Journal of Psychiatric Research 111 (2019) 140–144

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

A pilot investigation of neuroimaging predictors for the benefits from pivotal response treatment for children with autism

John P. Hegarty[a,*], Grace W. Gengoux[a], Kari L. Berquist[a], M. Estefanía Millán[a], Serena M. Tamura[a,c], Shweta Karve[a,d], Margaret D. Rosenthal[b], Jennifer M. Phillips[a], Antonio Y. Hardan[a]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA, 94305, USA
[b] Department of Human Biology, Stanford University, 450 Serra Mall, Stanford, CA, 94305, USA
[c] Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, 600 16th Street, San Francisco, CA, 94158, USA
[d] Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Central, WI, 333 Pine Ridge Blvd, Wausau, WI, 54401, USA

ARTICLE INFO

Keywords:
Inferior frontal
Superior temporal
Language
Communication
Biomarker
Early intervention

ABSTRACT

Children with autism spectrum disorder (ASD) frequently exhibit language delays and functional communication deficits. Pivotal response treatment (PRT) is an effective intervention for targeting these skills; however, similar to other behavioral interventions, response to PRT is variable across individuals. Thus, objective markers capable of predicting treatment response are critically-needed to identify which children are most likely to benefit from this intervention. In this pilot study, we investigated whether structural neuroimaging measures from language regions in the brain are associated with response to PRT. Children with ASD ($n = 18$) who were receiving PRT to target their language deficits were assessed with MRI at baseline. T1-weighted images were segmented with FreeSurfer and morphometric measures of the primary language regions (inferior frontal (IFG) and superior temporal (STG) gyri) were evaluated. Children with ASD and language deficits did not exhibit the anticipated relationships between baseline structural measures of language regions and baseline language abilities, as assessed by the number of utterances displayed during a structured laboratory observation (SLO). Interestingly, the level of improvement on the SLO was correlated with baseline asymmetry of the IFG, and the size of the left STG at baseline was correlated with the level of improvement on standardized parental questionnaires. Although very preliminary, the observed associations between baseline structural properties of language regions and improvement in language abilities following PRT suggest that neuroimaging measures may be able to help identify which children are most likely to benefit from specific language treatments, which could help improve precision medicine for children with ASD.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is defined by impairments in social communication and restricted/repetitive patterns of behaviors or interests (APA, 2013). ASD occurs early in life, typically within the first three years, but symptoms may not fully manifest until demands exceed an individual's skill level. Because early intervention is critical for an optimal outcome, it is recommended that treatment begin immediately following diagnosis (National Research Council, 2001). However, no specific predictors of treatment response have been identified to date, sometimes causing clinicians and families to try multiple treatments before effective intervention strategies are implemented. The identification of biological markers of treatment response could significantly improve precision medicine for children with ASD.

Although most biological alterations are variable across individuals, volumetric abnormalities, such as increased total brain volume in young children, are some of the most consistently reported brain differences in ASD (Amaral et al., 2008; Brambilla et al., 2003). The most frequently observed enlargements are in the frontal (Carper and

* Corresponding author. John Hegarty Autism and Developmental Disorders Research Program, Department of Psychiatry and Behavioral Sciences, Stanford University, School of Medicine, 401 Quarry Road, Stanford, CA, 94305, USA.

E-mail addresses: hegartyj@stanford.edu (J.P. Hegarty), ggengoux@stanford.edu (G.W. Gengoux), kbe@stanford.edu (K.L. Berquist), mmillan2@stanford.edu (M.E. Millán), serena.tamura@ucsf.edu (S.M. Tamura), skarve@mcw.edu (S. Karve), maggiedr@stanford.edu (M.D. Rosenthal), jenphil@stanford.edu (J.M. Phillips), hardanay@stanford.edu (A.Y. Hardan).

https://doi.org/10.1016/j.jpsychires.2019.02.001
Received 9 October 2018; Received in revised form 11 January 2019; Accepted 4 February 2019
0022-3956/

Courchesne, 2005) and temporal lobes (Schumann et al., 2004). The superior temporal gyrus (STG), which contains the primary receptive language regions, and the inferior frontal gyrus (IFG), which contains the primary expressive language regions, exhibit abnormal growth trajectories that are associated with the severity of functional communication deficits in individuals with ASD (Bigler et al., 2007; Knaus et al., 2009). Overall, children with ASD exhibit widespread alterations in grey matter (GM) and white matter (WM) in the brain and these differences may impact the development of brain networks that support receptive and expressive language.

A wide range of behavioral and educational interventions are being used in the treatment of language deficits in children with ASD (National Research Council, 2001). The timing of intervention is of the upmost importance because mounting evidence suggests that participation in specialized programs at young ages is crucial for optimizing long-term outcomes (Dawson, 2008). Pivotal response treatment (PRT) is a promising intervention for young children with ASD. PRT targets specific skills as well as core 'pivotal' areas (e.g., motivation) thought to result in gains in untargeted areas (e.g., joint attention) (Koegel et al., 2005; Mundy and Stella, 2000). This is accomplished through the combination of operant learning contingencies, behavior analytic motivational teaching strategies, and child-driven strategies that are used in other developmental treatment programs. A programmatic line of research has demonstrated the efficacy of PRT for children with ASD (Bryson et al., 2007; Hardan et al., 2015; Koegel et al., 1999a) and has shown that they can learn communication skills such as question asking, conversation, play, and social initiations (Boettcher, 2004; Koegel et al., 1997, 1999b; Schreibman et al., 1996). PRT has also been shown to result in increased number and length of utterances, speech intelligibility, and spontaneous language (Koegel et al., 1998, 2003, 2006) and may have targeted influence on language abilities in children with ASD (Hardan et al., 2015; Koegel et al., 1987; Mohammadzaheri et al., 2014).

The identification of objective neurobiological markers to aid in the prediction of response to PRT may help to reduce the time until children with ASD receive an effective intervention to improve their language abilities. This is particularly important for very young children when the brain is most plastic and time should not be wasted in implementing treatments that might not be beneficial. In this preliminary investigation, we examined the relationships between structural measures of language regions in the brain (IFG and STG) and changes in language abilities following PRT in young children with ASD. We hypothesized that the size of the primary language regions would be associated with the level of improvement following the trial.

2. Material and methods

2.1. Participants

Young children (aged 2–6 years) with history of ASD and significant language deficits who were receiving PRT to target language as part of ongoing research (NCT01881750, NCT02037022, NCT01882153; http://www.clinicaltrials.gov) were invited to participate in this investigation. Autism diagnosis was confirmed with the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) (Lord et al., 2012). Significant language deficit was determined by the Preschool Language Scale, 4th Edition (PLS-4) (Zimmerman et al., 2002), based on children with ASD who met the following thresholds in expressive language abilities: 2–3-year olds who were ≥1 *SD*; 4-year olds ≥ 2 *SD*s; and 5–6-year olds ≥ 3 *SD*s. Cognitive abilities were assessed with standardized scores from the Mullen Scales of Early Learning (MSEL), AGS Edition (Mullen, 1995). The methodology of the study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 and approved by the Institutional Review Board. All parents of participants or legal guardians were informed of the study procedures and provided written consent.

2.2. Pivotal Response Treatment

The PRT program included at least 12 parent training sessions with one meeting per week. During these sessions, parents were taught PRT skills to implement in the natural environment, as outlined in Hardan et al. (2015). Sessions were led by psychologists or Master's level clinicians utilizing PRT manuals, *How to Teach Pivotal Behaviors to Children with Autism* (Koegel et al., 1989) and *Pivotal Response Treatment: Using Motivation as a Pivotal Response* (Koegel, 2011), and a standard set of teaching materials and video examples (Minjarez et al., 2011). Participants were allowed to continue concomitant treatments which were stable for at least one month prior to baseline measures.

2.3. PRT trial outcome measures

Language abilities were assessed before and after 12 weeks of parent training. The primary outcome measure was the frequency of functional utterances that were exhibited during a 10-min structured laboratory observation (SLO), as previously described (Hardan et al., 2015). Standardized parental questionnaires, the Vineland Adaptive Behavior Scales, 2nd Edition (VABS), Expressive Communication subscale (standardized Vscale scores) and the MacArthur-Bates Communicative Developmental Inventories (CDI) Words Produced (out of 396 and 680), were collected as secondary measures. Blinded clinician ratings were also obtained based on the Clinical Global Impressions (CGI) Overall Severity and Improvement rating scales (Guy, 1976), as well as subscales specifically targeting Communication and Integrated Social Interaction and Communication.

2.4. Neuroimaging acquisition and processing

Neuroimaging data were obtained at baseline before any treatment was provided. Magnetic resonance imaging (MRI) was carried out at the Richard M. Lucas Center for Imaging on a GE 3T MR750 scanner (Waukesha, Wisconsin, USA) using a standard 8-channel head coil. To reduce potential motion artefacts and increase acquisition success, all scans were acquired during natural sleep after the child's normal bedtime (Almli et al., 2007; Nordahl et al., 2008). A structural T1 weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence was acquired in the oblique plane with the following parameters: TR 8.5 msec, TE 6 msec, Flip angles 15°, 1.2 mm thick, 0 mm gap, 1 NEX, FOV 22 cm, and a 256 × 192 matrix. Cortical reconstruction and volumetric segmentation of T1 images was performed using the FreeSurfer (Fischl, 2012) image analysis suite (http://surfer.nmr.mgh.harvard.edu) based on gyral and sulcal structure from the Destrieux atlas (Destrieux et al., 2010). Trained raters visually inspected all automated procedures and edited WM/GM segmentation when errors were present. Regions of interest (ROIs) included the left IFG, pars opercularis and triangularis subdivisions, and left STG, anterior (planum polare), middle/lateral, and posterior (planum temporale) subdivisions. Asymmetry quotients between the right and left hemisphere were also calculated using the following formula: (right – left)/[0.5 * (right + left)].

2.5. Statistical analyses

PRT trial outcome measures were compared pre- and post-treatment with paired samples t-tests. Correlations between outcome measures and baseline structural properties (volume, area, thickness, and curvature) were examined with Spearman's rho due to the pilot sample size. Correction for multiple comparisons was completed by controlling for the false discovery rate (FDR) (Benjamini and Hochberg, 1995) within classes of comparisons across subdivisions of the IFG and STG.

3. Results

3.1. Participants

Fifteen males and five females with ASD initially participated in this

Table 1
Demographics and clinical characteristics.

Demographics	Baseline (n = 18)	
	Mean	SD
Age (years)	4.49	1.14
Gender (M/F)	15/3	–
Ethnicity (A/B/W/MO)	7/1/7/3	–
SES (Hollingshead)	46.85	7.48
Clinical Characteristics		
MSEL		
Verbal IQ	38.22	18.39
Non-verbal IQ	55.23	13.86
Full Scale IQ	46.58	15.54
ADI-R		
Social Interaction	21.60	4.72
Verbal Communication	11.00	2.35
RRB	5.00	0.71
ADOS-2		
Social Affect	15.88	3.09
RRB	5.13	1.25
Comparison Score	7.75	1.67

A/B/W/MO = Asian/black/white/multiple or other.
Mullen Scales of Early Learning, AGS Edition (MSEL), standard scores, Autism Diagnostic Inventory – Revised (ADI-R) diagnostic algorithm, and Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) scores are provided. RRB: Restricted and Repetitive Behaviors; SES: Socioeconomic Status.

preliminary investigation. However, two female participants were excluded due to the poor quality of their SLO assessments. Table 1 summarizes the demographic information and clinical characteristics of the 18 participants who were included in the analyses.

3.2. PRT for targeting language

Following 12 weeks of PRT, participants exhibited gains in language and communication abilities on all of the primary and secondary outcome measures (Table 2). Clinician ratings from the CGI indicated that 83% of participants exhibited some improvement in overall severity and communication alone and 72% exhibited improvement in integrated social interaction and communication. The primary outcome measure, number of utterances during the SLO, was the only measure that was available from all participants; thus, primary analyses focused on the number of utterances.

3.3. Baseline structural properties of language regions

There were generally no relationships found between baseline structural properties of the primary language regions and the number of utterances exhibited during the SLO at baseline, $p < 0.05$ in most instances. There were some moderate associations between the number of utterances at baseline and baseline thickness of the STG, such as asymmetry of the anterior subdivision, which indicated more leftward asymmetry may have been associated with a higher number of utterances. However, none of these correlations survived correction for multiple comparisons.

3.4. Neuroimaging predictors of the benefits of PRT

Change in the number of utterances following 12 weeks of PRT was associated with asymmetry of the size of both subdivisions of the IFG as well as thickness of the lateral STG at baseline. The only correlation that survived correction for multiple comparisons was asymmetry of the IFG pars triangularis ($r_s = 0.57$, 95%CI [0.14,0.82]), $p = 0.01$), which indicated that more rightward asymmetry at baseline was associated with greater improvement at the end of the trial (Fig. 1). Importantly, this association remained significant when controlling for total brain volume ($r_s = 0.62$, 95%CI [0.22,0.84], $p = 0.01$), participant age ($r_s = 0.56$, 95%CI [0.13,0.81], $p = 0.02$), and the severity of functional communication deficits ($r_s = 0.62$, 95%CI [0.22,0.84], $p = 0.01$), as assessed by the CGI.

Correlations between changes in the secondary language endpoints (VABS and CDI) and baseline neuroimaging properties revealed several additional associations between structural measures and response to PRT. The majority did not survive correction for multiple comparisons, but there was a consistent relationship between the volume of the anterior subdivision of the STG (planum polare) and improvement following PRT (Fig. 2) for the VABS ($r = -0.63$, 95%CI [-0.88,-0.12],$p = 0.02$) and CDI, out of 396 ($r = -0.70$, 95%CI [-0.89,-0.29], $p = 0.003$) and 680 words ($r = -0.67$, 95%CI [-0.88,-0.26], $p = 0.005$).

4. Discussion

Young children with ASD exhibited a significant improvement in language and communication abilities following 12 weeks of PRT. As previously reported (Gengoux et al., 2015; Hardan et al., 2015; Minjarez et al., 2011), PRT parent training is an efficient and cost-effective therapy for targeting language development in children with ASD. In this preliminary investigation, we observed that children with ASD who displayed rightward asymmetry of the IFG at baseline, a primary language region, were more likely to exhibit improvement following PRT targeting language development. In an exploratory analysis, we also found that smaller volume of the anterior portion of the left STG at baseline, another primary language region, was also associated with improvement in standardized language measures following PRT.

Table 2
Language abilities before and after pivotal response treatment.

	Pre-PRT			Post-PRT			Pre vs Post			
	n	Mean	SD	n	Mean	SD	n	Mdiff	t	p
SLO										
# of Utterances	18	37.83	22.01	18	69.94	34.16	18	32.11	4.71	< 0.001**
VABS										
Expressive Communication (Vscale)	16	6.63	1.82	13	7.62	2.63	13	0.77	2.38	0.035**
CDI										
Words Produced (out of 396)	17	112.18	114.53	15	172.67	133.18	15	48.73	3.88	0.002**
Words Produced (out of 680)	17	149.06	150.80	16	236.81	176.78	16	72.06	2.88	0.011**

Functional communication measures are from before/after 12 weeks of Pivotal Response Treatment (PRT) parent training. SLO: Structured lab observation; VABS: Vineland Adaptive Behavior Scales; and CDI: MacArthur-Bates Communicative Developmental Inventories scores are displayed. Pre/Post comparisons are based on paired samples t tests.
* = sig. at $p < 0.05$.
** = sig. with FDR correction across all comparisons.

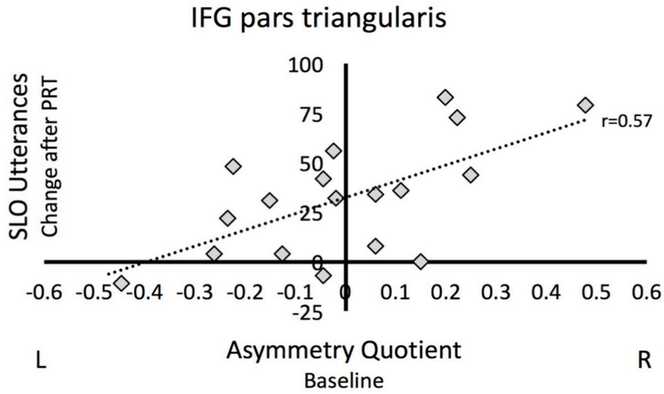

Fig. 1. Baseline Asymmetry of the IFG and Language Improvement after PRT. The relationship between the change in number of utterances from baseline to after 12 weeks of PRT, as assessed during standardized laboratory observation (SLO), and baseline asymmetry of the inferior frontal gyrus (IFG) pars triangularis subdivision is displayed.

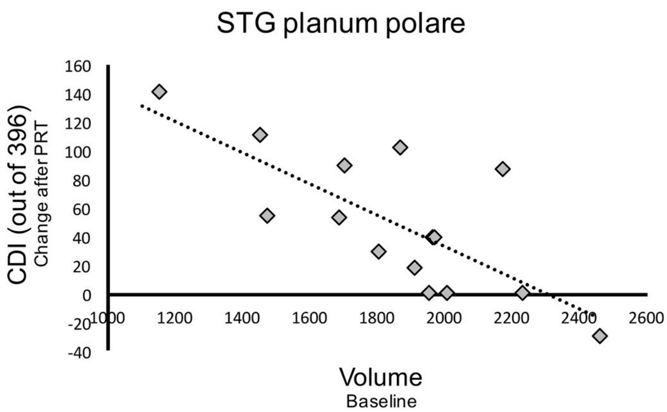

Fig. 2. Baseline Volume of the STG and Language Improvement after PRT. The relationship between the change in the number of words produced on the CDI (out of 396) from baseline to after 12 weeks of PRT and size of the left superior temporal gyrus (STG), anterior subdivision (planum porale), at baseline is displayed.

The development of language and communication abilities is associated with hemispheric 'specialization' of the primary language regions, typically leading to larger size of one hemisphere compared to the other, i.e., asymmetry (Josse and Tzourio-Mazoyer, 2004). Children with ASD, who commonly exhibit language delays, are more likely to display atypical rightward asymmetry of language regions compared to typically-developing (TD) controls (Herbert et al., 2005). However, these differences are variable across individuals and developmental periods (Knaus et al., 2009). In this pilot sample, we found that young children with ASD who exhibit language deficits may not display the anticipated association between language abilities and the degree of asymmetry of the primary language regions, STG (Brodmann area (BA) 22) and IFG (BA 44 and 45). There was a moderate relationship between asymmetry of the STG and the number of utterances that were displayed at baseline but this correlation did not survive correction for multiple comparisons. These findings, or lack thereof, indicate that altered 'specialization' of language regions in the brain may be associated with the language deficits that are often observed in children with ASD.

Lateralization of language regions may provide valuable information regarding the prediction of response to PRT targeting language. The presence of rightward asymmetry of the IFG at baseline, particularly in the par triangularis subdivision (BA 45), was associated with the level of improvement following 12 weeks of PRT. The IFG (Broca's area) is generally involved with the expressive (motor) aspects of speech (Fadiga et al., 2009), and the pars triangularis subdivision is also thought to mediate some additional aspects of semantic processing (Newman et al., 2003). The IFG is typically lateralized towards the left hemisphere in most TD individuals (Foundas et al., 1996) and this lateralization is associated with hemispheric language dominance (Foundas et al., 1998). Our preliminary findings suggest that young children with ASD who display atypical rightward asymmetry, or dominance, of the IFG may be more likely to respond to PRT targeting language development. We also observed that size of the left STG, specifically the anterior pole, was associated with response to PRT. This is particularly relevant because the left anterior STG is also associated with processing semantic information (Vigneau et al., 2006) and brain tissue enlargement is frequently reported in ASD (Amaral et al., 2008; Brambilla et al., 2003), including within the temporal lobe (Schumann et al., 2004). These preliminary results indicate that objective neurobiological markers could potentially aid in treatment planning for children with ASD, which is similar to previous studies that examined the ability of functional MRI measures to predict response to PRT targeting social deficits (Yang et al., 2016).

As with any preliminary research, there are some limitations that should be considered regarding this investigation. Participants were drawn from a convenience sample of children that were participating in multiple trials of PRT. Although PRT parent training implementation was similar across trials, differences across studies may have contributed to the variability in response. Handedness is also associated with variability in cerebral asymmetry (Toga and Thompson, 2003), but we were unable to reliably assess handedness because children in this age range typically demonstrate inconsistent hand preferences (Scharoun and Bryden, 2014). There may have also been relevant gender differences in these relationships, but we did not enroll enough females in this pilot sample to examine males and females separately. The uncontrolled design of this investigation might have also affected the findings, even though the imaging analyses were completed in a blinded manner. Finally, additional research will be necessary to determine whether these relationships are specific to PRT and children with severe language deficits or might be associated with other behavioral treatments targeting language development or other symptom domains in children with ASD.

In summary, PRT parent training is an effective and cost-efficient therapy to target language deficits in young children with ASD. Atypical development of language networks in the brain may be associated with the language delays and functional communication deficits that young children with ASD often exhibit and the neurobiological assessment of language regions may provide objective measures to aid in treatment planning for these domains. More importantly, the application of these techniques could allow more individualized prescription of interventions to young children with ASD and ultimately improve long-term outcomes. Future investigations should examine these relationships in a larger randomized controlled trial of PRT that has more power to assess other sources of variability (e.g., gender, IQ, concomitant interventions) in treatment response and neurobiology.

Funding

This work was supported by grants from the Mosbacher Family Fund for Autism Research, the Teresa and Charles Michael Fund for Autism Research, and the Stanford Bio-X Interdisciplinary Initiatives Program. The funding sources had no direct involvement in this investigation.

Acknowledgements

We would like to thank all of the participants and their families that were integral to this research and the support from the Stanford University School of Medicine, Autism Center, and Lucas Center for Imaging.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.001.

References

Almli, C.R., Rivkin, M., McKinstry, R., Group, B.D.C., 2007. The NIH MRI study of normal brain development (Objective-2): newborns, infants, toddlers, and preschoolers. Neuroimage 35 (1), 308–325.

Amaral, D.G., Schumann, C.M., Nordahl, C.W., 2008. Neuroanatomy of autism. Trends Neurosci. 31 (3), 137–145.

APA, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-V, Arlington, VA.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. 57 (1), 289–300.

Bigler, E.D., Mortensen, S., Neeley, E.S., Ozonoff, S., Krasny, L., Johnson, M., Lu, J., Provencal, S.L., McMahon, W., Lainhart, J.E., 2007. Superior temporal gyrus, language function, and autism. Dev. Neuropsychol. 31 (2), 217–238.

Boettcher, M.A., 2004. Teaching Social Conversation Skills to Children with Autism through Self- Management: an Analysis of Treatment Gains and Meaningful Outcomes. University of California, Santa Barbara, Unpublished Doctoral Dissertation.

Brambilla, P., Hardan, A., di Nemi, S.U., Perez, J., Soares, J.C., Barale, F., 2003. Brain anatomy and development in autism: review of structural MRI studies. Brain Res. Bull. 61 (6), 557–569.

Bryson, S.E., Koegel, L.K., Koegel, R.L., Openden, D., Smith, I.M., Nefdt, N., 2007. Large scale dissemination and community implementation of pivotal response treatment: program description and preliminary data. Res. Pract. Persons Severe Disabil. 32 (2), 142.

Carper, R.A., Courchesne, E., 2005. Localized enlargement of the frontal cortex in early autism. Biol. Psychiatry 57 (2), 126–133.

Dawson, G., 2008. Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev. Psychopathol. 20 (03), 775–803.

Destrieux, C., Fischl, B., Dale, A., Halgren, E., 2010. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage 53 (1), 1–15.

Fadiga, L., Craighero, L., D'Ausilio, A., 2009. Broca's area in language, action, and music. Ann. N. Y. Acad. Sci. 1169 (1), 448–458.

Fischl, B., 2012. FreeSurfer. NeuroImage 62 (2), 774–781.

Foundas, A.L., Eure, K.F., Luevano, L.F., Weinberger, D.R., 1998. MRI asymmetries of broca's area: the pars triangularis and pars opercularis. Brain Lang. 64 (3), 282–296.

Foundas, A.L., Leonard, C.M., Gilmore, R.L., Fennell, E.B., Heilman, K.M., 1996. Pars triangularis asymmetry and language dominance. Proc. Natl. Acad. Sci. Unit. States Am. 93 (2), 719.

Gengoux, G.W., Berquist, K.L., Salzman, E., Schapp, S., Phillips, J.M., Frazier, T.W., Minjarez, M.B., Hardan, A.Y., 2015. Pivotal response treatment parent training for autism: findings from a 3-month follow-up evaluation. J. Autism Dev. Disord. 45 (9), 2889–2898.

Guy, W., 1976. Clinical global impression scale. In: The ECDEU Assessment Manual for Psychopharmacology-Revised Volume DHEW Publ No ADM 76, pp. 218–222 (338).

Hardan, A.Y., Gengoux, G.W., Berquist, K.L., Libove, R.A., Ardel, C.M., Phillips, J., Frazier, T.W., Minjarez, M.B., 2015. A randomized controlled trial of Pivotal Response Treatment Group for parents of children with autism. JCPP (J. Child Psychol. Psychiatry) 56 (8), 884–892.

Herbert, M.R., Ziegler, D.A., Deutsch, C.K., O'Brien, L.M., Kennedy, D.N., Filipek, P.A., Bakardjiev, A.I., Hodgson, J., Takeoka, M., Makris, N., Caviness, J.V.S., 2005. Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. Brain 128 (1), 213–226.

Josse, G., Tzourio-Mazoyer, N., 2004. Hemispheric specialization for language. Brain Res. Rev. 44 (1), 1–12.

Knaus, T.A., Silver, A.M., Dominick, K.C., Schuring, M.D., Shaffer, N., Lindgren, K.A., Joseph, R.M., Tager-Flusberg, H., 2009. Age-related changes in the anatomy of language regions in autism spectrum disorder. Brain Imag. Behav. 3 (1), 51–63.

Koegel, L.K., 2011. Pivotal Response Treatment: Using Motivation as a Pivotal Response. University of California, Santa Barbara.

Koegel, L.K., Camarata, S.M., Valdez-Menchaca, M., Koegel, R.L., 1997. Setting generalization of question-asking by children with autism. Am. J. Ment. Retard. 102 (4), 346–357.

Koegel, L.K., Carter, C.M., Koegel, R.L., 2003. Teaching children with autism self--initiations as a pivotal response. Top. Lang. Disord. 23 (2), 134–145.

Koegel, L.K., Koegel, R.L., Brookman, L.I., 2005. Child-initiated interactions that are pivotal in intervention for children with autism. In: Hibbs, E.D., Jensen, P.S. (Eds.), Psychosocial Treatments for Child and Adolescent Disorders: Empirically Based Strategies for Clinial Practice, second ed. American Psychological Association, Washington, DC, pp. 633–657.

Koegel, L.K., Koegel, R.L., Harrower, J.K., Carter, C.M., 1999a. Pivotal response intervention I: overview of approach. J. Assoc. Persons Severe Handicaps 24 (3), 174–185.

Koegel, L.K., Koegel, R.L., Shoshan, Y., McNerney, E., 1999b. Pivotal response intervention II: preliminary long-term outcome data. Res. Pract. Persons Severe Disabil. 24 (3), 186–198.

Koegel, R.L., Camarata, S., Koegel, L.K., Ben-Tall, A., Smith, A.E., 1998. Increasing speech intelligibility in children with autism. J. Autism Dev. Disord. 28 (3), 241–251.

Koegel, R.L., Koegel, L.K., Boettcher, M.A., Harrower, J., Openden, D., 2006. Combining functional assessment and self-management procedures to rapidly reduce disruptive behaviors. In: Koegel, R.L., Koegel, L.K. (Eds.), Pivotal Response Treatments for Autism. Paul H. Brookes Publishing Company, Baltimore, MD, pp. 245–258.

Koegel, R.L., O'Dell, M.C., Koegel, L.K., 1987. A natural language teaching paradigm for nonverbal autistic children. J. Autism Dev. Disord. 17 (2), 187–200.

Koegel, R.L., Schreibman, L., Good, A., Cerniglia, L., Murphy, C., Koegel, L.K., 1989. How to Teach Pivotal Behaviors to Children with Autism: A Training Manual. University of California, Santa Barbara, CA.

Lord, C., Rutter, M., Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J. Autism Dev. Disord. 24 (5), 659–685.

Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., Bishop, S., 2012. Autism Diagnostic Observation Schedule, second ed. Western Psychological Corporation, Torrance, CA (ADOS-2).

Minjarez, M.B., Williams, S.E., Mercier, E.M., Hardan, A.Y., 2011. Pivotal response group treatment program for parents of children with autism. J. Autism Dev. Disord. 41 (1), 92–101.

Mohammadzaheri, F., Koegel, L.K., Rezaee, M., Rafiee, S.M., 2014. A randomized clinical trial comparison between pivotal response treatment (PRT) and structured applied behavior analysis (ABA) intervention for children with autism. J. Autism Dev. Disord. 44 (11), 2769–2777.

Mullen, E.M., 1995. Mullen Scales of Early Learning. AGS Circle Pines, MN.

Mundy, P., Stella, J., 2000. Joint attention, social orienting, and nonverbal communication in autism. In: Wetherby, A.M., Prizant, B.M. (Eds.), Autism Spectrum Disorders: a Transactional Developmental Perspective. Paul H. Brookes Publishing Company, Baltimore, MD, pp. 55–77.

National Research Council, 2001. Educating Children with Autism. National Academy Press, Washington DC.

Newman, S.D., Just, M.A., Keller, T.A., Roth, J., Carpenter, P.A., 2003. Differential effects of syntactic and semantic processing on the subregions of Broca's area. Cogn. Brain Res. 16 (2), 297–307.

Nordahl, C.W., Simon, T.J., Zierhut, C., Solomon, M., Rogers, S.J., Amaral, D.G., 2008. Brief report: methods for acquiring structural MRI data in very young children with autism without the use of sedation. J. Autism Dev. Disord. 38 (8), 1581–1590.

Scharoun, S.M., Bryden, P.J., 2014. Hand preference, performance abilities, and hand selection in children. Front. Psychol. 5, 82.

Schreibman, L., Stahmer, A.C., Pierce, K.L., 1996. Alternative applications of pivotal response training: teaching symbolic play and social interaction skills. In: Koegel, L.K., Koegel, R.L., Dunlap, G. (Eds.), Positive Behavioral Support: Including People with Difficult Behavior in the Community. Paul H. Brookes Publishing Co., Baltimore, MD, pp. 353–371.

Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., Lammers, C.R., Reiss, A.L., Amaral, D.G., 2004. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J. Neurosci. 24 (28), 6392–6401.

Toga, A.W., Thompson, P.M., 2003. Mapping brain asymmetry. Nat. Rev. Neurosci. 4, 37.

Vigneau, M., Beaucousin, V., Hervé, P.Y., Duffau, H., Crivello, F., Houdé, O., Mazoyer, B., Tzourio-Mazoyer, N., 2006. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. Neuroimage 30 (4), 1414–1432.

Yang, D., Pelphrey, K.A., Sukhodolsky, D.G., Crowley, M.J., Dayan, E., Dvornek, N.C., Venkataraman, A., Duncan, J., Staib, L., Ventola, P., 2016. Brain responses to biological motion predict treatment outcome in young children with autism. Transl. Psychiatry 6, e948.

Zimmerman, I., Steiner, V., Pond, R., 2002. Preschool Language Scale, fourth ed. The Psychological Corporation, San Antonio, TX (PLS-4).