sensations showed no significant differences when comparing verum to sham sessions (p=0.39). Participants received a significantly higher score on the EQ, Z = 4.47, $p \leq 0.00$, r = 1.82, and had significantly less inaccurate identifications of threatening facial emotion expressions, Z=2.37, $p \leq 0.02$, r = 0.63, after receiving verum tDCS compared to sham tDCS. Differences were approaching significance for overall accuracy in identifying the basic six emotions when comparing verum to sham tDCS, Z = 1.61, $p \leq .06$. Findings for the EQ and inaccurate identifications of threatening facial emotion expressions are depicted in Figures 1 and 2.

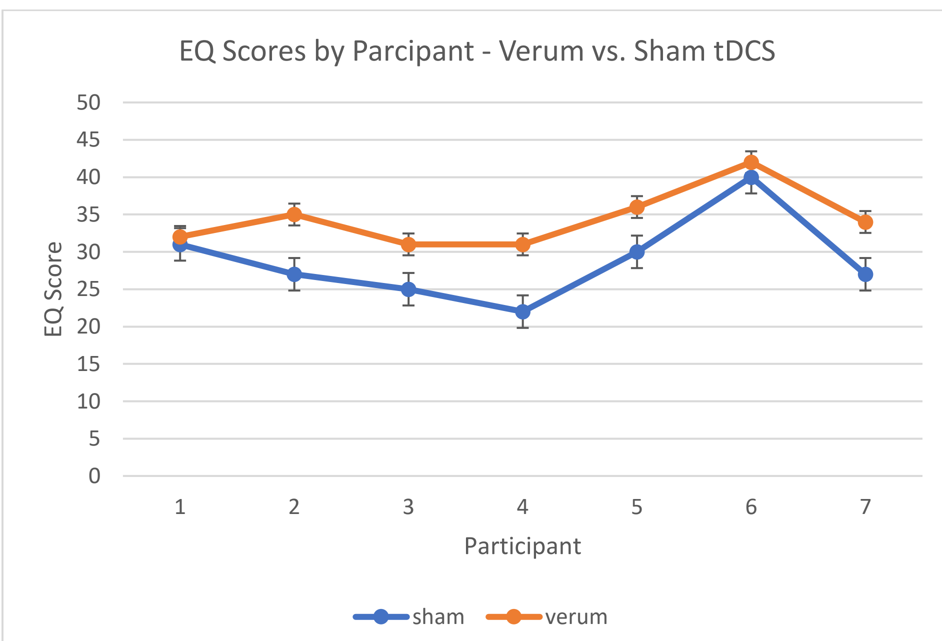


Fig. 1 A significant difference was found between verum and sham conditions for scores on Empathy Quotient (EQ) ($p \leq 0.00$). Verum and sham scores are shown for each participant.

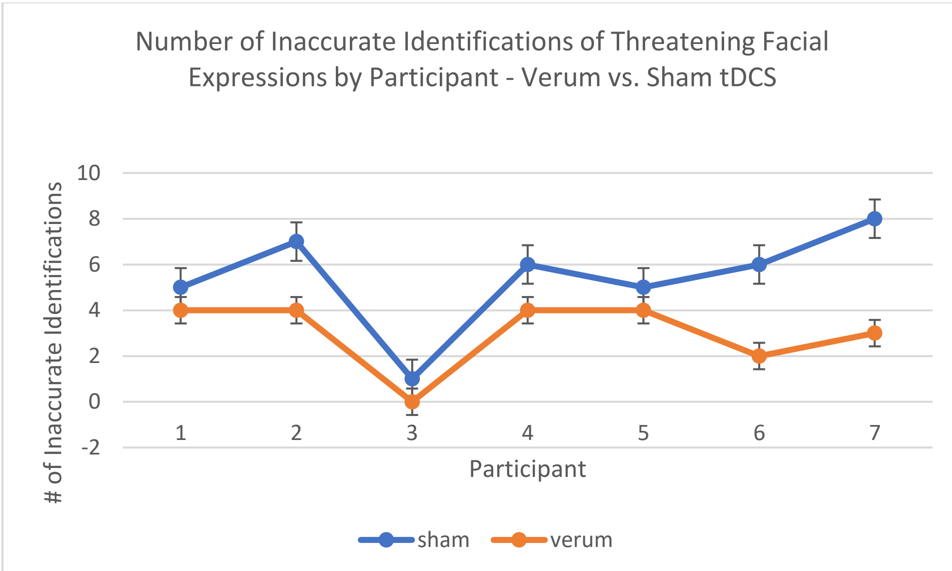


Fig. 2 A significant difference was found between verum and sham conditions for number of inaccurate identifications of threatening facial emotion expressions ($p \leq 0.02$). Verum and sham scores are shown for each participant.

Discussion

The present study compared the effects of a computer-based social cognition and social functioning treatment intervention paired with tDCS applied over the rTPJ (2.0 mA for 30 minutes) to sham tDCS (2.0 mA for 30 seconds) on measures of empathy (EQ scores) and FERP (testing overall recognition accuracy from briefly presented images, as well as accuracy on recognition of threat expressions) in adults with ASD with normal or higher cognitive functioning. It was hypothesized that participants would demonstrate (1) higher scores on the EQ, (2) reduction of inaccurate identifications on the FERP test for threat expressions, and (3) increased accuracy on the FERP test as a whole, after receiving verum tDCS compared to sham tDCS. Our hypothesis was correct for (1) and (2) with participants scoring significantly higher on the EQ and also reducing the number of inaccurate identifications for threat expressions on the FERP test after verum tDCS when compared to sham tDCS. Our hypothesis for (3) was found incorrect, although differences were approaching significance. These findings provide support for a preliminary proof-of-concept model for the use of social cognition and social functioning treatment interventions paired with tDCS on the rTJP for reducing inaccurate identifications of facial expressions depicting threat (fear, anger) and for increasing empathy skills.

The results of our study suggest that treatment interventions can be effective when using tDCS to modulate neural processing while simultaneously building skills and strategies for FERP and empathy. These findings are supported by studies demonstrating that some individuals with ASD are able to show improvement on measures of facial emotion recognition, despite a continued underlying presence of atypical neural processing (Harms et al., 2010; Krysko & Rutherford, 2009). These improvements are thought to be the result of the development of compensatory strategies. In our study we directly facilitate the development of strategies for FERP and capitalize on the relationship of FERP to empathy (Clark et al., 2008), while also utilizing tDCS over the rTPJ to additionally target underlying neural processing.

Because facial expressions convey emotion, previous studies utilizing tDCS have targeted brain regions known for facial emotion recognition, such as the right orbitofrontal cortex (Willis et al., 2015), the superior temporal cortex (Boggio et al., 2008), or the posterior superior temporal sulcus (Harms et al., 2010). While anger and fear facial expressions may also implicate these brain regions, in the context of our study anger and fear are expressions that represent the complexity of a threat, thus also requiring emotional processing found in the rTPJ. Our findings support this theory and the role of the rTPJ for empathy and facial emotion processing in adults with ASD, which is an extension of previous research utilizing tDCS on the rTPJ to improve emotion processing during emotional verbal fluency tasks with adults with ASD (Esse Wilson, Trumbo, et al., 2018). Future directions may utilize tDCS on the rTPJ with individuals with ASD to examine emotion processing of facial and body expressions, as well as emotion-based words and phrases, that convey threat. Additionally, future research may incorporate tDCS applied over other brain regions, such as the orbitofrontal cortex, the superior temporal cortex, or the posterior superior temporal sulcus, in conjunction with treatment interventions for social functioning and social cognition. While the present study includes empathy and FERP measures, future studies might also investigate utilizing measures specific to ToM.

While this study is a proof-of-concept pilot, a limitation is our sample size, suggesting the usefulness of completing a larger randomized controlled trial to further investigate the use of tDCS paired with social function and social cognition treatment interventions. Additionally, participants in our study self-identified as having ASD, with a score of 32 or higher required on the AQ for participation. Future studies might also confirm diagnosis with a standardized clinical assessment tool. Last, use and safety of tDCS with children (Ciechanski & Kirton, 2017; Palm et al., 2016) suggests that a future direction of this study may be to extend participation to adolescents.

Conclusions

Our study investigated the use of anodal tDCS over the rTPJ during a computer-based social cognition and social functioning treatment interventions with adults with ASD with normal or higher cognitive functioning. Verum or sham tDCS was randomly assigned in a within-subjects, repeated-measures, double-blinded design over two visits separated by one week. Outcomes were assessed using the EQ and a FERP test. Data were analyzed using a Wilcoxon signed-rank test for paired data to examine if group differences existed (verum tDCS, sham tDCS). It was predicted there would be differences on these measures when comparing verum tDCS to control tDCS. Participants received a significantly higher score on the EQ and had significantly less inaccurate identifications of threatening facial emotion expressions after receiving verum tDCS compared to sham tDCS. These findings confirm the role for the rTPJ in empathy and FERP in adults with ASD and provide optimism for the use of tDCS with social cognition and social functioning treatment interventions.

Acknowledgments

Funding: This work was supported in part by funding from the Grice Foundation and from the University of New Mexico's Graduate Student Professional Association.

Dissertation Conclusions

The results of the studies that comprise the three articles of this dissertation suggest that treatment intervention paired with verum, anodal tDCS delivered over the rTPJ is useful for improving social cognition and social functioning for individuals with ASD. These results have theoretical implications that fall within a Language in Motion Framework (Wilcox, 2012). The foundational claim of this framework is that language and gesture are manifestations of a general human expressive ability which is grounded in embodied cognition and the need for humans to make sense of their environment. The Framework rests on three pillars: (1) To explain how language and gesture are implemented in the brain as skilled action, a theory of cognitive neuroscience is required, (2) language is a skilled action that occurs within a dynamic, real-time process as we use language in the world, and (3) language is embodied, with meanings being shaped by physical forces as we utilize sensorimotor and emotional capacities to move, perceive, and act on the world. Each of these three pillars is discussed in terms of the findings of this dissertation.

Pillar 1 – A Cognitive Neuroscience Explanation: tDCS-Induced Neural Modulation to the rTPJ with Individuals with ASD Affects Social Functioning and Social Cognition Performance

In the Language in Motion Framework, to account for how language and gesture are implemented in the brain as skilled action, a theory of cognitive neuroscience is required (Wilcox, 2012). In each of the three studies that comprise this dissertation, tDCS-induced neural modulation improved performance on differing aspects of social functioning and social cognition. This suggests that these cognitive processes are susceptible to neural modulation by tDCS, a tool of neuroscience. This view is supported by studies showing other cognitive processes have been susceptible to tDCS-induced modulation, such as improvements in individuals with aphasia (difficulty with speech or language after a head injury or stroke) on naming tasks (Monti et al., 2008; J. Wang, Wu, Chen, Yuan, & Zhang, 2013; Wu, Wang, & Yuan, 2015), auditory comprehension, and word repetition tasks (Wang et al., 2013), as well as with individuals with a traumatic brain injury (TBI), finding tDCS-induced improvements in working memory and attention (Ulam et al., 2015), skills both necessary for language. However, only a limited number of tDCS studies have been completed with individuals with ASD, with these focusing on delivering stimulation to the dorsolateral prefrontal cortex (DLPFC), with a range of positive results also found including decreased levels of hyperactivity (D'Urso et al., 2015, 2014), behavior (Amatachaya et al., 2014, 2015), and increased syntax acquisition (Schneider & Hopp, 2011) and sociability (Amatachaya et al., 2014, 2015). Two studies have been completed investigating the use of tDCS with individuals with ASD showing improved performance on social functioning measures (Esse Wilson, Quinn, et al., 2018) and measures for emotional verbal fluency (Esse Wilson, Trumbo, et al., 2018) after receipt of tDCS applied on the rTPJ.

The rTPJ participates in a large-scale neural network for social cognition (Kennedy & Adolphs, 2012), playing a critical role in higher-level social cognitive processes, such as empathy and theory of mind, as well as during lower-level social cognitive processes, such as processing sensory stimuli from the environment (Decety & Lamm, 2007). In this sense, the role of the rTPJ in FERP suggests that this brain region is capable of processing facial emotions by utilizing higher-level social cognitive processing, while also processing detailed facial features from environmental stimuli as a lower-level social cognitive process.

Treatment interventions are time-consuming and laborious to complete. The goal of the studies of this dissertation was to demonstrate how tDCS paired with treatment interventions may accelerate and/or enhance learning for social functioning and social cognition. While tDCS has been shown to modulate neural activities in the stimulated and interconnected regions of the brain (Antal, Terney, Kühnl, & Paulus, 2010), it does not induce actual neuronal firing. However, tDCS does have the ability to induce cortical excitability, suggesting that pairing tDCS with treatment interventions for individuals with ASD may help facilitate improvements through the theory of neuronal group selection or “neural Darwinism” (Edelman, 2017), where Edelman said, “…it becomes that neurons that are connected, even at a distance, that fire together will... will influence which neurons wire together.” That is, using tDCS to increase cortical excitability while the brain simultaneously learns and build skills for social functioning and social cognition may ‘wire together’ and facilitate new patterns of neural activity specific to these processes.

Pillar 2 - Language is a Skilled Action Occurring Within a Dynamic Process: Treatment Interventions are Effective Because They Occur Inside of Usage-Based, Dynamic Systems

The Language in Motion Framework describes language as a dynamic, real-time process where meanings are conceptualized as we use language in the world and develop meaning-form pairings that become symbols (Langacker, 2008; Wilcox, 2012).

Language is skilled behavior (Bolinger, 1968), which allows evidence-based treatment interventions to build specific social language skills, allowing an individual with ASD to build up their linguistic system through association and layering of perceptual events for the purpose of extracting commonalities and interpreting them within the context of previously existing structures. Because this process is occurring inside a disorder, the extractions and interpretations may end up being formed as a collection of information gathered from sensory input that wasn't salient to interpreting the communicative intent. New experiences continue to associate with previous ones through the same process. The disordered system continues to run and build experiences and associations.

Several cognitive processes impact linguistic structure: categorization, identifying tokens as an instance of a particular type, the formation of sequential units through repetition, stored memory from experience, and mapping novel events to existing experiences (Bybee, 2010). These processes begin when infants engage with their environment through daily interactions with caregivers. Infants with ASD display preference for directing eye gaze to toys rather than to people and exhibit deficits in social attention and eye contact (Bhat, Galloway, & Landa, 2010). The quality of future social exchanges may be impacted early in the life of an infant who begins to exhibit these ASD characteristics. Caregivers may unintentionally engage in fewer exchanges of eye contact with an infant who is more focused on toys than an infant who is focused on people. In a cognitive, usage-based linguistic model, this difference in exchange may begin a process of reduced formation of sequential units through repetition, similarly reduced stored memories from experience will then impact the mapping of novel events to existing experiences necessary for developing functional FERP skills.

The mind responds to repetition, specifically formation of sequential units through repetition (Bybee, 2006). Individuals with ASD demonstrate atypical eye gaze fixation (Baron-Cohen et al., 1995), where eye gaze is directed to view facial features that aren't most-salient to the communication exchange. When this occurs, the sequential units of information that are repeating are gathered from eye gaze fixations on facial features that are only peripherally related to the salient messages from the social exchange.

Treatment interventions often utilize explicit repetition of sequential units with the goal of building new experiences recognizing information that is key to the message. In the case of complex, dynamic systems, treatment intervention can be thought of as moving someone's attractor basins (collections of perceptual events and extracted commonalities) through a form of manual manipulation (Spivey, 2007). In a dynamic system in a state of constant movement, treatment intervention offers a form of engineered cognitive routine based on input from an intentionally repetitive delivery format, supporting the theory that the effectiveness of treatment interventions is only explained through cognitive, usage-based theory and language as a skilled action, which are key components of a Language in Motion Framework (Wilcox, 2012).

For example, accurately understanding emotions and mental states is key to engaging in social interactions with others (Baron-Cohen, 2003). Development of these skills is core to an individual with ASD's ability to empathize or engage in ToM (Golan & Baron-Cohen, 2006; Wellman & Liu, 2004). Studies 2 and 3 used the *Mind Reading Interactive Guide to Emotions,* an evidence-based treatment intervention for understanding emotions and mental states that utilizes interactive media (LaCava, Golan, Baron-Cohen, & Smith Myle, 2007; Thomeer et al., 2015; Weinger & Depue, 2011). Participants saw randomly presented emotion vocabulary words on a computer screen and heard an audio reading of the word. Each emotion vocabulary word was then followed by a brief video that depicted a scene acting out a situation based on the word accompanied by an audio definition and description of the salient aspects of the scene. The use of visual and audible input, along with written words and real-world scenarios, was intended to provide repetitive input for building perceptual events and extracted commonalities that are based on effective communication models.

Similarly, studies 1-3 utilized portions of video-modeling of specific social interactions, which has demonstrated effectiveness for teaching social functioning (Delano, 2007; Sansosti & Powell-Smith, 2008; Thiemann & Goldstein, 2001). The use of a video model allows participants to witness sequential units for rules for social interaction across various settings. Our studies utilized *The Science of Making Friends* video models (Laugeson, 2013), which were developed in collaboration with the evidence-based Program for the Education and Enrichment of Relational Skills (PEERS®) (Laugeson & Frankel, 2010). The video models highlight which social cues to look for and provide strategies on how to respond to others in situations such as when someone tries to enter a new conversation, how to leave a conversation that they don’t feel accepted in, or how to respond to rumors. The video models each include a brief introduction describing the scene and drawing attention to the social patterns and expectations of the interaction. This format corresponds with cognitive, usage-based processes by categorizing social scenarios, forming sequential units through repetition of material, and creating new memories from the novel experiences of video models. The video model scenarios are practiced, to provide necessary repetitions, with support and assistance to facilitate the mapping of these new events to existing experiences, thus forming new effective communication models.

Similarly, disengaged cognition (Langacker, 2008), while described for neurotypical functioning, states that "cognitive structures give rise to mental structures, at successful levels of organization, whose connection with such experience is progressively more remote". As our mental life becomes remote, or disengaged, from our immediate bodily experiences we create simulations of the world. In the case of social functioning and social cognition in ASD, these simulations may not be accurately constructed for effective use in society. Treatment interventions assist in modifying the simulations of the world that exist for an individual with ASD, which alters future usage-based inputs.

Pillar 3 - Language is Embodied: Facial Emotion is Embodied

To communicate, humans create perceptible signals produced by moving parts of our bodies. Embodied cognition drives human expressive ability. This includes language, with meanings being shaped by physical forces as we utilize sensorimotor and emotional capacities to move, perceive, and act on the world (Langacker, 2008; Wilcox, 2012). In this sense, language isn't just meaningful, it reflects our experiences and helps us make sense of our environment.

Among the many complex aspects of social interaction, there is one embodied aspect that creates an immediate communication of emotion and intention: facial expression. Facial expression is often delivered first during an interaction and expresses the feelings of someone who may have not yet formulated them into words or yet even realized the presence of the emotion themselves. In this sense, facial expressions allow observers important insight into people and social situations. For individuals with ASD, the understanding of these non-worded messages can be elusive (Clark et al., 2008).

Research indicates that human infants begin to recognize facial expression as early as 10 weeks old by responding to the expressions of their mothers (Walker-Andrews, Krogh-Jespersen, Mayhew, & Coffield, 2011). By five months, they respond with distress when they see their mothers in a depressed state, and by seven months they engage in such complexity as to discern information from only the upper half of a face. I posit that the rapid and subtle recognition process that begins with infancy is possible because facial expressions are processed in the same manner as other linguistic units.

Consider viewing only the top one-third of a human face with just one muscle movement visible - the inner corners of the eyebrows are raised. While we might be able to make guesses at what facial emotion expression is intended by viewing the raised eyebrows alone, this singular muscle movement doesn't provide enough information to determine the intended facial emotion expression. However, when a whole face is shown with these three perceptible facial muscle movements (Ekman, 2003): (1) eyebrow inner corners raised, (2) lip corners pulled down, and (3) eyelids loose, they combine to form the facial emotion expression that is typically processed quickly by most viewers as *sadness.*

A similar analysis can be made when using words. Consider hearing only the word *we.* While one word might assist a listener in guessing a phrase the speaker is intending to say, the singular word *we* doesn't provide enough information to determine what phrase it belongs to. However, when we hear four, perceptible words together in this order: (1) *we* (2) *have* (3) *to* (4) *talk*, they form what is typically processed quickly by most listeners as the highly frequent phrase *we have to talk.*

It's been demonstrated that word phrases that are used with high frequency become processed as whole units that override the phrase's individual syntactic and semantic components (Bybee & Scheibman, 1999). For example, listeners process the high-frequency, chunked, four-word phrase *we have to talk* more quickly than the lower-frequency, chunked, four-word phrase *we have to sit* (Arnon & Snider, 2010). Additionally, as frequent phrases become processed as whole units they become stronger lexical representations than low-frequency forms, which demonstrates that meaning-form pairings extend beyond individual words to multi-word expressions. It has also been suggested that these pairings extend to patterns of gestures (Wilcox, 2012), with support found from evidence that demonstrates the more frequently a facial emotion expression occurs, the more quickly and accurately it is processed (Calvo, Gutiérrez-García, Fernández-Martín, & Nummenmaa, 2014). Further, people continue to construct accurate mental representations for high-frequency facial emotion expressions despite nearly a third of these expressions being presented with multifaceted features with varying degrees of intensity that often make emotional classifications into discrete categories difficult (Riediger, Voelkle, Ebner, & Lindenberger, 2011). The ability to make accurate identifications of multifaceted and varied high-frequency facial emotion expressions speaks to the strength and efficiency of whole-unit processing.

Sign languages are structured like spoken languages at every linguistic level (So, Coppola, Licciardello, & Goldin-Meadow, 2005). There is evidence that at least some collocations of high-frequency signs have also undergone a chunking process (Wilkinson, 2016), suggesting that their semantic and syntactic components are not processed individually, but instead as a whole unit. The ability of high-frequency signs to process as whole units provides more support for suggesting that a similar process may exist for facial emotion expressions, because, like sign languages, facial emotion expressions also utilize a visual modality, occur spatially, and convey meaning.

Machine-learning models of facial emotion recognition are described as starting from a fixed state and moving through sequential events towards an end state (Pagariya & Bartere, 2013), very much like the process of human, usage-based cognition. Presumably, high-frequency collocational facial features comprising whole-face facial emotions exist with enough routinization across human users that programmers have built Facial Action Coding (FACS) systems with the capability of teaching machines to identify individual facial muscle movements and make whole-face emotion predictions (Hamm, Kohler, Gur, & Verma, 2012). FACS assembles even the most ambiguous and subtle of facial movements and expressions, analyzing the smallest differences in facial affect and even reading faces in a video format by extracting geometric and texture features to create temporal profiles of each facial muscle movement and compute frequencies of Action Units.

The processing of facial expressions as highly frequent forms in whole-units has implications for individuals with ASD. It has been proposed that some of the difficulties individuals with ASD exhibit when reading facial emotions is because they process faces through a feature-by-feature analysis, rather than through whole-face processing (Black, Chen, Lipp, Bölte, & Girdler, 2020; Deruelle, Rondan, Salle-Collemiche, Bastard-Rosset, & Da Fonséca, 2008). This feature-by-feature analysis aligns with overall superior performance found by individuals with ASD on tasks that involve focused processing on details (Happé & Frith, 2006). Additionally, neuroimaging studies show high activation in the fusiform gyrus of neurotypical individuals during whole-face processing, but reduced activation of the same region when individuals with ASD are presented with whole faces, suggesting that a feature-by-feature strategy is being used to process facial expressions, rather than whole-face processing, which may contribute to difficulties with FERP (Bolte et al., 2006).

The role of the rTPJ for completing lower-level processing suitable for recognizing perceptible facial features, as well as higher-level processing suitable for evaluating and processing whole-face emotions (Decety & Lamm, 2007) supports FERP as a system that operates on a continuum of lower-level processing of individual linguistic features (e.g., facial muscle movements, individual facial features) to higher-level mental representations of whole-face emotional expressions. The treatment interventions used in the studies of this dissertation, such as the *Mind Reading Interactive Guide to Emotions* (Baron-Cohen, 2003) and *The Science of Making Friends* (Laugeson, 2013), successfully capitalized on varied levels of processing along this continuum. Given our findings showing significant improvements in social functioning and social cognition, I feel confident in saying that tDCS applied at the rTPJ of individuals with ASD accelerates and/or enhances processing of social functioning and social cognition treatment interventions occurring inside a Language in Motion Framework.

References

Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience*, *4*(3), 165–178. https://doi.org/10.1038/nrn1056

Amatachaya, A., Auvichayapat, N., Patjanasoontorn, N., Suphakunpinyo, C., Ngernyam, N., Aree-Uea, B., … Auvichayapat, P. (2014). Effect of anodal transcranial direct current stimulation on autism: A randomized double-blind crossover trial. *Behavioural Neurology*, *2014*, 1–7. https://doi.org/10.1155/2014/173073

Amatachaya, A., Jensen, M. P., Patjanasoontorn, N., Auvichayapat, N., Suphakunpinyo, C., Janjarasjitt, S., … Auvichayapat, P. (2015). The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: A randomized crossover controlled trial. *Behavioural Neurology*, *2015*, 1–11. https://doi.org/10.1155/2015/928631

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

American Speech-Language-Hearing Association. (2016). Social Language Use (Pragmatics). Retrieved from http://www.asha.org/public/speech/development/Pragmatics/

Annals of Neurology. (2016). cover imag. *Annals of Neurology*, *80*(5). https://doi.org/10.1002/ana.24822

Antal, A., Terney, D., Kühnl, S., & Paulus, W. (2010). Anodal transcranial direct current stimulation of the motor cortex meliorates chronic pain and reduces short intracortical inhibition. *Journal of Pain and Symptom Management*, *39*(5), 890–903. https://doi.org/10.1016/j.jpainsymman.2009.09.023

Arnon, I., & Snider, N. (2010). More than words: Frequency effects for multi-word phrases. *Journal of Memory and Language*, *62*(1), 67–82. https://doi.org/10.1016/j.jml.2009.09.005

Ashwin, C., Chapman, E., Colle, L., & Baron-Cohen, S. (2007). Impaired recognition of negative basic emotions in autism: A test of the amygdala theory. *Social Neuroscience*, *1*(3–4), 349–363. https://doi.org/10.1080/17470910601040772

Azevedo, F. A. C., Carvalho, L. R. B., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., … Herculano-Houzel, S. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *Journal of Comparative Neurology*, *513*(5), 532–541. https://doi.org/10.1002/cne.21974

Baron-Cohen, S. (2003). *Mind Reading the Interactive Guide to Emotions*. London: Jessica Kingsley Publishers, Inc.

Baron-Cohen, S. (2009). Autism: The empathizing-systemizing (E-S) theory. *Annals of the New York Academy of Sciences*, *1156*, 68–80. https://doi.org/10.1111/j.1749-

6632.2009.04467.x

Baron-Cohen, S., Campbell, R., Karmiloff-Smith, A., Grant, J., & Walker, J. (1995). Are children with autism blind to the mentalistic significance of the eyes? *British Journal of Developmental Psychology, 13*(4), 379–398. https://doi.org/10.1111/j.2044-835X.1995.tb00687.x

Baron-Cohen, S., Richler, J., Bisarya, D., Gurunathan, N., & Wheelwright, S. (2003). The systemizing quotient: An investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 358*(2), 361–374. https://doi.org/10.1098/rstb.2002.1206

Baron-Cohen, S., & Wheelwright, S. (2004). The Empathy Quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders, 34*(2), 163–175.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism Spectrum Quotient: evidence from Asperger syndrome/high functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*, 5–17. https://doi.org/10.1023/A:1005653411471

Baruth, J. M., Casanova, M. F., El-Baz, A., Horrell, T., Mathai, G., Sears, L., & Sokhadze, E. (2010). Low-frequency repetitive transcranial magnetic stimulation modulates evoked-gamma frequency oscillations in autism spectrum disorder. *Journal of Neurotherapy, 14*(3), 179–194. https://doi.org/10.1080/10874208.2010.501500

Bellini, S. & Akullian, J. (2013). A meta-analysis of video modeling and video self-modeling interventions for children and adolescents with autism spectrum disorders. *Exceptional Children, 73*(3), 264–287.

Bernardi, S., Anagnostou, E., Shen, J., Kolevzon, A., Buxbaum, J. D., Hollander, E., … Fan, J. (2010). In vivo 1 H-magnetic resonance spectroscopy study of the attentional networks in autism. *Brain Research, 1380*, 198–205. https://doi.org/10.1016/j.brainres.2010.12.057

Berthoz, S., Wessa, M., Kedia, G., Wicker, B., & Grèzes, J. (2008). Cross-cultural validation of the empathy quotient in a French-speaking sample. *Canadian Journal of Psychiatry, 53*(7), 469–477. https://doi.org/10.1177/070674370805300712

Bhat, A. N., Galloway, J. C., & Landa, R. J. (2010). Social and non-social visual attention patterns and associative learning in infants at risk for autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 51*(9), 989–997. https://doi.org/10.1111/j.1469-7610.2010.02262.x

Black, M. H., Chen, N. T. M., Lipp, O. V, Bölte, S., & Girdler, S. (2020). Complex facial emotion recognition and atypical gaze patterns in autistic adults. https://doi.org/10.1177/1362361319856969

Blumberger, D. M., Tran, L. C., Fitzgerald, P. B., Hoy, K. E., Daskalakis, Z. J., & Palm,

U. (2012). A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. *Frontiers in Psychiatry*, *3*(August), 1–8. https://doi.org/10.3389/fpsyt.2012.00074

Bögels, S., Magyari, L., & Levinson, S. C. (2015). Neural signatures of response planning occur midway through an incoming question in conversation. *Scientific Reports*, *5*(12881), 1–11. https://doi.org/10.1038/srep12881

Boggio, P. S., Rocha, R. R., da Silva, M. T., & Fregni, F. (2008). Differential modulatory effects of transcranial direct current stimulation on a facial expression go-no-go task in males and females. *Neuroscience Letters*, *447*(2–3), 101–105. https://doi.org/10.1016/j.neulet.2008.10.009

Bolinger, D. (1968). *Aspects of Language*. New York: Harcourt, Brace, & World.

Bolte, S., Hubl, D., Feineis-Matthews, S., Prvulovic, D., Dierks, T., & Poustka, F. (2006). Facial affect recognition training in autism: Can we animate the fusiform gyrus? *Behavioral Neuroscience*, *120*(1), 211–216. https://doi.org/10.1037/0735-7044.120.1.211

Bybee, J. (2006). From usage to grammar: The mind's response to repetition. *Language*, *82*(4), 711–733. https://doi.org/10.1353/lan.2006.0186

Bybee, J. (2010). *Language as a Complex Adaptive System: The Interaction of Cognition, Culture and Use*. Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9780511750526.011

Bybee, J., & Scheibman, J. (1999). The effect of usage on degrees of constituency: The reduction of don't in English. *Linguistics*, *37*(4), 575–596. https://doi.org/10.1515/ling.37.4.575

Calvo, M. G., Gutiérrez-García, A., Fernández-Martín, A., & Nummenmaa, L. (2014). Recognition of facial expressions of emotion is related to their frequency in everyday life. *Journal of Nonverbal Behavior*, *38*(4), 549–567. https://doi.org/10.1007/s10919-014-0191-3

Casanova, M. F., Baruth, J. M., El-Baz, A., Tasman, A., Sears, L., & Sokhadze, E. (2012). Repetitive transcanial magnetic stimulation (RTMS) modulates event-related potential (ERP) indices of attention in autism. *Translational Neuroscience*, *3*(2), 170–180. https://doi.org/10.2478/s13380-012-0022-0

Center for Disease Control. (2016). Autism Spectrum Disorder: Data and Statistics. Retrieved from http://www.cdc.gov/ncbddd/autism/data.html

Center for Disease Control and Prevention. (2014). *Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network , 11 Sites , United States , 2010*. *Surveillance Summaries* (Vol. 63). Atlanta, GA.

Chugani, D. C. (2012). Neuroimaging and neurochemistry of autism. *Pediatric Clinics of North America*, *59*(1), 63–73.

Ciechanski, P., & Kirton, A. (2017). Transcranial direct-current stimulation can enhance motor learning in children. *Cerebral Cortex*, *27*(5), 2758–2767. https://doi.org/10.1093/cercor/bhw114

Clark, T., Winkielman, P., & McIntosh, D. N. (2008). Autism and the extraction of emotion from briefly presented facial sxpressions: Stumbling at the first step of empathy. *Emotion*, *8*(6), 803–809. https://doi.org/10.1037/a0014124

Clark, V. P., Coffman, B. A., Trumbo, M. C., & Gasparovic, C. (2011). Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a 1 H magnetic resonance spectroscopy study. *Neuroscience Letters*, *500*(1), 67–71. https://doi.org/10.1016/j.neulet.2011.05.244

Coffman, B. A., Trumbo, M. C., & Clark, V. P. (2012). Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. *BMC Neuroscience*, *13:108*, 1–8. https://doi.org/1186/1471-2202-13-108

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: From synapse to symptoms. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2044–2055. https://doi.org/10.1016/j.neubiorev.2012.07.005

D'Urso, G., Bruzzese, D., Ferrucci, R., Priori, A., Pascotto, A., Galderisi, S., … Bravaccio, C. (2015). Transcranial direct current stimulation for hyperactivity and noncompliance in autistic disorder. *The World Journal of Biological Psychiatry*, *16*(5), 361–366.

D'Urso, G., Ferrucci, R., Bruzzese, D., Pascotto, A., Priori, A., Altamura, C. A., … Bravaccio, C. (2014). Transcranial direct current stimulation for autistic disorder. *Biological Psychiatry*, *76*(5), e5–e6. https://doi.org/10.1016/j.biopsych.2013.11.009

Dawson, A. G., & Rogers, S. (2010). Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. *Pediatrics*, *125*(1). https://doi.org/10.1542/peds.2009-0958

Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: From physiology to network dynamics and back. *Nature Publishing Group*, *16*(7), 838–844. https://doi.org/10.1038/nn.3422

Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: How low-level computational processes contribute to meta-cognition. *The Neuroscientist*, *13*(6), 580–593. https://doi.org/10.1177/1073858407304654

Delano, M. E. (2007). Video modeling interventions for individuals with autism. *Remedial and Special Education*, *28*(1), 33–42. https://doi.org/10.1177/07419325070280010401

Deruelle, C., Rondan, C., Salle-Collemiche, X., Bastard-Rosset, D., & Da Fonséca, D. (2008). Attention to low- and high-spatial frequencies in categorizing facial identities, emotions and gender in children with autism. *Brain and Cognition*, *66*(2), 115–123. https://doi.org/10.1016/j.bandc.2007.06.001

Dimitrijević, A., Hanak, N., Vukosavljević-Gvozden, T., & Opačić, G. (2012). Psychometric properties of the Serbian version of the Empathy Quotient (S-EQ). *Psihologija*, *45*(3), 257–276. https://doi.org/10.2298/PSI1203257D

Ebisu, T., Rooney, W. D., Graham, S. H., Weiner, W., & Maudsley, A. A. (1994). N-Acetylaspartate as an in vivo marker of neuronal viability in kainate-induced status epilepticus: 1 H magnetic resonance spectroscopic imaging. *Journal of Cerebral Blood Flow and Metabolism*, *14*(3), 373–382.

Edelman, G. M. (2017). Gerald Edelman - The theory of neural Darwinism. Retrieved from https://www.youtube.com/watch?v=DX8q3Gv2_-I

Ekman, P. (2003). *Emotions Revealed*. New York: St. Martin's Press.

Endo, T., Shioiri, T., Kitamura, H., Kimura, T., Endo, S., & Masuzawa, N. (2007). Altered chemical metabolites in the amygdala-hippocampus region contribute to autistic symptoms. *Biological Psychiatry*, *62*(9), 1030–1037. https://doi.org/10.1016/j.biopsych.2007.05.015

Enticott, P. G., Fitzgibbon, B. M., Kennedy, H. A., Arnold, S. L., Elliot, D., Peachey, A., … Fitzgerald, P. B. (2014). A double-blind, randomized trial of deep repetitive transcranial magnetic stimulation (rTMS) for autism spectrum disorder. *Brain Stimulation*, *7*(2), 206–211. https://doi.org/10.1016/j.brs.2013.10.004

Esse Wilson, J., Quinn, D. K., Wilson, J. K., Garcia, C. M., & Tesche, C. D. (2018). Transcranial direct current stimulation to the right temporoparietal junction for social functioning in autism spectrum disorder. *The Journal of ECT*, *34*(1), e10–e13. https://doi.org/10.1097/YCT.0000000000000445

Esse Wilson, J., Trumbo, M. C., Wilson, J. K., & Tesche, C. D. (2018). Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). *Journal of Neural Transmission*, *125*(12), 1857–1866. https://doi.org/10.1007/s00702-018-1938-5

Fein, D., Barton, M., Eigsti, I., Kelley, E., Naigles, L., Schultz, R. T., … Tyson, K. (2013). Optimal outcome in individuals with a history of autism. *Journal of Child Psychology and Psychiatry*, *54*(2), 195–205. https://doi.org/10.1111/jcpp.12037.Optimal

Fernell, E., Eriksson, M. A., & Gillberg, C. (2013). Early diagnosis of autism and impact on prognosis: A narrative review. *Clinical Epidemiology*, 33–43.

Ferrucci, R., Brunoni, A. R., Parazzini, M., Vergari, M., Rossi, E., Fumagalli, M., … Priori, A. (2013). Modulating human procedural learning by cerebellar transcranial direct current stimulation. *Cerebellum*, *12*(4), 485–492. https://doi.org/10.1007/s12311-012-0436-9

Ferrucci, R., Giannicola, G., Rosa, M., Fumagalli, M., Boggio, P. S., Hallett, M., … Priori, A. (2012). Cerebellum and processing of negative facial emotions: Cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness. *Cognition & Emotion*, *26*(5), 786_799. https://doi.org/10.1080/02699931.2011.619520

Freitag, C. M., Feineis-Matthews, S., Valerian, J., Teufel, K., & Wilker, C. (2012). The Frankfurt early intervention program FFIP for preschool aged children with autism spectrum disorder: a pilot study. *Journal of Neural Transmission*, *119*(9), 1011–1021. https://doi.org/10.1007/s00702-012-0792-0

Gaetz, W., Bloy, L., Wang, D. J., Port, R. G., Blaskey, L., Levy, S. E., & Roberts, T. P. L. (2014). GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. *NeuroImage*, *86*, 1–9. https://doi.org/10.1016/j.neuroimage.2013.05.068

Geier, D. A., Kern, J. K., & Geier, M. R. (2013). A comparison of the Autism Treatment Evaluation Checklist (ATEC) and the Childhood Autism Rating Scale (CARS) for the quantitative evaluation of autism. *Journal of Mental Health Research in Intellectual Disabilities*, *6*(4), 255–267. https://doi.org/10.1080/19315864.2012.681340

Gill, J., Shah-Basak, P. P., & Hamilton, R. (2015). It’s the thought that counts: Examining the task-dependent effects of transcranial direct current stimulation on executive function. *Brain Stimulation*, *8*(2), 253–259. https://doi.org/10.1016/j.brs.2014.10.018

Golan, O., Ashwin, E., Granader, Y., McClintock, S., Day, K., Leggett, V., & Baron-Cohen, S. (2010). Enhancing emotion recognition in children with autism spectrum conditions: An intervention using animated vehicles with real emotional faces. *Journal of Autism and Developmental Disorders*, *40*(3), 269–279. https://doi.org/10.1007/s10803-009-0862-9

Golan, O., & Baron-Cohen, S. (2006). Systemizing empathy: Teaching adults with Asperger syndrome or high-functioning autism to recognize complex emotions using interactive multimedia. *Development and Psychopathology*, *18*, 591–617. https://doi.org/10.1017/S0954579406060305

Gouveia, V., Milfont, T., Gouveia, R., Neto, J., & Galvão, L. (2012). Brazilian-Portuguese Empathy Quotient: Evidences of its construct validity and reliability. *The Spanish Journal of Psychology*, *15*(2), 777–782.

Groen, Y., Fuermaier, A. B. M., Den Heijer, A. E., Tucha, O., & Althaus, M. (2015). The Empathy and Systemizing Quotient: The psychometric properties of the Dutch version and a review of the cross-cultural stability. *Journal of Autism and Developmental Disorders*, *45*(9), 2848–2864. https://doi.org/10.1007/s10803-015-2448-z

Hamm, J., Kohler, C. G., Gur, R. C., & Verma, R. (2012). Automated Facial Action Coding System for dynamic analysis of facial expressions in neuropsychiatric disorders. *Journal of Neuroscience Methods*, *200*(2), 237–256. https://doi.org/10.1016/j.jneumeth.2011.06.023.Automated

Happé, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 36*(1), 5–25. https://doi.org/10.1007/s10803-005-0039-0

Harms, M. B., Martin, A., & Wallace, G. L. (2010). Facial emotion recognition in autism spectrum disorders: A review of behavioral and neuroimaging studies. *Neuropsychology Review*, *20*(3), 290–322. https://doi.org/10.1007/s11065-010-9138-6

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: A four-to six-year follow-up. *Journal of Autism and Developmental Disorders*, *30*(2).

Hedley, D., Uljarevi, M., Cameron, L., Halder, S., Richdale, A., & Dissanayake, C. (2016). Employment programmes and interventions targeting adults with autism spectrum disorder: A systematic review of the literature. *Autism*, *21*(8), 1–13. https://doi.org/10.1177/1362361316661855

Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): A study in Dutch population and patient groups. *Journal of Autism and Developmental Disorders*, *38*, 1555–1566. https://doi.org/10.1007/s10803-008-0538-x

Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Ståhlberg, O., … Leboyer, M. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry*, *9*(35), 1–9. https://doi.org/10.1186/1471-244X-9-35

Jeste, S. S., & Geschwind, D. H. (2014). Disentangling the heterogeneity of autism spectrum disorder through genetic findings. *Nature Reviews. Neurology*, *10*(2), 74–81. https://doi.org/10.1038/nrneurol.2013.278

Jung, I., Lim, J. Y., Kang, E. K., Sohn, H. M., Paik, N., & Ph, D. (2011). The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. *Annals of Rehabilitation Medicine*, 460–469.

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, *16*(11), 559–572. https://doi.org/10.1016/j.tics.2012.09.006

Kern Koegel, L., Ashbaugh, K., Navab, A., & Koegel, R. L. (2016). Improving empathic communication skills in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *46*(3), 921–933. https://doi.org/10.1007/s10803-015-2633-0

Kessler, S. K., Turkeltaub, P. E., Benson, J. G., & Hamilton, R. H. (2013). Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimulation*, *5*(2), 155–162. https://doi.org/10.1016/j.brs.2011.02.007.Differences

Kim, J., & Lee, S. J. (2010). Reliability and validity of the Korean version of the Empathy Quotient scale. *Psychiatry Investigation*, *7*(1), 24–30.

https://doi.org/10.4306/pi.2010.7.1.24

Krall, S. C., Volz, L. J., Oberwelland, E., Grefkes, C., Fink, G. R., & Konrad, K. (2016). The right temporoparietal junction in attention and social interaction: A transcranial magnetic stimulation study. *Human Brain Mapping*, *37*(2), 796–807. https://doi.org/10.1002/hbm.23068

Krause, B., Márquez-Ruiz, J., & Kadosh, R. C. (2013). The effect of transcranial direct current stimulation: A role for cortical excitation / inhibition balance? *Frontiers in Human Neuroscience*, *477*(September), 171–178. https://doi.org/10.3389/fnhum.2013.00602

Krishnan, C., Santos, L., Peterson, M. D., & Ehinger, M. (2016). Safety of noninvasive brain stimulation in children and adolescents. *Brain Stimulation*, *8*(1), 76–87. https://doi.org/10.1016/j.brs.2014.10.012.Safety

Krysko, K. M., & Rutherford, M. D. (2009). A threat-detection advantage in those with autism spectrum disorders. *Brain and Cognition*, *69*(3), 472–480. https://doi.org/10.1016/j.bandc.2008.10.002

Kubas, B., Ku, W., Sobaniec, W., Tarasow, E., U, Ł., & Walecki, J. (2012). Metabolite alterations in autistic children: a 1 H MR spectroscopy study. *Advances in Medical Sciences*, *57*(1), 152–156. https://doi.org/10.2478/v10039-012-0014-x

LaCava, P., Golan, O., Baron-Cohen, S., Smith Myle, B. (2007). Using assistive technology to teach emotion recognition to students with Asperger Syndrome. *Remedial and Special Education*, *28*(3), 174–181.

Langacker, R. W. (2008). *Cognitive Grammar A Basic Introduction* (1st ed.). Oxford: Oxford University Press.

Lartseva, A., Dijkstra, T., Kan, C. C., & Buitelaar, J. K. (2014). Processing of emotion words by patients with autism spectrum disorders: Evidence from reaction times and EEG. *Journal of Autism and Developmental Disorders*, *44*(11), 2882–2894. https://doi.org/10.1007/s10803-014-2149-z

Laugeson, E. A. (2013). *The Science of Making Friends*. San Francisco: Jossey-Bass.

Laugeson, E. A., Ellingsen, R., Sanderson, J., Tucci, L., & Bates, S. (2014). The ABC's of teaching social skills to adolescents with autism spectrum disorder in the classroom: The UCLA PEERS® program. *Journal of Autism and Developmental Disorders*, *44*(9), 2244–2256. https://doi.org/10.1007/s10803-014-2108-8

Laugeson, E. A., & Frankel, F. (Eds. . (2010). The PEERS treament manual. New York: Routlege.

Laugeson, E. A., Frankel, F., Mogil, C., & Dillon, A. R. (2009). Parent-assisted social skills training to improve friendships in teens with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(4), 596–606. https://doi.org/10.1007/s10803-008-0664-5

Laugeson, E. A., Gantman, A., Kapp, S. K., Orenski, K., & Ellingsen, R. (2015). A randomized controlled trial to improve social skills in young adults with autism spectrum disorder: The UCLA PEERS® Program. *Journal of Autism and Developmental Disorders*, *45*(12), 3978–3989. https://doi.org/10.1007/s10803-015-2504-8

Lawrence, E. J., Shaw, P., Baker, D., Baron-Cohen, S., & David, A. S. (2004). Measuring empathy: Reliability and validity of the Empathy Quotient. *Psychological Medicine*, *34*, 911–924.

Lecavalier, L., Leone, S., & Wiltz, J. (2006). The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. *Journal of Intellectual Disability Research*, *50*(3), 172–183. https://doi.org/10.1111/j.1365-2788.2005.00732.x

Lepage, J.-F., Lortie, M., Taschereau-Dumouchel, V., & Théoret, H. (2009). Validation of French-Canadian versions of the empathy quotient and autism spectrum quotient. *Canadian Journal of Behavioural Science / Revue Canadienne Des Sciences Du Comportement*, *41*(4), 272–276.

Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., & Baron-Cohen, S. (2011). Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. *NeuroImage*, *56*(3), 1832–1838. https://doi.org/10.1016/j.neuroimage.2011.02.067

Lundqvist, L.-O., & Lindner, H. (2017). Is the Autism-Spectrum Quotient a valid measure of traits associated with the autism spectrum? A Rasch validation in adults with and without autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *47*(7), 2080–2091. https://doi.org/10.1007/s10803-017-3128-y

Mai, X., Zhang, W., Hu, X., Zhen, Z., Xu, Z., & Zhang, J. (2016). Using tDCS to explore the role of the right temporo-parietal junction in theory of mind and cognitive empathy. *Frontiers in Psychology*, *7*(March), 1–7. https://doi.org/10.3389/fpsyg.2016.00380

Maljaars, J., Noens, I., Jansen, R., Scholte, E., & Berckelaer-onnes, I. Van. (2011). Intentional communication in nonverbal and verbal low-functioning children with autism. *Journal of Communication Disorders*, *44*(6), 601–614. https://doi.org/10.1016/j.jcomdis.2011.07.004

Manenti, R., Cotelli, M., Robertson, I. H., & Miniussi, C. (2012). Transcranial brain stimulation studies of episodic memory in young adults, elderly adults and individuals with memory dysfunction: A review. *Brain Stimulation*, *5*(2), 103–109. https://doi.org/10.1016/j.brs.2012.03.004

Martino, A. Di, Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., & Milham, M. P. (2008). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *BPS*, *65*(1), 63–74. https://doi.org/10.1016/j.biopsych.2008.09.022

Matsumoto, D., & Hwang, H. S. (2011). Evidence for training the ability to read microexpressions of emotion. *Motivation and Emotion*, *35*(2), 181–191.

https://doi.org/10.1007/s11031-011-9212-2

Mohammadzaheri, F., Koegel, L. K., Rezaei, M., & Bakhshi, E. (2015). A randomized clinical trial comparison between Pivotal Response Treatment (PRT) and adult-driven Applied Behavior Analysis (ABA) intervention on disruptive behaviors in public school children with autism. *Journal of Autism and Developmental Disorders*, *45*(9), 2899–2907. https://doi.org/10.1007/s10803-015-2451-4

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., … Priori, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(4), 451–453. https://doi.org/10.1136/jnnp.2007.135277

Mori, T., Mori, K., Fujii, E., Toda, Y., & Miyazaki, M. (2012). Evaluation of the GABAergic nervous system in autistic brain: I-iomazenil SPECT study. *Brain and Development*, *34*(8), 648–654. https://doi.org/10.1016/j.braindev.2011.10.007

Moseley, R. L., Shtyrov, Y., Mohr, B., Lombardo, M. V, Baron-Cohen, S., & Pulvermüller, F. (2015). Lost for emotion words: what motor and limbic brain activity reveals about autism and semantic theory. *NeuroImage*, *104*, 413–422. https://doi.org/10.1016/j.neuroimage.2014.09.046

Myers, S. M., & Johnson, C. P. (2007). Management of children with autism spectrum disorders. *Pediatrics*, *120*(5), 1162–1182. https://doi.org/10.1542/peds.2007-2362

Nasseri, P., Nitsche, M. A., & Ekhtiari, H. (2015). A framework for categorizing electrode montages in transcranial direct current stimulation. *Frontiers in Human Neuroscience*, *9*(February), 1–5. https://doi.org/10.3389/fnhum.2015.00054

Nitsche, M. A., & Paulus, W. (2000a). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527 Pt 3*, 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., & Paulus, W. (2000b). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*, *527*(pt 3), 633–639. https://doi.org/PHY_1055 [pii]

Oberman, L. M., Enticott, P. G., Casanova, M. F., Rotenberg, A., Pascual-leone, A., & Mccracken, J. T. (2016). Transcranial magnetic stimulation in autism spectrum disorder: challenges, promise, and roadmap for future research. *Autism Research: Official Journal of the International Society for Autism Research*, *9*(2), 184–203. https://doi.org/10.1002/aur.1567

Ohrmann, P., Rauch, A. V., Bauer, J., Kugel, H., Arolt, V., Heindel, W., & Suslow, T. (2007). Threat sensitivity as assessed by automatic amygdala response to fearful faces predicts speed of visual search for facial expression. *Experimental Brain Research*, *183*(1), 51–59. https://doi.org/10.1007/s00221-007-1022-0

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113.

Oswald, D. P., & Sonenklar, N. A. (2007). Medication use among children with autism spectrum disorders. *Journal of Child and Adolescent Psychopharmacology*, *17*(3), 348–355. https://doi.org/10.1089/cap.2006.17303

Otsuka, S., Uono, S., Yoshimura, S., & Zhao, S. (2017). Emotion perception mediates the predictive relationship between verbal ability and functional outcome in high-functioning adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *47*(4), 1166–1182. https://doi.org/10.1007/s10803-017-3036-1

Pagariya, R. R., & Bartere, M. M. (2013). Facial emotion recognition in videos using Hmm. *International Journal of Computational Engineering Research*, *3*(4), 111–118.

Page, L. A., Daly, E., Schmitz, N., Simmons, A., Toal, F., Deeley, Q., … Murphy, D. G. M. (2006). In vivo 1 H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. *American Journal of Psychiatry*, *163*(12), 2189–2192.

Palm, U., Segmiller, F. M., Epple, A. N., Freisleder, F., Koutsouleris, N., Schulte-Korne, G., & Padberg, F. (2016). Transcranial direct current stimulation in children and adolescents: A comprehensive review. *Journal of Neural Transmission*, *123*, 1219–1234. https://doi.org/10.1007/s00702-016-1572-z

Peters-Scheffer, N., Didden, R., Korzilius, H., & Matson, J. (2012). Cost comparison of early intensive behavioral intervention and treatment as usual for children with autism spectrum disorder in the Netherlands. *Research in Developmental Disabilities*, *33*(6), 1763–1772. https://doi.org/10.1016/j.ridd.2012.04.006

Preti, A., Vellante, M., Baron-Cohen, S., Zucca, G., Petretto, D. R., & Masala, C. (2011). The Empathy Quotient: A cross-cultural comparison of the Italian version. *Cognitive Neuropsychiatry*, *16*(1), 50–70. https://doi.org/10.1080/13546801003790982

Ramdoss, S., Machalicek, W., Rispoli, M., Mulloy, A., Lang, R., & O'Reilly, M. (2012). Computer-based interventions to improve social and emotional skills in individuals with autism spectrum disorders: A systematic review. *Developmental Neurorehabilitation*, *15*(2), 119–135. https://doi.org/10.3109/17518423.2011.651655

Reichow, B., & Volkmar, F. R. (2010). Social skills interventions for individuals with autism: Evaluation for evidence-based practices within a best evidence synthesis framework. *Journal of Autism and Developmental Disorders*, *40*(2), 149–166. https://doi.org/10.1007/s10803-009-0842-0

Reniers, R. L. E. P., Corcoran, R., Völlm, B. A., Mashru, A., Howard, R., & Liddle, P. F. (2012). Moral decision-making, ToM, empathy and the default mode network. *Biological Psychology*, *90*(3), 202–210. https://doi.org/10.1016/j.biopsycho.2012.03.009

Richardson, J. D., Fillmore, P., Datta, A., Truong, D., Bikson, M., & Fridriksson, J. (2014). Toward development of sham protocols for high-definition transcranial direct current stimulation (HD-tDCS). *NeuroRegulation*, *1*(1), 62–72.

https://doi.org/10.15540/nr.1.1.62

Riediger, M., Voelkle, M. C., Ebner, N. C., & Lindenberger, U. (2011). Beyond “Happy, angry, or sad?”: Age-of-poser and age-of-rater effects on multi-dimensional emotion perception. *Cognition and Emotion*, *25*(6), 968–982. https://doi.org/10.1080/02699931.2010.540812

Rigonatti S.P., Boggio P.S., Myczkowski M.L., Otta E., Fiquer J.T., Ribeiro R.B., Nitsche M.A., Pascual-Leone A., F. F. (2008). Transcranial direct stimulation and fluoxetine for the treatment of depression. *European Psychiatry*, *23*, 74–76. https://doi.org/10.1016/j.eurpsy.2007.09.006

Rochas, V., Rihs, T. A., Rosenberg, N., Landis, T., & Michel, C. M. (2014). Very early processing of emotional words revealed in temporoparietal junctions of both hemispheres by EEG and TMS. *Experimental Brain Research*, *232*(4), 1267–1281. https://doi.org/10.1007/s00221-014-3843-y

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., & Brown, M. S. (2014). Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. *NeuroImage*, *86*, 28–34. https://doi.org/10.1016/j.neuroimage.2013.01.045

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation / inhibition in key neural systems. *Genes, Brain and Behavior*, *2*(5), 255–267. https://doi.org/10.1046/j.1601-183X.2003.00037.x

Rubio, B., Boes, A. D., Laganiere, S., Jeurissen, D., & Pascual-leone, A. (2017). Noninvasive brain stimulation in pediatric ADHD: A review. *Journal of Child Neurology*, *31*(6), 784–796. https://doi.org/10.1177/0883073815615672.Noninvasive

Ruzich, E., Allison, C., Smith, P., Watson, P., Auyeung, B., Ring, H., & Baron-cohen, S. (2015). Measuring autistic traits in the general population: a systematic review of the Autism-Spectrum Quotient (AQ) in a nonclinical population sample of 6,900 typical adult males and females. *Molecular Autism*, *6*(2), 1–12.

Sansosti, F. J., & Powell-Smith, K. a. (2008). Using computer-presented social stories and video models to increase the social communication skills of children with high-functioning autism spectrum disorders. *Journal of Positive Behavior Interventions*, *10*(3), 162–178. https://doi.org/10.1177/1098300708316259

Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2012). Enhancing social ability by stimulating right temporoparietal junction. *Current Biology*, *22*(23), 2274–2277. https://doi.org/10.1016/j.cub.2012.10.018

Sass, K., Heim, S., Fetz, K., Oetken, S., & Habel, U. (2013). Emotional verbal fluency: a new task on emotion and executive function interaction. *Behavioral Sciences*, *3*(3), 372–387. https://doi.org/10.3390/bs3030372

Schneider, H. D., & Hopp, J. P. (2011). The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. *Clinical Linguistics &*

Phonetics, *25*(6–7), 640–654. https://doi.org/10.3109/02699206.2011.570852

Sellaro, R., Nitsche, M. A., & Colzato, L. S. (2016). The stimulated social brain: Effects of transcranial direct current stimulation on social cognition. *Annals of the New York Academy of Sciences*, *1369*(1), 218–239. https://doi.org/10.1111/nyas.13098

Shipley, W. C., Gruber, C. P., Martin, T. A., & Klein, A. (2009). *Shipley-2*. Los Angeles: Western Psychological Services.

So, W. C., Coppola, M., Licciardello, V., & Goldin-Meadow, S. (2005). The seeds of spatial grammar in the manual modality. *Cognitive Science*, *29*(6), 1029–1043. https://doi.org/10.1207/s15516709cog0000_38

Sokhadze, E., Baruth, J., Tasman, A., Mansoor, M., Ramaswamy, R., Sears, L., … Casanova, M. F. (2010). Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Applied Psychophysiology Biofeedback*, *35*(2), 147–161. https://doi.org/10.1007/s10484-009-9121-2

Sokhadze, E., Casanova, M., El-Baz, A., Farag, H. E., Li, X., & Wang, Y. (2016). TMS-based neuromodulation of evoked and induced gamma oscillations and event-related potentials in children with autism. *NeuroRegulation*, *3*(3), 101–126. https://doi.org/10.15540/nr.3.3.101

Sokhadze, E., El-Baz, A. S., Sears, L. L., Opris, I., & Casanova, M. F. (2014). rTMS neuromodulation improves electrocortical functional measures of information processing and behavioral responses in autism. *Frontiers in Systems Neuroscience*, *8*(August), 1–17. https://doi.org/10.3389/fnsys.2014.00134

Sokhadze, E., El-Baz, A. S., Tasman, A., Sears, L. L., Wang, Y., Lamina, E. V., & Casanova, M. F. (2014). Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: an exploratory study. *Applied Psychophysiology Biofeedback*, *39*(3–4), 237–257. https://doi.org/10.1007/s10484-014-9264-7

Sowden, S., Wright, G. R. T., Banissy, M. J., Catmur, C., & Bird, G. (2015). Transcranial current stimulation of the temporoparietal junction improves lie detection. *Current Biology*, *25*(18), 2447–2451. https://doi.org/10.1016/j.cub.2015.08.014

Spek, A. A., van Ham, N. C., & Nyklíček, I. (2013). Mindfulness-based therapy in adults with an autism spectrum disorder: a randomized controlled trial. *Research in Developmental Disabilities*, *34*(1), 246–253. https://doi.org/10.1016/j.ridd.2012.08.009

Spivey, M. (2007). *The Continuity of Mind*. Oxford: Oxford University Press.

Stagg, C. J., Best, J. G., Stephenson, M. C., Shea, J. O., Wylezinska, M., Kincses, Z. T., … Johansen-berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of Neuroscience*, *29*(16), 5202–5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009

Stone, D. B., & Tesche, C. D. (2009). Transcranial direct current stimulation modulates shifts in global/local attention. *Neuroreport*, *20*(12), 1115–1119. https://doi.org/10.1097/WNR.0b013e32832e9aa2

Tebartz van Elst, L., Maier, S., Fangmeier, T., Endres, D., Mueller, G. T., Nickel, K., … Biscaldi, M. (2014). Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: Evidence in support of the excitatory/inhibitory imbalance hypothesis. *Molecular Psychiatry*, *19*(May), 1314–1325. https://doi.org/10.1038/mp.2014.62

Thiemann, K. S., & Goldstein, H. (2001). Social stories, written text cues, and video feedback: Effects on social communication of children with autism. *Journal of Applied Behavior Analysis, 34*(4), 425–446. https://doi.org/10.1901/jaba.2001.34-425

Thomeer, M. L., Smith, R. A., Lopata, C., Volker, M. A., Lipinski, A. M., Rodgers, J. D., … Lee, G. K. (2015). Randomized controlled trial of mind reading and in vivo rehearsal for high-functioning children with ASD. *Journal of Autism and Developmental Disorders*, *45*(7), 2115–2127. https://doi.org/10.1007/s10803-015-2374-0

Tottenham, N., Tanaka, J. W., & Leon, A. C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Ulam, F., Shelton, C., Richards, L., Davis, L., Hunter, B., Fregni, F., & Higgins, K. (2015). Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. *Clinical Neurophysiology*, *126*(3), 486–496. https://doi.org/10.1016/j.clinph.2014.05.015

Vangkilde, A., Jepsen, J. R. M., Schmock, H., Olesen, C., Arnarsdóttir, S., Baaré, W. F. C., … Olsen, L. (2016). Associations between social cognition, skills, and function and subclinical negative and positive symptoms in 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders*, *8*(1), 1–13. https://doi.org/10.1186/s11689-016-9175-4

Wakabayashi, A., Baron-Cohen, S., Uchiyama, T., Yoshida, Y., Kuroda, M., & Wheelwright, S. (2007). Empathizing and systemizing in adults with and without autism spectrum conditions: Cross-cultural stability. *Journal of Autism and Developmental Disorders*, *37*(10), 1823–1832. https://doi.org/10.1007/s10803-006-0316-6

Walker-Andrews, A. S., Krogh-Jespersen, S., Mayhew, E. M. Y., & Coffield, C. N. (2011). Young infants' generalization of emotional expressions: Effects of familiarity. *Emotion*, *11*(4), 842–851. https://doi.org/10.1037/a0024435

Wang, J., Wu, D., Chen, Y., Yuan, Y., & Zhang, M. (2013). Effects of transcranial direct current stimulation on language improvement and cortical activation in nonfluent variant primary progressive aphasia. *Neuroscience Letters*, *549*, 29–33. https://doi.org/10.1016/j.neulet.2013.06.019

Wang, Y., Hensley, M. K., Tasman, A., Sears, L., Casanova, M. F., & Sokhadze, E. (2016). Heart rate variability and skin conductance during repetitive TMS course in children with autism. *Applied Psychophysiology Biofeedback*, *41*(1), 47–60. https://doi.org/10.1007/s10484-015-9311-z

Watkins, L., O'Reilly, M., Kuhn, M., Gevarter, C., Lancioni, G. E., Sigafoos, J., & Lang, R. (2015). A review of peer-mediated social interaction interventions for students with autism in inclusive settings. *Journal of Autism and Developmental Disorders*, *45*(4), 1070–1083. https://doi.org/10.1007/s10803-014-2264-x

Weinger, P. M., & Depue, R. A. (2011). Remediation of deficits in recognition of facial emotions in children with autism spectrum disorders. *Child & Family Behavior Therapy*, *33*(1), 20–31. https://doi.org/10.1080/07317107.2011.545008

Wellman, H. M., & Liu, D. (2004). Scaling of theory-of-mind tasks. *Child Dev*, *75*(2), 523–541. https://doi.org/10.1111/j.1467-8624.2004.00691.x CDEV691 [pii]

Whitley, E., & Ball, J. (2002). Statistics review 6: nonparametric methods. *Critical Care*, *6*(6), 509–513. https://doi.org/10.1186/cc1820

Wilcox, S. (2012). Language in motion: A framework for unifying spoken language, signed language, and gesture. *Anuari De Filologia. Estudis De Lingüística*, *0*(2), 49–57. https://doi.org/10.1344/afel2012.2.4

Wilkinson, E. (2016). Finding frequency effects in the usage of NOT collocations in American Sign Language. *Sign Language & LinguisticsSign Language and Linguistics*, *19*(1), 82–123. https://doi.org/10.1075/sll.19.1.03wil

Willis, M. L., Murphy, J. M., Ridley, N. J., & Vercammen, A. (2015). Anodal tDCS targeting the right orbitofrontal cortex enhances facial expression recognition, (April), 1677–1683. https://doi.org/10.1093/scan/nsv057

Wong, C., Odom, S. L., Hume, K. A., Cox, A. W., Fettig, A., Kucharczyk, S., … Schultz, T. R. (2015). Evidence-based practices for children, youth, and young adults with autism spectrum disorder: A comprehensive review. *Journal of Autism and Developmental Disorders*, *45*(7), 1951–1966. https://doi.org/10.1007/s10803-014-2351-z

Wu, D., Wang, J., & Yuan, Y. (2015). Effects of transcranial direct current stimulation on naming and cortical excitability in stroke patients with aphasia. *Neuroscience Letters*, *589*, 115–120. https://doi.org/10.1016/j.neulet.2015.01.045

Ye, H., Chen, S., Huang, D., Zheng, H., Jia, Y., & Luo, J. (2015). Modulation of neural activity in the temporoparietal junction with transcranial direct current stimulation changes the role of beliefs in moral judgment. *Frontiers in Human Neuroscience*, *9*(DEC), 1–10. https://doi.org/10.3389/fnhum.2015.00659

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., Shea, D. J. O., … Deisseroth, K. (2011). Neocortical excitation / inhibition balance in information processing and social dysfunction. *Nature*, *477*(7363), 171–178. https://doi.org/10.1038/nature10360

Zablotsky, B., Black, L. I., Maenner, M. J., Schieve, L. A., Danielson, M. L., Bitsko, R. H., … Boyle, C. A. (2019). Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. *Pediatrics*, *144*(4), 2009–2017. https://doi.org/10.1542/peds.2019-0811

Zhang, L., Sun, Y., Chen, F., Wu, D., Tang, J., Han, X., … Wang, K. (2016). Psychometric properties of the Autism-Spectrum Quotient in both clinical and non-clinical samples: Chinese version for mainland China. *BMC Psychiatry*, *16*(213), 1–10. https://doi.org/10.1186/s12888-016-0915-5

Zürcher, N. R., Rogier, O., Boshyan, J., Hippolyte, L., Russo, B., Gillberg, N., … Hadjikhani, N. (2013). Perception of social cues of danger in autism spectrum disorders. *PLoS ONE*, *8*(12). https://doi.org/10.1371/journal.pone.0081206