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Impacting Development in Infants with Tuberous Sclerosis Complex: Multidisciplinary Research Collaboration

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Abstract

The Tuberous Sclerosis Complex Autism Center of Excellence Network (TACERN) is a six-site collaborative conducting longitudinal research on infants with tuberous sclerosis complex (TSC), focused on identifying early biomarkers for autism spectrum disorder (ASD). A multidisciplinary research team, which includes the specialties of psychology, neurology, pediatrics, medical genetics, and speech-language pathology, is working together to conduct studies on neurological status, brain structure and function, neurodevelopmental phenotype, and behavioral challenges in this population. This manuscript provides insights into the roles of the multidisciplinary multisite team and lessons learned from the collaboration, in terms of research as well as training of future researchers and clinicians. In addition, the authors detail the major findings to date, including those related to the identification and measurement of early symptoms of ASD, relationship between seizures and early development, and early biomarkers for epilepsy and developmental delay in infants and young children with TSC.

Keywords

infant; tuberous sclerosis complex; neurodevelopment; autism spectrum disorder; multidisciplinary research

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Genetically defined syndromes with increased prevalence of autism spectrum disorder (ASD) offer an opportunity to understand the brain pathophysiology that manifests as ASD, which can lead toward development of molecular-based targeted therapies. The long-range goal of the Tuberous Sclerosis Complex (TSC) Autism Center of Excellence (TACERN) consortium is mechanistic analysis of a Mendelian disorder, TSC, with high penetrance of ASD, to shed light on molecular pathways and targets relevant to ASD. The short-term goal of the consortium is to better characterize the ASD phenotype of TSC and to identify biomarkers that predict risk for development of this behaviorally-defined disorder. Such biomarkers may improve early ASD detection and intervention, thereby altering long-term

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neurodevelopmental sequelae. In addition, the knowledge and infrastructure established by TACERN provides opportunities for further study of TSC-specific treatments. TACERN is a complex multiteam system (Mathieu, Marks, & Zaccaro, 2001), incorporating multi-site, multidisciplinary contributions. The role of psychologists has been essential throughout the project, including original study design, selection of phenotyping measures, grant writing, data collection and interpretation, and manuscript preparation as both lead and co-authors. Further, the psychology team provides oversight of neurodevelopmental assessments and ensures fidelity in measurement. As such, this project provides a valuable example of the role of psychologists in team science. Challenges faced, lessons learned, and recommendations for other multidisciplinary teams have implications beyond the specific example of this consortium. Although this work applies specifically to ASD in the context of TSC, the team's successes and challenges over the last five years are relevant to all multidisciplinary/multisite studies involving psychologists.

TSC is an autosomal dominantly inherited genetic disorder that causes tumors to form in various organs, primarily the brain, eyes, heart, kidneys, skin, and lungs (Northrup, Koenig, Pearson, & Au, 2015). The disorder is rare, occurring in approximately one in 6,000 to 14,000 births (Curatolo & Bombardieri, 2008; Hallett, Foster, Liu, Blieden, & Valentim, 2011). Seizures occur in over 80% of individuals with TSC, most commonly beginning in the first year of life (Chu-Shore, Major, Camposana, Muzykewicz, & Thiele, 2010). Neurodevelopmental disorders, defined as TSC-Associated Neuropsychiatric Disorders (TAND), are also frequently observed and include ASD, intellectual disability, and psychiatric disorders. TAND affects approximately 50% of individuals with TSC and is often the most prominent issue reported by parents (Curatolo, Moavero, & de Vries, 2015; de Vries et al., 2015; Joinson et al., 2003; Winterkorn, Pulsifer, & Thiele, 2007). TSC is one of the single-gene disorders associated with ASD, affecting approximately 50% of children with TSC (as compared to less than 2% in the general population). Small pilot studies have demonstrated that infants with TSC who eventually get diagnosed with ASD begin to show delays as early as 9 months and show subsequent decline in nonverbal abilities from 12 to 36 months (Jeste et al., 2014; McDonald et al., 2017). TSC also has a high prevalence of developmental delay/intellectual disability, which can make differentiating global delay from ASD difficult at young ages (Humphrey, Williams, Pinto, & Bolton, 2004; Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008; Jesti et al., 2014; van Eeghen, Chu-Shore, Pulsifer, Camposano, & Thiele, 2012). Given that TSC can be diagnosed in utero via prenatal ultrasound, and given that up to 50% of infants with TSC will develop ASD, it is possible to examine the development of infants with TSC to see how development is different—starting from birth—in babies with TSC who will develop ASD versus those who will not. By comparing these two subgroups of infants with TSC prospectively, it may be possible to identify biomarkers associated with a higher risk for development of ASD. To the extent that ASD is similar in TSC to that in the general pediatric population, TSC provides a unique opportunity to study development in ASD essentially from birth.

The TACERN team is conducting a longitudinal study of neurodevelopment in infants with TSC, followed from age 3 to 36 months, with the primary outcome of interest being ASD clinical diagnosis at age 36 months. The study began in September 2012 and was funded by the National Institute of Neurological Disorders and Stroke and Eunice Kennedy Shriver

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National Institute of Child Health and Human Development for five years; the project is currently in its sixth year through a funding extension. Primary multidisciplinary team goals are: (1) to create an infrastructure for clinical treatment trials in infants with TSC at risk for ASD, including training of future multidisciplinary professionals, (2) to characterize the developmental precursors of ASD in 150 infants with TSC using a prospective multi-center design, (3) to identify biomarkers with advanced diffusion tensor imaging that help predict development of ASD in infants with TSC, and (4) to identify biomarkers with electroencephalogram (EEG) that help predict development of ASD in infants with TSC.

The project team successfully created the infrastructure for clinical trials including the multidisciplinary teams at each site with trainees across disciplines. The study enrolled 165 infants with TSC, and has retained 150 participants who have completed the planned neurodevelopmental and ASD assessments. Data has been collected using advanced diffusion tensor imaging and EEG to enable identification of early biomarkers in infants who later were diagnosed with ASD. The study is finalizing the 36 month assessments at this time, with final data analyses for the primary aims in progress. A more detailed description of major research findings to date will be presented after discussing the functioning of the research team.

Development and Composition of the TACERN Multidisciplinary, Multisite Team

TACERN grew out of earlier collaborative efforts among the principal investigators (PIs), including clinical trials (Krueger et al., 2017), serving on the professional advisory board of the Tuberous Sclerosis Alliance, and the 2012 TSC International Consensus Conference. At the 2011 Summit on Drug Discovery in TSC and Related Disorders, the five sites chose to develop the TACERN collaborative based on four main criteria: (1) the presence of a large TSC patient population in the targeted age-group for the study to ensure meeting recruitment goals; (2) clinician researchers with knowledge of the medical concerns, neurodevelopmental assessment, and treatment of TSC and ASD; (3) the facilities and expertise to perform 3T MRI, diffusion tensor imaging and high frequency EEG acquisition; and (4) ability to support training of future clinicians and researchers in the field. Each site needed to include collaboration with a Leadership Education in Neurodevelopmental Disabilities (LEND) interdisciplinary training program (Maternal & Child Health, 2018).

The TACERN consortium consists of researchers from six children’s hospitals in academic medical institutions from five cities spread across the United States. Each TACERN site brings specific expertise to the consortium and provides leadership for that aspect of the study (i.e., data management, EEG analysis, genetic materials repository, imaging, and neurodevelopmental assessment). Within each site, a local team includes, at a minimum, a pediatric neurologist with expertise in TSC and a lead psychologist with expertise in the assessment and diagnosis of developmental disorders including ASD. All five lead psychologists have advanced training in psychological and developmental assessment, including research certification in the key ASD measures and experience with assessing young infants. Four out of the five are clinical psychologists; the fifth is a developmental

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psychologist. One has an additional specialization in pediatric neuropsychology. In addition, four of the five psychologists have specific expertise in assessment and treatment of children with genetic disorders. Additional key disciplines in the consortium include biostatistics, data analytics and management, electrophysiology, genetics, nursing, pharmacology, public health, radiology, and speech-language pathology. This collaboration provides the study with a diverse group of specialists to explore many aspects of assessing biomarkers, treatment, and outcomes. Each specialist had input into the selection of best practice measures in order to comprehensively document information necessary to further the study goals.

Challenges, Lessons Learned, and Recommendations for Effective Team Research

TACERN is an ongoing project, and many lessons are emerging over time. As articulated by Shuffler and Carter (2018), the component teams within our multisite team each have their own attributes, processes, states, and team goals, and each team also contributes to one overarching, interdependent system. Overall, these independent and interdependent systems have been functioning effectively and producing desired outcomes in terms of: (1) recruiting and retaining research participants; (2) developing a longitudinal natural history database of carefully characterized neurological and developmental assessments for 150 young children with TSC; (3) training future researchers and clinicians across disciplines; and (4) dissemination of key findings. Nonetheless, challenges have emerged which have led to lessons learned and recommendations that may prove useful to other multidisciplinary teams.

Shared Leadership Across Disciplines and Sites

Leadership processes that are integrated and managed across and within the multisite team are essential to ensuring inter-team coordination and success in meeting goals (Shuffler & Carter, 2018). TACERN had the potential for challenges in leadership due to the number of different disciplines involved, the size and complexity of the project, and geographic spread of the sites. Although the neurologist leads had collaborated on past projects across sites, many of the other team members, including most of the psychologists, had not worked together before. Effective team leadership started with the NIH's establishment in 2007 of the trans-NIH Autism Centers of Excellence (ACE) Program, which provided the mechanism for developing and funding an ACE research network. The purpose of the ACE program is to support large-scale multidisciplinary studies on ASD, with the goal of determining the disorders' causes and potential treatments. Many other NIH centers are based at single institutions, whereas the complexity of rare diseases with both medical and psychological implications, such as TSC and ASD, require a multi-center approach. The research agenda of the Interagency Autism Coordinating Committee helped to set the frame for the TACERN goals and focus.

In implementing the TACERN project, the PIs and co-investigators demonstrated both formal and informal leadership influences that helped to develop a sense of belonging across teams, and motivated and inspired group efforts by creating a shared vision and connecting the identities of project staff across sites. This leadership began with the grant-writing

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process, in which the contributions of psychologists and speech-language pathologists were considered by the neurologist leads to be central to development of a robust study design and competitive grant proposal. The launch meeting at the beginning of the project brought everyone together and provided opportunities for the various sub-teams within the multisite team to begin to form their identities. For example, psychologists participated in cross-disciplinary meetings where they gained knowledge about TSC and the NIH ACE mission. Smaller discipline-specific meetings focused on certification and reliability training in neurodevelopmental measures.

In addition to central leadership, TACERN was designed to include opportunities for each site to take leadership of one component of the larger project, including neurodevelopmental assessment, epilepsy/seizure measurement, maintenance of the genetic data repository, brain imaging, administration, and regulatory aspects of the project. This sharing of leadership roles led to high levels of motivation and engagement at each of the sites. Similarly, opportunities for psychologists to take a lead role in autism measurement and LEND training provided shared leadership within the cross-disciplinary teams at individual sites.

Recommendations related to leadership of multidisciplinary research teams.

- The role of NIH in providing a global mission and strategic plan for autism research was central to launching and guiding the leadership of this team. It is recommended that research teams carefully consider the overall mission of the funder, incorporate their input at each step of the process, and share the guiding principles of the funding mechanism both in person and through written documents with all members of the multidisciplinary research team.
- Including the voices of all key disciplines from the beginning of the planning and grant-writing process is essential. This collaborative approach is important to all stages of project implementation, including the selection of measures and development of the study design; development of procedures, structures and fidelity measurement; implementation of all project procedures; and dissemination of research through publications and presentations.
- Motivation and commitment are increased when members of the research team have opportunities for autonomy in the leadership of smaller aspects of the project.
- Future research consortiums involving psychologists should address the need for ongoing communication, at all levels. In addition to psychologists communicating with each other (e.g., via email distribution lists and annual meetings), it is critical that psychologists at every site in a consortium communicate with other professionals at their site (e.g., physicians, geneticists) as well as with the central leadership of the project.

Team Formation and Functioning

Processes related to team formation, as well as cognitive, motivational/affective, and behavioral influences on team functioning, have been found to have important roles in effective team science (Hall et al., 2018). Because TSC is a rare disorder, researchers in this

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field may not encounter other experts within their same institution; therefore, the cross-pollination of experience over time and location was needed for the team to develop important hypotheses and study aims. The TACERN consortium emerged following a period of collaboration on other projects. Similarly, TACERN leveraged the existing structure of the LEND interdisciplinary training programs, which already had shared goals for training, research, and service within the developmental disability field. Thus, prior experience with collaboration and cross-disciplinary work was important to the formation and shared goals of the TACERN team.

Physical proximity engendered through face-to-face meetings followed up with regular phone and email interactions have been essential to TACERN team building. These meetings led to a shared body of knowledge about TSC, epilepsy, and ASD, as well as the roles of different disciplines in execution of the project goals. In addition, the initial launch meeting and annual recalibration meetings have provided key opportunities for collaboration and camaraderie between psychologists, psychology trainees, and PIs. Serendipitous weather events during annual psychologist recalibration meetings, including a tornado in Birmingham complete with midnight evacuation to the basement of the hotel, a severe storm in Houston leading to anxious calls home, and a surprise late Spring storm in Boston leading to a canceled meeting and two psychology fellows stranded en route, all lent an emotional valence to the professional connections that were made over the years. Repeated interactions at national conferences have led to a sense of community within the study and the clinical and research arena of ASD.

One challenge to team functioning has been sustaining the face-to-face interactions and consistent communication with personnel changes and decreased funds for meetings as the study nears completion. Although it can be tempting to forgo the time and expense of meeting after the project is running smoothly, limited opportunities to meet in person toward the end of the project can mean less cross-pollination of research ideas during the stage of manuscript development.

Recommendations related to team formation and functioning.

- For a project of this complexity, building on and leveraging existing collaborative relationships increases the probability of success in assembling an effective team.
- Face-to-face interactions are critical to building the relationships needed to effectively launch and maintain study integrity and reliability. Although costly for a geographically diverse consortium, the in-person launch meeting (incorporating all key disciplines) and annual meetings of smaller teams for specific purposes is worth the investment.
- Mechanisms to incorporate new research personnel are essential to provide continuity of the study and continued collaboration across sites.

Recruitment, Retention, and Family-Centered Research

All longitudinal research projects, particularly involving rare disorders, require considerable efforts to ensure adequate recruitment and retention to reach study goals. In TACERN, many

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families travel great distances to participate in the study, and they make a significant time commitment over three years. Nonetheless, to date over 90% of participants have remained enrolled in the longitudinal study. Although many factors contribute to successful recruitment and retention, discussions with families suggest that obtaining detailed information about their child's development over time, together with consultation about navigating the service system, contributed to family's engagement and commitment to the study.

Psychologists in TACERN contributed to a family-centered research approach by discussing the child's developmental and behavioral profile as it pertains to TSC and answering questions about early intervention and special education services. Providing feedback to families in an interdisciplinary fashion, including the input of neurologists, psychologists, and speech-language pathologists, has enabled families to obtain an integrated understanding of their child's strengths and needs across domains. Psychologists researched resources in the communities where families lived, wrote letters, and talked with service providers to advocate for needed services and supports. Psychologists were also of benefit to the families whose children were at high risk of developmental delays and ASD due to their TSC diagnosis but were found by the study evaluations to be developing within normal limits. In these cases, the psychologists were able to help the family understand the aspects of their child's behavior and/or development that were more within the realm of typical development but might have been exacerbated by the parents' concern about possible delays (e.g., not implementing developmentally-appropriate behavior management due to concerns they might blame a child for a delay-related issue).

Study psychologists' infant-family mental health expertise positioned them uniquely to be able to support whole families' needs in an integrated fashion during study visits by supporting family members who also have TSC, identifying concerning behaviors in siblings, and supporting the young child through difficult medical procedures. Discussing information about their child's development and behavior, the role of early intervention providers, and concerns about future development, all led to therapeutic exchanges in which psychologists had opportunities to support parents.

Recommendations related to recruitment, retention, and family-centered research.

- Psychologists play important roles in studies that involve talking with parents about potentially challenging information regarding their infants' development and implications for long-term functioning. One way to increase families' engagement and the value of the study for them is to think about the research study visits as therapeutic encounters, which can help parents increase their knowledge of their child's unique needs, learn about available services and supports, increase their confidence in advocating for their child, and shift the narrative of the family's perspective about their child's medical and developmental condition and the implications for the future.
- In a related manner, psychologists generate study data that has clinical relevance, e.g., developmental test scores. This information is potentially highly valuable to families because it can enable them to access services. Brief research reports

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containing this information are an incentive for families to remain in a long-term study over time.

- To create effective family-centered and therapeutic encounters, psychologists should use moments that emerge during developmental testing, parent interviews, or other procedures to engage with the parents, validate feelings and concerns, narrate the child's experience and support their engagement in study procedures (thereby also modeling this approach for parents and providers from other disciplines).
- In a longitudinal study, the psychologist conducting developmental assessments and parent interviews spends time with the family in an extended relationship during key touchpoints in the child's life. Providing continuity in the psychologist provider over time helps the family to utilize this relationship to increase their understanding of their child's development and gain confidence in seeking and utilizing community resources to support their child.

Autism Assessment and Diagnosis: Structure and Control Mechanisms

Multiteam system structures, work designs, and control mechanisms are critical to managing the complexity of the component team collaborations, and to ensure achievement of team goals (Shuffler & Carter, 2018). These factors were critical to preventing and resolving challenges related to the complex task of assessing and diagnosing ASD in this unique population. Several structure and control mechanisms were put in place for the overall project. The detailed TACERN manual of operating procedures was shared with all investigators and is updated regularly to ensure that all aspects of data collection and entry are completed with fidelity across sites, and the Data Coordinating Center ensures accuracy in data entry. Further, the requirement by the NIH ACE program to include data in the National Database for Autism Research ensures harmonization to a common standard of the data collection process. Control mechanisms have been essential to maintaining fidelity of data collection, particularly of the neurodevelopmental measures, which require a high degree of training and calibration. In TACERN, rigorous tracking was set up to ensure that all administrators of neurodevelopmental measures reached established training and reliability criteria for all measures.

Recalibration meetings, held annually, were designed to ensure that test administrators maintained reliability in administration, scoring, and interpretation. Psychologists and other test administrators from around the country met in person to review videotapes of assessments, conduct consensus scoring, and check reliability. The annual recalibration meetings have allowed for discussion of questions or concerns about test administration and scoring and ensure that autism-specific assessments are administered at each site with research fidelity. Due to this careful planning and training, the project currently has a robust and accurate database of carefully characterized infants and young children with longitudinal data.

Some examples illustrate challenges in cross-site calibration of developmental assessment, and ways the team addressed these. Psychologists and neurologists observed that in some cases reaching a definitive ASD diagnostic decision was challenging due to factors such as

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severe developmental delay, differences in parent report compared to observational measures, and the occurrence of seizures during testing. Therefore, the team added an ASD clinical diagnosis certainty score, including information about reasons for lack of certainty, to ensure that these factors would be documented and could be considered in interpretation of data. More recently, analysis of preliminary 24-month data revealed differences across sites in the rate of ASD diagnoses, similar to what has been observed in other multisite ASD studies (Arnold et al., 2000; Lord et al., 2012). This observation led to adding more discussion of diagnostic decisions to the recalibration meetings and highlighted the relative importance of waiting for greater diagnostic certainty at the 36-month visit versus capturing early concerns about ASD symptoms that may be below threshold for a definitive diagnosis.

Recommendations related to assessment and diagnostic procedures for complex disorders.

- It is essential to ensure that all administrators of measures have completed required training and documented scoring reliability before administering measures for the study. In the case of ASD measures, this training can be a lengthy process and may delay the start of a study if qualified examiners are not part of the team from the beginning.
- Regional differences have been found in interpretation of ASD measures and resulting clinical diagnoses in multisite studies. Therefore, it is important to have regular opportunities for clinicians to compare their interpretations of tests as well as their clinical decision-making in reaching diagnoses and certainty scores. Reliability in scoring is not sufficient; recalibration needs to also include discussions about the diagnostic process.
- In multidisciplinary studies, there may be more than one discipline with expertise in ASD assessment and/or diagnosis (e.g. in TACERN, neurologists, psychologists, and speech-language pathologists all contributed to autism measurement). Therefore, procedures need to be put in place to discuss differences in diagnostic conclusions and ways to address these differences consistently across sites.

Team Research, Data Use and Authorship

TACERN developed and implemented a data access policy and protocol for study personnel to propose and obtain approval to conduct studies utilizing the central dataset. The overriding principles guiding data use and sharing include maintaining the integrity of the study, fairness in access and use by all contributing investigators, and advancement of scientific knowledge in TSC, ASD, and epilepsy. Any investigator can submit a request to access data to conduct a study, with all requests processed by the Clinical Coordinating Center and reviewed by the lead PIs. Central coordination ensures that the PIs are involved in decisions about data usage, avoids duplication of effort, and helps to connect researchers from different sites who have similar research interests. Thus, cross-site collaboration on publications is encouraged.

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Over the course of study implementation, central leadership has had an important role in the configuration of writing teams and the process for accessing the centralized database. The streamlined process for proposing research projects, approval by the central body, and having PI support for success of manuscripts has encouraged both individual initiative and collaborative teamwork across disciplines and sites. On the other hand, there have been times when data analysis related to one research-approved question has led to findings that overlap with the work being pursued by a separate writing team. In those cases, cross-consultation and collaboration between teams and the inclusion of the primary PIs has been essential to ensure that manuscripts are coordinated and that all involved co-authors receive appropriate credit and opportunities to contribute. Monthly phone meetings of the PIs provide an opportunity to review data requests and the progress of manuscript writing to identify and resolve potential conflicts.

The Science of Team Science research summarized by Hall et al. (2018) provides another perspective about the outcomes of work by teams of researchers. The value of team science is evidenced by findings that “boundary-spanning” across geographic and organizational boundaries leads to great productivity and scientific impact, and that moderate levels of cross-disciplinary heterogeneity yield highest impact publications (Onal Vural, Dahlander, & George, 2013; Yegros-Yegros, Rafols, & D’Este, 2015). Although TACERN is in the early stages of completing planned research manuscripts, those published so far evidence the potential impact of cross-disciplinary and cross-site collaboration; each has included named authors from all six sites and across at least three disciplines.

Hall et al. (2018) also considered the influence of team composition on research impact. For TACERN, the large size of the full team combined with the control processes outlined above has enabled efficient collaboration despite the complexity of the project. Regarding gender, Hall et al. (2018) noted that gender diversity in science teams has been correlated with more citations, and yet many science teams include few if any women (Kegen, 2013; Stvilia et al., 2011). On the TACERN team, three of the five PIs are women as are all five of the psychology leads. Finally, inclusion of team members with a range of academic ranks and roles including postdoctoral fellows has been shown to lead to more publications and more breakthrough publications (Conti & Liu, 2015; Cook, Grange, & Eyre-Walker, 2015). Although it may be too soon to determine if these factors will influence the ultimate success of TACERN, so far six out of the seven publications had junior faculty first authors and four had female first authors.

Recommendations related to team research, data use, and authorship.

- Large teams that span disciplines, universities, departments, and geographic locations have challenges in ensuring smooth coordination of manuscript development. Essential to success is strong, engaged leadership, as well as frequent communication. A central process for vetting data use and manuscript proposals, and for joining researchers across sites and disciplines with similar interests, leads to synergy of ideas, stronger ultimate publications, and fair opportunities for authorship.

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- Although complexity and diversity of research teams complicates efficient completion of manuscripts, considering diversity in gender, academic rank, discipline, and inclusion of postdoctoral fellows and students may increase the impact and meaningfulness of resulting publications.

Psychology Training Incorporated in Team Science

The TACERN collaborative has contributed to training of psychologists and other allied health disciplines through collaboration with LEND interdisciplinary training programs as a key component toward the aim of building an infrastructure for clinical trials of ASD in infants with TSC. Since the 1950s, Federally-funded LEND programs have provided graduate and post-graduate level interdisciplinary training with an emphasis on developing future leaders in the field of neurodevelopmental disabilities. ASD-specific LEND goals include increasing the number of health professionals who can provide evidence-based screening, diagnosis, and treatment for ASD and other developmental disabilities. LEND trainees come from more than 14 allied health disciplines and include family members of children with disabilities and self-advocates (i.e., trainees with a disability). Engaging LEND trainees through the TACERN study reflects priorities for both programs to enhance the training of future researchers and leaders in academic, policy, and clinical realms with combined expertise in ASD and TSC. This collaboration within and across TACERN and affiliated LEND sites has stimulated the development of additional didactic, clinical, and research experiences to include specialized exposure to TSC. A long-term goal of the collaboration is to develop clinical researchers with agendas focused on a specific genetic disease as a model of ASD and to develop, investigate, and disseminate effective interventions across the range of individuals affected by ASD.

Psychology interns, graduate level practicum students, and undergraduate psychology students rotate through the TSC clinics to learn about neurodevelopmental assessment and multi-site, multidisciplinary research. Psychology trainees developed and delivered presentations on topics such as early identification and screening of ASD, intellectual disabilities, and neurodevelopmental disorders and co-occurring mental health conditions to the interdisciplinary audience of LEND trainees, as well as to other community audiences including early intervention providers, mental health professionals, and pediatric residents. In addition, psychology trainees gain clinical skills in early screening and diagnosis of ASD through supervision and mentoring by TACERN investigators; their funded roles in the study include administering, scoring, and interpreting developmental and ASD diagnostic assessments and providing feedback, recommendations, and referrals to the families. At one site, 10 psychology postdoctoral fellows over the course of the study have reached research reliability in the diagnostic assessments for ASD. At some sites, fellows provide supervision to psychology interns or graduate students. In addition to being directly involved in data collection, psychology trainees have utilized the larger TACERN data set, under the mentorship of TACERN investigators, to conduct original research. Projects in progress include analysis of equity in access to early intervention services, differential diagnosis of ASD in toddlers, and evaluation of repetitive and restricted behaviors in young children with genetic syndromes.

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Trainees have remarked that these experiences have greatly enhanced their clinical acumen when working in a fast-paced medical setting, strengthened their understanding of medical and pharmacological impacts on development and behavior in a high-risk population, and influenced their subsequent training goals and career objectives. The training opportunities meet psychology accreditation standards for competency in interprofessional skills in clinical and research roles. A number of psychology trainees from TACERN obtained academic positions at universities, including in University Centers for Excellence in Developmental Disabilities. Others are utilizing their highly specialized skills in clinical settings, such as university and children's hospitals, primary care, community mental health centers, and schools.

The primary challenges in integrating a training component into the larger grant goals have related to the timing of training requirements that may not be aligned with the larger project. At the beginning of the project, the recruitment and selection of psychology postdoctoral fellows occurred prior to decisions about grant funding, and the fellowship training year began before the project was ready to launch. Therefore, flexibility was needed in order to incorporate trainees in the first year. In later years, having multi-year funding enabled some sites to recruit fellows specifically to work on the grant which improved the fit between fellow interests and grant requirements. A second timing challenge involved the length of time needed to fully train to reliability in the ASD measures. At one site, having a two-year fellowship meant that fellows could learn the measures in their first year, and then use that training to have a funded role on the grant in their second year. However, other sites found this timing too difficult to achieve and so trainees observed but did not directly provide ASD assessments. A last timing challenge was incorporating trainees in data analysis and manuscript development on teams across sites and disciplines. For example, one fellow joined a TACERN data analysis project to meet her fellowship scholarly project requirement, but then decisions were made by the larger team to postpone final analysis of data until 36-month data had been collected. This meant that the fellow's portion of the project could not be completed within the training year and alternate plans were made. However, an equitable solution was reached--inviting the fellow to participate in ongoing publications using the data after fellowship completion.

Recommendations related to incorporating psychology training within multidisciplinary research.

- Although it may be simpler to conduct large, complex research projects without incorporating trainees, the added work involved in integrating a training component has important benefits. Trainees bring new perspectives and commitment to the actual work of the project, and they benefit from the hands-on learning about team research. Incorporation of a research component into a clinically-oriented fellowship provided opportunities for fellows to develop new career pathways and skills. Involvement in team science during fellowship was an opportunity to prepare trainees to be future competent investigators.
- Providing flexibility in the specific ways that different sites incorporate trainees allows the overall project to include a training component without putting undue burden on sites that have different training programs and goals.

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Research Collaboration and Major Findings to Date

Although longitudinal data collection is still in progress and the primary aims of the study have not been published, we have learned important information about our patient population in terms of early developmental trajectories; relationship between EEG findings and subsequent development of seizures; and the relationship between seizures, development, and autism-specific characteristics.

Presentation and Diagnosis of TSC in Infants

As noted above, TSC is an ideal genetic disorder to study ASD because diagnosis can often be made early in infancy or even prenatally. Davis et al. (2017) explored the TACERN database to identify ages at which major and minor features of TSC emerged in 130 infants with TSC who were followed up to 36 months of age. The most common initial presenting features included cardiac rhabdomyomas (59%, often identified prenatally) and hypomelanotic macules on the skin (39%), which became more common as development progressed (94%). Subsequent prevalent diagnostic features included tubers/other cortical dysplasias (94%), subependymal nodules (90%), and cardiac rhabdomyomas (82%). By one year of age, 73% of the sample had developed seizures consistent with an epilepsy diagnosis, which is consisted with what is reported in the literature (Chu Shore et al., 2010).

Autism Identification

Capal, Horn, et al. (2017) examined the utility of a relatively new instrument for assessing ASD symptomatology, the Autism Observation Scale for Infants (AOSI), administered at 12 months, with predicting ASD symptoms on the ADOS-2 and the ADI-R at 24 months in 79 infants from the TACERN study sample. The AOSI is a semi-structured assessment for infants 6 to 18 months old, designed for research and not yet validated for clinical purposes. The measure includes items tapping sensory and motor behaviors, attention, visual tracking and social emotional behaviors (Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008). Capal and her colleagues found that higher AOSI scores at 12 months were associated with a higher risk for ASD classification on the Autism Diagnostic Observation Schedule-2 (ADOS-2) and Autism Diagnostic Interview-Revised (ADI-R) scores at 24 months. Scores of greater than 13 on the AOSI were strongly predictive of subsequent ASD classification on the ADOS-2 (with specificity of 0.89 to detect ASD symptoms with the ADOS-2). Specific items on the AOSI associated with subsequent ADOS ASD classification included: orients to name, imitation of action, anticipatory responses, reciprocal social smile, social interest and shared affect, motor control and behavior, engagement of attention, and sharing an interest. High scores on the AOSI were also predictive of greater abnormalities in reciprocal social interaction and communication abnormalities on the ADI-R. This study suggested that the AOSI could be used as a tool for early identification of infants with TSC who are at high risk for developing ASD symptomatology at 24 months; future data analyses will shed light on whether the AOSI predicts ASD clinical diagnosis in children with and without developmental delay.

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Seizures and Impact on Development

Capal, Bernardino-Cuesta, et al. (2017) investigated the relationship between seizure activity and developmental outcomes in this same cohort of 130 infants with TSC (0–36 months) and found that infants with a history of seizures exhibited lower scores on the Mullen Scales of Early Learning, the Preschool Language Scale-5th Edition, and the Vineland Adaptive Behavior Scales, 2nd Ed. This relationship was seen for seizures in general, as well as for infantile spasms in particular. Although some delays were seen as early as 6 months, by 12 months of age significant differences emerged in all areas and persisted through 24 months of age. Patients with a history of seizures also demonstrated more symptoms of ASD on the AOSI (at age 12 months), and the ADOS-2 and communication domain of the ADI-R (at age 24 months). Infantile spasms have been shown previously in retrospective studies to strongly associate with unfavorable developmental outcomes including higher risk for ASD symptoms (Bolton, Park, Higgins, Griffiths, & Pickles, 2002; Chu-Shore et al., 2010; Humphrey et al., 2014; Jozwiak, Schwartz, Janniger, Michalowicz, & Chmielik, 1998; Vignoli et al., 2013). Using a more robust longitudinal, prospective design with comprehensive standardized developmental assessments, the TACERN study not only confirmed this important relationship, but also showed that the negative impact of infantile spasms on neurodevelopment is already present by 12 months of age. Although infantile spasms and higher seizure frequency were strong predictors of developmental delay, earlier age of seizure onset was the most important factor in predicting developmental outcome. Furthermore, all of the infants without a seizure history had normal developmental outcomes as of 24 months. Findings such as these provide an early window of opportunity for identifying a disease that is associated with significant neurological and developmental sequelae. The authors conclude that infants with TSC can be identified early in life, before the onset of neurologic sequelae—and at a time when treatment could alter neurodevelopmental outcomes such as medication-refractory epilepsy, developmental delay, and ASD.

Wu et al. (2016) assessed the clinical utility of routine visual EEGs in predicting the onset of seizure activity. Twenty-eight seizure-free infants (< 7 months) received one-hour standardized video EEG at 1.5, 3, 4.5, 6, 9, 12, 18, and 24 months of age. Of these infants, 19 (68%) developed seizures, and 14 of those 19 (73.7%) demonstrated epileptiform discharges on EEG prior to the onset of clinical seizures. The average interval between the appearance of epileptiform discharges on EEG and subsequent clinical seizures was 2.8 months (median 1.9 months). No epileptiform discharges were detected prior to seizure onset in the other five infants who developed seizures (26.3%). This study provided prospectively collected evidence supporting the utility of repeated EEG's for clinical management in infants with TSC (Curatolo, Jóźwiak, & Nabbout, 2012) and led to the PREVeNT Trial, which leverages this finding that there is a substantial window of abnormal EEG with no clinical seizures during which one can test the efficacy of anti-seizure medications in preventing developmental delay and epileptogenesis.

Biomarkers of Developmental Delay: MRI, EEG, Genetics

The TACERN dataset has also led to investigation into possible biomarkers for developmental delay and epilepsy. Srivastava et al. (2018) examined the relationship

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between cerebellar volume on MRI and developmental status in 70 TACERN study infants (age 12 months). For infants with the *TSC2* mutation, greater cerebellar volume was associated with higher Mullen Scales of Early Learning scores. Along with motor function, the cerebellum is associated with a number of other neurocognitive functions including language, cognition, working memory, executive function, and processing speed (Sundberg & Sahin, 2015) and it is hypothesized that the smaller cerebellar volumes associated with poorer neurodevelopmental outcomes may reflect Purkinje cell degeneration—at least in individuals with *TSC2* mutations. Cerebellar volume may represent a potential biomarker of severity of TSC, and volumetric analysis of the cerebellum volume may provide families with affected children a more refined prognosis than other measures such as tuber burden or genotype alone.

Bernardo et al. (2018) examined the association between interictal fast ripples (FR; 250–500 Hz) on scalp EEG and epilepsy in seven infants with TSC (mean age = 17.6 months) and four controls (mean age = 27.8 months). Although high frequency oscillations (HFO) such as FR have been proposed as a biomarker for epileptogenic zones in the brain, these HFOs have typically been obtained using invasive macroelectrode recordings. Using human visual identification techniques carried out by experienced EEG reviewers, FR was detected in all seven infants with TSC and further verified by multiple modalities, including co-localization to MRI-visible cortical tubers at the lobar level, time-frequency analysis, and a semi-automated detector. FR was detected in none of the control infants. Within the TSC group, 86.5% of FR was detected in cortical areas containing cortical tubers identified on MRI. Across all FR events, 61.5% of FR were associated with spikes, and 78.8% occurred in channels that contained epileptic spikes, spike-wave discharges, or paroxysmal fast activity. Bernardo et al. concluded that interictal FR from scalp EEG appears to be a promising non-invasive biomarker of epilepsy in infants, which have thinner skulls than adults, perhaps making scalp FR more detectable. Noting that 80% of patients with TSC develop medically refractory epilepsy (Chu-Shore et al., 2010) and that 67% of patients undergoing surgical treatment attain seizure freedom (Wu et al., 2010), the authors speculate that these non-invasive scalp FR might be used to aid in pre-operative delineation of the epileptogenic zones. If subsequent studies with larger numbers of participants replicate these findings, scalp FR may become a particularly powerful tool for the TSC population, given that the epileptogenic network is often widespread in TSC (Okanishi et al., 2014).

Farach et al. (2016) examined six cases (descriptions ranging from birth to 15 years) of individuals with *TSC2* c1864C>T, considered to be a pathogenic variant of the *TSC2* gene. In general, individuals with *TSC2* variants are thought to have more severe phenotypes than those with *TSC1* variants (e.g., Au et al., 2007; Kothare et al., 2014); however, there have been some reports that specific variants of *TSC2* are associated with milder phenotypes. Most of the six patients in this case report did not meet the clinical criteria for definite TSC, although they carried *TSC2* c1864C>T. Developmental testing revealed cognitive and language functioning within the average range for one patient. This study underscored the importance of genotyping as a prognostic tool for developmental outcome in TSC.

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Emerging Research Reports

Future analyses are focused on discrepancies seen between measures of ASD symptoms (ADOS-2, ADI-R, and AOSI) and clinical ASD diagnosis, and implications for specificity of the measures in young children with comorbid developmental delay and epilepsy. In addition, comparison of ASD diagnosis at 24 and 36 months in children with different levels of developmental delay, will lead to insights into the symptom course of ASD in young children with co-morbid conditions. There is interest in looking more deeply into seizure onset and semiology during the first year of life, as well as the impact of various treatments (e.g. medications; epilepsy surgery) on seizure outcomes.

A common theme underscoring emerging TACERN study reports is the utility of psychological assessment in infants with TSC in terms of relating developmental function to genotype, neurological status, and behavioral/emotional/adaptive function. Without this critical information, clinical interpretation of neurological and genetic data would be impossible. Psychologists have thus played a critical role in identifying potential biomarkers of neurodevelopmental delay and ASD in infants with TSC in the TACERN study.

Conclusions

In summary, TACERN has been effective in bringing together researchers across six sites and multiple disciplines toward common goals of understanding the development of and improving the care for young children with TSC and their families. Key to success have been leadership approaches that encourage team building across and within sites and disciplines, through centralized and decentralized, formal and informal leadership components. Building on existing collaborations and networks led to relatively fast and efficient team formation and coordination. Face-to-face meetings that cross-pollinate across disciplines and sites have increased engagement, conflict resolution, and motivation among team members and led to opportunities for shared learning, problem-solving, and applications of knowledge across both research and clinical settings. Careful control processes have been necessary to ensure fidelity in methods for data collection, scoring, interpretation, and data entry across all measures, sites, and disciplines. An open yet carefully coordinated approach to data use, sharing and publication development is needed to ensure motivation, innovation, and cross-disciplinary input to research outputs. This cross-disciplinary collaboration has fully incorporated the broad skill set of psychologists in measurement approaches, diagnostic acumen, clinical skill for engaging families, and research knowledge related to infant development across domains, ASD phenotypes, and the intersection of medical, developmental, and family influences on behavior. Finally, it enhanced the training of future health service psychologists in clinical and research endeavors in the context of interprofessional teams.

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