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Effects of Sertraline Treatment for Young Children with Fragile X Syndrome: Family Perspectives via Case Studies

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Effects of Sertraline Treatment for Young Children with Fragile X Syndrome: Family Perspectives via Case Studies

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Abstract

Current research on children with Fragile X Syndrome (FXS) lacks inclusion of qualitative outcomes on the child's daily occupational performance. Standardized measurements are frequently utilized and provide useful information, however, can be less sensitive to change (Berry Kravis et al., 2013) and miss capturing family perspectives and improvements within meaningful occupations. This research incorporates family perspectives via semi-structured interviews to promote an in-depth understanding about FXS and its impact on child and family occupations in addition to standardized assessment scores through in-depth case study analysis. This study used a mixed method research design examining four male participants who were given sertraline in an in-depth case study analysis. Caregivers were interviewed using a semi-structured interview protocol at baseline and at six months post-treatment to discuss their child, occupations, and any potential impacts of sertraline. Baseline and post-testing standardized assessment results were compared to the occupation centered semi-structured interviews. The data was collected from a pre-existing database in a previous study determining the outcome measures of sertraline. Dedoose software was used to code for categories and themes found in the FXS family interviews. Results indicated that standardized assessments have limited sensitivity to fully capture the lived experiences of families with FXS. Standardized assessments test for performance skills that may not necessarily translate to daily occupations as reported by families. While future practitioners should use standardized assessments in their evaluations, they should also include what families report in their daily lives to fully conclude the child's abilities to participate and engage in their daily occupations

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Introduction

Fragile X Syndrome and Occupations

Fragile X syndrome (FXS) is relatively rare, however the premutation in the FMR1 gene is relatively common. Incidence of FXS is 1 in 4000 males are affected and 1 in 6000 females of all races and ethnics groups are affected (NFXF, 2017). Additionally, 1 in 259 females carrying fragile x could pass it onto their children (NFXF, 2017). According to the National Fragile X Foundation, FXS is a genetic condition causing intellectual disability, behavioral and learning challenges, and has various physical characteristics (2017). Much of the research completed for FXS is anchored in the medical model, focusing on quantitative results and lacks inclusion of qualitative measures of occupational performance. Occupational performance can be defined as "the ability to perceive, desire, recall, plan and carry out roles, routines, tasks and sub-tasks for the purpose of self-maintenance, productivity, leisure and rest in response to demands of the internal and/or external environment" (Ranka, J., & Chapparo, C., 1997, p. 58). Furthermore, occupations can be defined as "[the] various kinds of life activities in which individuals, groups, or populations engage, including activities of daily living, instrumental activities of daily living, rest and sleep, education, work, play, leisure, and social participation" (Occupational Therapy Practice Framework: Domain and Process, 2017, p. S19). Our research study aims to analyze transcribed audio interviews case by case to gain the perspectives from families and their daily lived experience to further look into occupations in addition to the child's test scores from various assessments.

Fragile X Syndrome - Background Information

FXS is the most common inherited form of intellectual and developmental disability (IDD) and the most common single gene cause of autism spectrum disorder (ASD) (Hess et al., 2016). Statistically, 46% males and 16% females with FXS has been diagnosed for ASD (NFXF, 2017). While FXS occurs in both genders, males are more severely affected than females. Ouyang et al., (2014) stated, "Children with FXS may have more functional limitations, complex health care and service needs and unmet needs than those with ASD or ID only" (p. 1525). Individuals with FXS may have a range of developmental concerns, behavioral symptoms, adaptive behavior deficits and cognitive impairments. Characteristics of FXS include anxiety, hyperactivity, impulsivity, and sensory processing deficits (Wheeler et al., 2015). Life expectancies are not affected since there are no life-threatening health concerns (NFXF, 2017). Children with FXS have functional limitations that interfere with occupational performance when engaging in their daily life activities in terms of independence and capability due to their behavioral phenotype. These occupational performance limitations include: school engagement, community participation, family occupations (e.g. holidays, travel), wherein there is both a disconnect between the child's needs and their contexts as well as decreased access and opportunity for engagement.

Genetics

FXS is a genetic X-linked disorder caused by a genetic mutation or repeats of CGG nucleotides. The cause of FXS is due to decreased or absent levels of fragile X mental retardation protein (FMRP) (Hagerman et al., 2009). FMRP is found at the fragile x mental retardation 1 gene region (FMR1). Mutation, deletion or CGG repeats in FMR1 region, leads to

lower levels of FMRP and IDD (Hagerman et al., 2009). Essentially, there are four identified forms of the FMR1 gene in respect to the repeat length of CGG nucleotide. These four forms include: normal, intermediate or gray zone, premutation, and full mutation (Hagerman, 2002).

Normal form. Typically, for most of the population, individuals have less than 45 CGG repeats (Hagerman et al., 2009). In this normal form, there are no physical or mental impacts.

Premutation and Intermediate or Gray Zone Form. Premutation consists of 55 to 200 repeats of the CGG nucleotide. The premutation does not cause decreased FMRP levels but leads to enhanced production of FMR1 messenger RNA (mRNA) two to eight times the normal levels (Hagerman et al., 2009). Offspring, with mothers identified as premutation carriers, are at risk for genetically obtaining FXS (Hagerman, 2002). Male and female premutation carriers do not typically exhibit overt cognitive or behavioral deficits (Hagerman et al., 2009). When there is an overlap between normal and premutation forms of the FMR1 gene, averaging between 40 and 60 repeats, this form is called intermediate or gray zone alleles (Hagerman, 2002).

Full mutation. The full mutation of the FMR1 region is defined as having over 200 CGG repeats. The resulting consequence of this mutation entails little or no mRNA production. The full mutation form of FXS is expressed due to the lack of FMRP production. Individuals with full mutation FXS express with a variety of IDD and ASD characteristics.

Physical Phenotype

The magnitude of the FMRP deficit is correlated with severity of FXS physical phenotype (Hagerman et al., 2009). Typically, males exhibit stronger physical features associated with FXS than females. Physical features in males may include: large ears, long face, soft skin, and macroorchidism or enlarged testicals post-puberty. Further, individuals with FXS

are more susceptible to ear infections, flat feet, high arched palate, double-jointed fingers and hyper-flexible joints (NFXF, 2017). Females exhibit more mild physical features, and in some cases, females express no physical features associated with FXS (NFXF, 2017).

Behavioral Phenotype

Sensory processing. When compared to children with ASD or attention deficit hyperactivity disorder, children with FXS tend to have the most severe form sensory processing disorder (Baranek et al., 2002). Sensory processing disorder is feeling extra sensitive in a hyperarousal situation, which can be through auditory, visual, or tactile stimuli (Hagerman, 2002). Hyperarousal can be related to strong reactions to sensory stimuli, such as auditory, tactile, visual, and olfactory input (Miller et al., 1999). This can manifest in tactile defensiveness, hyper-activity, hyperarousal, hand flapping, and gaze aversion. Boys with FXS are more inattentive, hyperactive, and impulsive than boys with other forms of IDD, which may be related to sensory hyperactivity and lack of stimulus inhibition (Hagerman et al., 2002). Over 90% of boys with FXS have sensitivity to visual stimuli or visual avoidance (Miller et al., 1999). Children with FXS have difficulty habituating with new sensory environments and experience, which can be overwhelming for them. In overwhelming situations, children with FXS may experience a fight or flight response which oftentimes leads to a more disorganized state, decreased self-regulation, and decreased communication and language skills. Baranek et al. (2002) found 15 boys with FXS performed substantially below the “typical” sensory processing functions and criterion for occupational performance compared to typically developing peers. Children who avoid sensory experiences played with novel toys for shorter amounts of time and

were less independent in self-care tasks. Due to the severity of their sensory processing disorder, children with FXS require more assistance with engagement in their daily occupations.

Anxiety. Anxiety is one of the most frequent and impairing conditions associated with FXS and can negatively impact a child with FXS's occupational engagement in social participation within family, peers, and the community. Tonnsen, Shinkareva, Deal, Hatton, & Roberts (2013) defined anxiety as a cyclical process involving situational cues, negative affect, hypervigilance, and cognitive bias. The child may attempt to self-cope with avoidance and anxiety to reduce the intensity of the situation (Tonnsen et al., 2013). Berry-Kravis, Russo-Ponsaran, Yesensky, & Hessl (2014) found that parents most frequently noted social anxiety, separation anxiety, irritability, and tantrums in their child. Furthermore, treatment in anxiety for FXS lacks empirical support and relies significantly on clinical settings without valid outcome measures (Berry-Kravis et al., 2014). Berry-Kravis et al., (2014) explored the feasibility of administering the Pediatric Anxiety Rating Scale (PARS-R) to parents or caregivers of individuals with FXS. Since a large portion of anxiety is expressed by internalized symptoms, the study found it difficult to assess lower functioning and nonverbal populations for anxiety. These outcome measures are not adequate to assess and determine improvements in children with FXS abilities to regulate their anxiety and participate in daily occupations. Children with FXS are frequently less engaged in their occupational performance because of the severity of their anxiety and avoidance behaviors (Berry-Kravis et al., 2014).

Intellectual and Developmental Disabilities (IDD). Intellectual and developmental disability is a hallmark feature of FXS (Frolli, Piscopo, & Conson 2015). Children with FXS may have developmental delays in motor, language, cognitive, and adaptive skills that can interfere with a child with FXS's occupational performance in activities of daily living (ADLs).

Beginning in early childhood, children with FXS show a slower acquisition of skills. For example, typically developing children can sit unsupported at 6-7 months, whereas children with FXS tend to sit unsupported at 10 months. Children with FXS may begin to walk and say their first clear word at 20 months, whereas in typical development this occurs around 12 months (NFXF, 2017). Additionally, Frolli et al., (2015) studied 47 participants to measure developmental changes in cognitive and behavioral functioning. Specifically, one of the scales used was the Vineland Adaptive Behavior Scale (VABS), where they investigated the domains on communication, daily living, socialization, and motor skills. The VABS is a commonly used measure for neurodevelopmental disorders. In the study, the VABS did not show improvement in daily living skills after intervention. Frolli et al., (2015) found a decline in the domains of adaptive behavior for children with FXS as they age. Without adaptive behavior, children with FXS continue to have difficulty performing everyday activities that involve personal self-care tasks, learning in the educational setting, and social participation. Occupational performance in ADLs such as toileting, bathing, and eating are negatively impacted and this can be highly burdensome for families, community and social participation, and overall quality of life..

Symons, Clark, Roberts, and Bailey (2001) reported a decrease in IQ scores over time for children with FXS, especially during puberty. The decline occurs in quantitative skills, verbal reasoning, visual and abstract thinking, and short-term memory. While children with FXS are still making steady gains in their learning, so are typically developing children. Thus, comparing children with FXS to typically developing children's learning will show larger gaps, which shows children with FXS having decreased IQ scores. Symons et al., (2001) indicated weaknesses in sequential processing, auditory processing, academic and learning deficits. Deficits in learning can occur in mathematics, visual-spatial, visual-motor coordination,

executive functioning, and language. The large learning gaps within children with FXS impact on their occupation in education and can be evident through poor occupational performance pertaining to academic activities such as reading, writing, and solving mathematical problems.

Language, communication, and socialization. Another common behavioral phenotype in children with FXS affecting their engagement in social participation is delayed language development, which may cause expressive language skills to be achieved slower than receptive language skills. Expressive language in FXS can be tangential and repetitive prone to pragmatic error (Martin et al., 2017). Pragmatic and social language is comprised of multifaceted speech acts, topic maintenance, turn taking, and ability to repair communication breakdowns (Martin et al., 2017). Boys with FXS tend to have more trouble with articulation and clutter language. When cluttering is present, the rate of speech becomes rapid and fluctuates with repetitions of sounds, words, and phrases and occasional garbled, slurred, or disorganized speech (NFXF, 2017). During conversation, children with FXS often show symptoms of autism when taking appropriate turns to communicate, such as responding for clarification or repairing communication breakdowns. Additionally, verbal skills (verbal reasoning, labeling, vocabulary, and verbal comprehension) may vary between children based on individual strengths and weaknesses (Martin et al., 2017). About 10% of boys with FXS are nonverbal and have socially avoidant behaviors (Martin et al., 2017). Although, they do not remain socially withdrawn or avoid familiar people, they move away from new objects and situations (Martin et al., 2017). Barriers in language, communication, and socialization negatively impact a child with FXS's occupational performance in social participation, which includes but is not limited to engaging in activities involving interaction with communities (e.g. neighborhood or school), family, and peers.

Behavioral Excesses and Self-Injurious Behaviors. Repetitive and excessive behavior commonly seen in children with FXS can impact their everyday function in their occupations. According to Oakes et al., (2016) repetitive behavioral patterns are described as, "numerous behaviors are included in the broad umbrella of repetitive behavior, including stereotypes, ritualistic behaviors, obsessive and compulsive behaviors, restricted interests, perseverations, [aggression], and self-injurious behaviors" (p. 55). Occupations such as social participation and education are impacted by excessive and repetitive behaviors within children with FXS as they have a difficult time acquiring social skills such as self-regulating, matching linguistic styles, and expressing emotion in a socially appropriate manner. Poor performance in socializing and learning may prevent the child with FXS from forming meaningful relationships with peers and engaging in educational activities. According to Hessl, Glaser, Dyer-Friedman, & Reiss, (2002), behavioral problems and increased cortisol production have a significant, positive association and correlation. Individuals with FXS who show excessive and repetitive behaviors may be due to an increase in stress levels when placed in environmentally stressful situations-which increases cortisol. Consequently, children with FXS are known to resort to self-injurious and aggressive behaviors. Repetitive and excessive behaviors within children with FXS remain poorly understood and require more extensive research in order to find better ways to support their engagement in occupation.

Impacts on Family

Adaptation. Researchers have described parental adaptation to children with special needs as lifelong, complex process that continuously changes throughout the child's life (Hauser-Cram et al., 2001). Family cohesion is a strong determinant in a family's ability to cope with parenting

stress. A study found that low levels of stress and high levels of hope in families with FXS influence a mothers' optimism, which results in increased quality of life.

High levels of social support increase optimism which results in positive outcomes as families are able to feel a sense of satisfaction and lower their risk of depression, stress, and anxiety (Raspa, Bailey, Bann, & Bishop, 2014). A study based on qualitative analysis of interview data examined maternal adaptation to a child's diagnosis of FXS (Landry et al., 2001). Important themes emerged from the narratives including, but not limited to, the importance of context, a mother's' emotional response to the diagnosis and development, and strategies used to cope. Each of these themes plays an important role in the family's ability to adapt and determine whether they have a positive or negative experience raising a child with special needs. The contextual themed involved the presence of support, or lack thereof, from spouses, family members, medical professionals, and school professionals (Landry et al., 2001). Mothers are the core of the family dynamic and play an important role in supporting the child with FXS (Landry et al., 2001). A mother's maternal responsivity plays a key role in promoting a child's language development as well as cognitive, emotional, and social development (Landry et al., 1998; Landry et al., 2001).

A mixed methods study explored the relation between quality of life and FXS and found that 75 percent of the women in the study scored high in their overall quality of life (Wheeler, Skinner, Bailey, 2008). Positive schemas were found such as strong support systems with family and friends, and engagement in social and community services. Some mothers of children with FXS have reported the same quality of life as the general population (Wheeler et al., 2008). Families with that use resources in their community, have strong support systems, and strong

parental adaptability have been shown to be determinants of positive outcomes (Hauser-Cram et al., 2001).

A study that surveyed 1,099 families of children with FXS found that families with more education showed greater parenting knowledge which helped them with parenting/coping strategies and knew more about how to help their child develop (Raspa et al., 2014). Those with an active social life and social support provided more resources to parenting knowledge to learn from other families. Learning coping strategies can help other families learn how to adapt in family occupations such as grocery shopping, family parties, and trips to the local park. Findings have shown that positive adaptation and coping have a positive impact for good outcomes in both the child and family members in their daily occupations.

Negative Outcomes. There are many negative correlations associated with families that have children with a disability. Families not only have to deal with a sudden change in their lives, but may also face social stigma that comes with having a child with a disability. Parents of children who co-diagnosed with FXS and ASD report negative adaptation due to more behavioral issues including tactile defensiveness, hyperactivity, and hyperarousal (Raspa et al., 2014). These behavior issues may interfere with a family's ability to enjoy family occupations such as going to the grocery store, park, and birthday parties. Parents find that it is difficult to help their children with behavior challenges, and feel that they do not have the resources to access benefits in their communities (Raspa et al., 2014).

Families with children with FXS report a significant financial burden and an impact on employment (Ouyang, Grosse, Raspa, & Bailey, 2010). Families must take time off to care for their child and bring them to necessary appointments, therapy sessions, and school. Demographics have shown different impacts due to the varying education levels of family members, which affect their knowledge, employment, social status, and access to services in the community (Ouyang et al., 2010). In most cases, families who are affected by FXS dedicate a majority of their time and energy to their child. Time may be spent establishing a routine that involves medical visits, therapy sessions, child supervision, special

education, and social services. A quantitative study evaluated the average healthcare cost associated with FXS and found that patients covered with commercial Medicare insurance was an annual average expense of $8,752 for adults (18 years old and over), and $5,668 - $7,852 for children (0-17 years old), (Vekeman et. al., 2015).

A study that evaluated patient and caregiver burden with FXS found that families with a child that had a diagnosis of both FXS and ASD faced marked financial burden (Vekeman et al., 2015). Having a child 5-11 years old with FXS and ASD was significantly associated with caregiver financial burden and resulted in reduced work hours (Ouyang et al., 2014). Families with children diagnosed with FXS face multiple challenges in providing financial resources and time dedicated to supporting their children's needs in terms of addressing fulfillment in their daily occupations. There is a need for these families to have access to professionals to help them adapt and engage in their daily occupations.

Interventions

Special Education. Children with FXS often receive special education services (Stackhouse, Wilson, O'Connor, Scharfenaker, & Hagerman 2002). Learning in a general education classroom is difficult for many students with FXS (Symons et al., 2001). They tend to have lower participation and engagement in school activities, which can be related to avoidant behavior (Symons et al., 2001). Social anxiety, sensory processing, attention problems, and hyperactivity and cognitive delay can affect students' tolerance and ability to learn (Stackhouse et al., 2002). Research found that special education with a one on one ratio or small groups can increase students with disabilities' engagement in classroom behaviors and academics (Stackhouse et al., 2002). Symons et al., (2001) indicated students with FXS were moderately engaged in class activities in special education classrooms. Students were engaged with

academic material or combination of materials and peer interactions. Symons et al., (2001) found only half the students had behavioral problems, and among the half, only three engaged in self-injurious behavior. The classroom's quality correlated with the level of engagement for both students with FXS and their peers. Stackhouse et al., (2002) indicated intensive behavioral interventions such as, Lovaas Therapy and Applied Behavioral Analysis (ABA) strategies have been found to help children with FXS develop skills that are necessary for higher level learning, such as attention, cooperation, and imitation. Symons et al., (2001) indicated a need for more research about special education to form a more conclusive statement of the effects of special education for students with FXS. This will provide information for families and students with FXS about the effectiveness of special education.

OT and Speech Therapy. Occupational therapists (OTs) along with Speech and Language Pathologists (SLPs) often receive referrals for children with FXS to mitigate sensory processing and language difficulties and help families cope more effectively (Baranek et al., 2002). OTs and SLPs focus on providing assistance and modifications for children with FXS given their complex needs. Some interventions include regulation of hypersensitivity, self-regulation, motor planning, social skills, language and communication, speech production, cognitive deficits, and limited adaptive skills (Hagerman 2002).

Occupational therapists as members of an interdisciplinary team play a unique role in addressing deficits seen in children with FXS. Occupational therapists help people engage in activities they find meaningful and important through therapeutic use of daily occupations (meaningful activities) (Hagerman 2002). An occupational therapist may observe a child's occupational performance to assess their strengths and weakness when performing occupations followed by making adaptations to the environment or task to fit the person. Occupational

therapy supports children with FXS to continue engaging in everyday meaningful occupations via a holistic perspective. FXS associated behaviors in children may impact his or her occupational performance. Occupational therapists can offer services to help increase a child's engagement in their meaningful occupations (Hagerman 2002).

Parenting and Behavior Management Strategies. Behavior problems in children with FXS have a close association with maternal depression and anxiety symptoms (Zeedyk & Blacher, 2017). Some families report that having a child with a disability has a positive impact on their lives as it provides meaning and purpose and reframes their perspective on what is really important in life (Wheeler, Skinner, & Bailey, 2008). A mother's ability to cope or their ability to perceive their situation positively can lead to decreased stress and more optimism. A mother's maternal responsivity is defined as the healthy relationship between the mother and child that involves warmth, nurturance, and stability (Sterling, Barnum, Skinner, Warren, & Fleming, 2012). When a mother is highly responsive to a child needs they engage in a parenting style that maintains the child's attention, expands initiations, and limits the child to a new topic unless it's necessary which helps both the mother and child's ability to help control behavior (Sterling, Barnum, Skinner, Warren, & Fleming, 2012).

Medication. Medications are one of the many ways to help treat the symptoms of FXS related to anxiety and mood disorders. Commonly known medications such as Risperidone (Risperdal) and Aripiprazole (Abilify) help treat aggression while anticonvulsant medications such as lamotrigine (Lamictal), oxcabazepine (Tripetal), zonisamide (Zonegram), and levetiracetam (Keppra) help control seizures (Hagerman et al., 2009). Clonidine (Catapres), Baclofen (Gablofen), and Guanfacine (Intuniv ER) can help address behavior and cognitive problems. Recent studies have focused on selective serotonin reuptake inhibitors (SSRI's), in

particular sertraline, commercially known as Zoloft® (Hess et al., 2016; Winarni et al., 2012). SSRI's have been widely used to treat anxiety, depression, and obsessive compulsive disorder (OCD) in many conditions for individuals over 5 years of age. In clinical practice, sertraline has been used to treat anxiety in young children with FXS which can have further beneficial outcomes in regards to language development compared to those not treated with sertraline (Winarni et al., 2012). Winarni et al., (2012) found that the 11 children ages 12-50 months treated with sertraline showed an improvement in both expressive and receptive language development via retrospective chart reviews. This research supported a larger controlled trial of low dose sertraline treatment for young children with FXS. In a later study, Hess et al., (2016) found no significant differences in improved language between those who did and did not take sertraline but found significant results for improvement in fine motor skills of children with FXS in addition to visual perception, social participation, and expressive language when compared to placebo. Studies on sertraline are still under ongoing investigation to further evaluate its long-term side effects. Yet, these analyses did not include qualitative measures and rather included traditional batteries for standardized assessments as outcome measures.

Outcome Measures. There has been considerable research in the medical aspect of FXS; however, there is limited research that focuses on the impact on family occupations. Further research is still ongoing to find more appropriate ways to address behaviors and performance in daily life for children and families with FXS. Medications have been able to produce encouraging results in behavior of children with FXS. Outcome measures commonly used in controlled trials do not capture daily life changes within family dynamics of those who have a child with FXS and how a child with FXS may show a change in occupational performance when engaging in meaningful activities across occupations in context. According to Berry Kravis

et al., (2013): no single measure currently exists that meets all criteria for an ideal clinical endpoint that can be used to evaluate treatment for FXS. Furthermore, Berry Kravis et al., (2013) indicated that the set of measures should reliably capture the core cognitive impairments and underlying neurological mechanisms of FXS and include behavioral and emotional domains. Thus far, clinical trials have focused on standardized assessments as outcome measures and these instruments are limited in consideration of context, voice, family perspectives and occupational performance.

Statement of Purpose

Current research studies on children with FXS lack the inclusion of qualitative, contextually based, occupation centered, family reported outcomes on the child's daily occupational performance as they have primarily focused on the quantitative assessment results. Previous research on children with FXS has focused on the medical model and quantitative data based on the results from standardized assessments to determine the amount of progress the child has made. Often, standardized assessments as outcome measures can be insensitive to functional, daily life changes for children and families living with FXS. Findings from previous studies exhibit a lack of family voice and context within those more traditional outcome measures. The purpose of this research study is to provide more information on occupation centered outcomes from a family's perspective on children with FXS and understand the impacts on occupational performance after sertraline treatment. By including qualitative measures and getting perspectives from families and their daily-lived experiences, we can better understand occupations in context, rather than being limited to specific performance skills as measured by traditional developmental assessments. Therefore the purpose of this study is to conduct in depth case by case analyses by comparing baseline and post family interviews to the child's baseline and post treatment standardized assessment scores. The research team coded for themes based on family report as well as areas of improvement described by families enrolled in the sertraline trial. The results of this study will answer the following research question: How can semi-structured interviews reveal occupational performance changes in response to medication in a more contextually valid and sensitive manner when compared to traditional standardized outcome measures?

Definitions and Variables

Fragile X syndrome is a monogenic neurodevelopmental disorder caused by a CGG repeat expansion in the fragile x mental retardation (FMR1) gene on the X chromosome and is the most common heritable genetic condition causing intellectual disability and the most common single gene cause of autism spectrum disorder - ASD (Hess et al., 2016).

Occupational performance is the ability to perform daily occupations, such as school function, self-care, play, and social participation (Baranek et al. 2002).

Sertraline (trade name Zoloft®) is a selective serotonin reuptake inhibitor, which has been widely used to treat anxiety, depression, and obsessive compulsive disorder in individuals over five years of age (Hess et al., 2016).

Behavioral phenotypes are caused by the deficit of FMRP protein resulting in changes that lead to behavioral and cognitive problems in individuals with FXS, such as sensory processing, anxiety, IDD, repetitive behavior, and language and communication deficits (Hagerman et al., 2002).

Theoretical Framework

The theoretical framework utilized for this study is person, environment and occupation – PEO model (Law et al., 1996). The PEO framework highlights person, environment and occupation individually but also as interrelated and overlapping ideas. Law, Cooper, Strong, Steward, and Rigby, and Letts created PEO in 1996 to identify the interaction between the person, environment, and occupation.

In the model, the first component is P- person, which focused on the person as a whole without other contextual influences. Law et al. (1996) stated the model assumed the person is constantly motivated and interacting with the environment. Occupational therapists consider the situation and emotional response of the person and their degree of autonomy (Law et al., 1996). In relation to our present FXS study, the level of P in PEO would consider both the child individually and the family living with FXS. Children with FXS experience behaviors, which include tactile defensiveness, hyperactivity, and hyperarousal which interfere with daily occupations. Children with FXS can have decreased language and communication skills and sensory processing disorder, which affects them from engaging in their daily occupations. Children with FXS are resilient and have the ability to blossom when they feel supported and confident. Families experience financial hardships, stress, anxiety, and dedicate time on appointments and extra care for the child with FXS. Although, having children with FXS can have a negative societal stigma, families will feel more confident when they feel educated, supported, and hopeful. The PEO framework was utilized in this study to consider the needs of the child and family.

The second component of the PEO model is E- environment (Law et al., 1996). Environment can be divided into cultural, socioeconomic, institutional, physical and social

contexts. The environment is unique to each person and is adaptable to fit a person needs. In this FXS research, the E is focused on all environments and contexts for the child and family with FXS. Raising a child with FXS may cause serious conflicts impacting the relationships within families. Social and economical contexts are frequently impacted. Often, parental relationships are affected, which can negatively impact family dynamics. Children with FXS and their families may also have difficulty adapting to environments with multiple sensory stimuli and distractions. Families report feelings of isolation and decreased social participation in their communities. They do not attend social events, go shopping, or go on vacation etc. The choice to avoid these situations is often an attempt to ameliorate overwhelming scenarios, but at a cost of isolation. Occupational therapists consider what needs to be adapted in the environment for the child and family living with FXS.

The last component of the PEO model is O- occupations, which includes meeting the person's intrinsic needs for self-maintenance, expression, and fulfillment in relation to the person's role and environment (Law et al., 1996). Occupations include self-directed meaningful tasks and activities done to accomplish a purpose for person's fulfillment. In this research the O is strongly linked to the semi-structured interview questions and asking families about the impact of living with FXS and specifics that the FXS phenotype may have on their daily lives. Children with FXS experience functional limitations preventing them for engaging in their daily occupations. They may feel a lack of accomplishment when they cannot participate in daily tasks from being simple as brushing their teeth to complex as receiving good grade on a homework assignment or meaningful socializing with peers. Furthermore, families may face difficulty participating in their daily routines, such as going to the grocery store or eating at a restaurant.

As mentioned above, this is an example of how E and O greatly influence each other. If the environments are overwhelming, then the occupational participation decreases.

This study applied the PEO model to dive deeper into the perspectives of the children with FXS and their families. All three components, person, environment, and occupation are addressed in the study and will inform our qualitative coding for the family interviews. Explored in this study are engagement in occupations from children with FXS and their family that may not be captured in standardized assessments. This study applied PEO the components in order to examine family voice and daily-lived experiences in the context of a clinical trial of sertraline treatment.

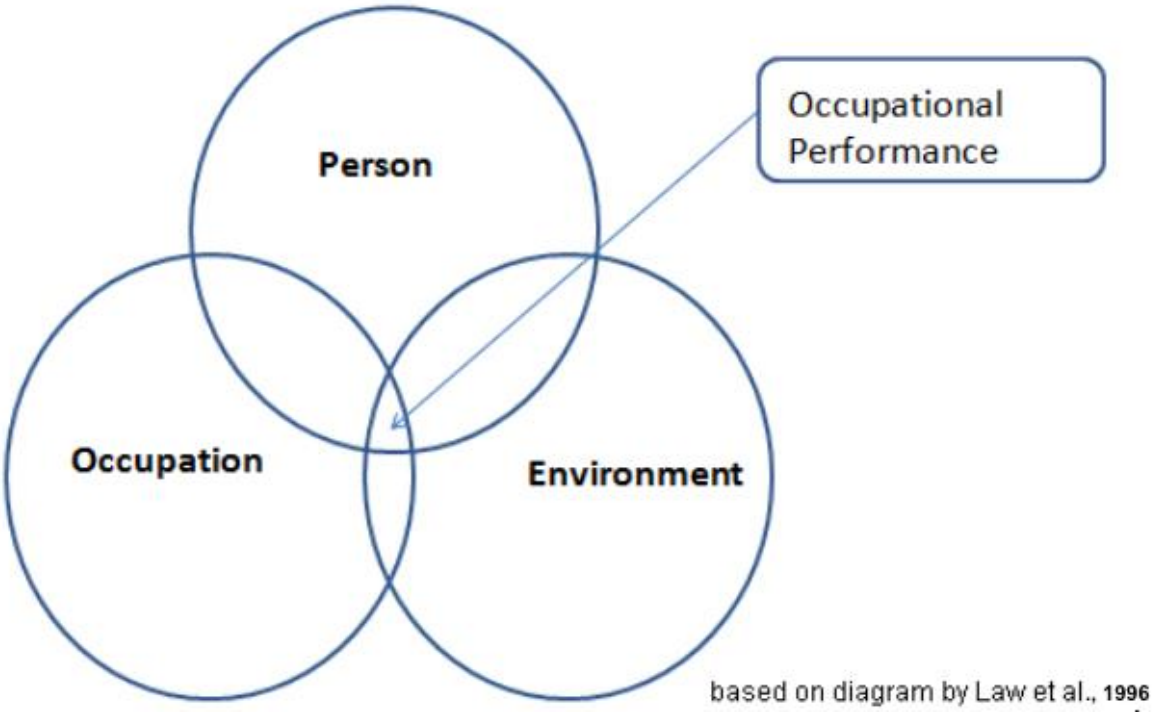

Figure 1 PEO Model of Occupational Performance – The model consists of three components P- person, E- environment, and O- occupations. The interaction and overlap of the three components results in occupational performance.

Ethical and Legal Considerations

The study abides by American Occupational Therapy Association Code of Ethics (2015), demonstrating the principles of beneficence, nonmaleficence, autonomy, justice, veracity, and fidelity.

Beneficence. Beneficence includes all forms of actions intended to benefit the other person(s) (AOTA, 2015). Family participants gave full consent to be in the study and were asked permission to be audio recorded for research use.

Nonmaleficence. Nonmaleficence includes an obligation to not impose risks of harm even if potential risk is without malicious or harmful intent (AOTA, 2015). Family participants had the right to speak or withhold personal information about their lives when being asked in depth, personal questions about their daily lives and family dynamics. Families were allowed to share what they were comfortable in speaking upon.

Autonomy. Autonomy includes allowing the individual to have the right to make a determination regarding care decisions that directly affect their lives (AOTA, 2015). Prior to the study, families in the study were well informed on the intentioned use of the audio recorded interviews. Family participants were given the autonomy to withdraw from the study anytime.

Justice. Justice relates to the fair, equitable, and appropriate treatment of persons (AOTA, 2015). Each family was treated fairly and equally as they were given the same set of questions to answer in their interview, by a licensed occupational therapist.

Veracity. Veracity is based on virtues of truthfulness, candor, and honesty and refers to the accurate transmission of information (AOTA, 2015). Family participants were informed of the purpose of the study and were given truthful and accurate information for them to receive a better understanding of their contribution to the study.

Fidelity. Fidelity refers to the duty one has to keep a commitment once it is made (AOTA, 2015). Participants in the study were informed on how confidentiality will be kept and how research students and faculty advisor for this study are committed to keeping the personal interviews private and protected from the public.

Methodology

Mixed Methods, In-depth Case Studies

This research study is a mixed method design using semi-structured interviews and standardized assessments to complete four in-depth case study analysis exploring families' perspectives on the outcomes of sertraline treatment for children with FXS and their occupational performance in daily occupations and routines. The qualitative analysis used the constant comparison method to develop codes and themes from the interview data collected for each child (Corbin & Strauss, 1990). The quantitative analysis examined raw scores and standard scores of the Mullen Scales of Early Learning (MSEL) Early Learning Composite 1995, Sensory Processing Measure (SPM-P) Preschool Home Form 2010, and Preschool Language Scale, Fifth Edition (PLS-5) 2011. This study examined whether children with FXS are improving their engagement in daily occupations as reported by semi-structured interviews in comparison to their standardized assessment scores.

Research Design

In this research study, student researchers analyzed the improvements in occupational performance of the child and family as reported by parents via semi-structured interviews. This study was a mixed methods research design, in which parents of the child with FXS consented to a prior study (Hess et al., 2016), conducted at the U.C. Davis MIND Institute, about the effects of sertraline and we had access to this existing database with permission (see Appendix A and B).. Caregivers were interviewed using semi-structured interview questions at baseline and again at six months post-treatment to discuss their child, daily life, and any impacts of the medication

(Appendix C). The standardized assessments in the original study were given at baseline and again at six months post-treatment to determine if there were statistically significant gains in quantitative outcome measures between placebo and treatment groups. For this additional, separate analysis, we have chosen four children who were all originally randomized to the sertraline treatment group and conducted in-depth case study analyses to compare their standardized assessments and semi-structured interviews at baseline and at post-testing.

Grounded theory was used as part of the qualitative analysis of our study. Grounded theory is a systematic method of qualitative research that is used to create new theory to explain phenomenon (Corbin & Strauss, 1990). Grounded theory often incorporates the constant comparative method of data and consists of categories, properties, and hypothesis (Corbin & Strauss, 1990). There are conceptual links between categories and properties. This study included analyses based on individual interview cases. Student researchers compared the baseline and post- sertraline interviews to the standardized assessment to determine the improvement in daily occupations. While comparing the interviews, student researchers looked for themes of repeated concepts and ideas reported by the families. Codes were generated to capture these recurring ideas. These codes were grouped together to form categories, which can lead to the basis of a new theory. The research explored the lived experiences of children and families with FXS. The research results can further inform the role of OT in support of children and families with FXS.

Participants

Participants in this study consisted of children ages 2 to 6 with FXS and their immediate family members. Inclusion criteria included children with FXS, age 2 to 6 years old, English

speaking, and able to participate and travel to appointments at the U.C. Davis MIND Institute in Sacramento, CA. Exclusion criteria included central nervous system disease, or any other disease other than FXS. Children with the diagnosis of FXS, and the diagnosis of both FXS and ASD were involved in this study. This study is accessing a previously developed database from a completed clinical trial of sertraline (Hess et al., 2016). This study will analyze the qualitative interviews case by case and compare and integrate these findings with scores from the standardized assessments. The sample chosen for this study were four boys who had been originally randomized to sertraline treatment. This participant selection was intentionally made to have a more homogeneous group for this in-depth case study analysis.

Data Collection and Management Procedures

The data collection used in this study was collected from a pre-existing database in a previous study determining the outcome measures of sertraline. The Dominican research students received approval from the principal investigator of the previous study (Appendix A and B).

Qualitative Data: Semi-Structured Interviews, Administered at baseline and post-treatment. Semi-Structured interviews were administered at both baseline and post-testing (Appendix C.) Original interviews were audio recorded and then transcribed verbatim using Express Scribe software. The interview transcripts were securely stored on USB drives, locked in cabinet, in a locked room, with a sign in and out procedure. The transcriptions have all personal information removed and any names used in the interviews were transcribed as "BOY/GIRLXXX". USB drives have subject numbers and the participants have assigned research numbers or a pseudonym. Only the research team had access to the room and interviews. Only the research team had access to the standardized assessment scores. Participants were only identified with subject numbers.

Quantitative Data: Standardized Assessments – Administered at baseline and post-treatment

Mullen Scales of Early Learning© (MSEL) Early Learning Composite (Mullen, 1995). The MSEL is a direct assessment measuring cognitive and motor abilities. The five scales are gross motor, visual reception, fine motor, expressive language, and receptive language to determine the strengths and weakness for children up to 68 months. The MSEL scales are represented as T-scores with a mean of 50 and standard deviation of ±10. The early learning composite (ELC) score on the Mullen is based on a mean of 100 ± 15 and represents an IQ (Mullen EM, 1995).

Sensory Processing Measure© - (SPM-P) Preschool Home Form (Miller, 2010). The SPM-P is a parent response questionnaire, which examines a child's sensory processing difficulties at home with questions caregivers answer about his or her child. The seven scales are vision, hearing, touch, body awareness, balance and motion, planning and ideas, and social participation. Planning and ideas and social participation are activities and occupations that could be negatively affected due to sensory processing deficits. The SPM-P scales are based on T-scores with a mean of 50 and standard deviation of ± 10. The SPM-P scale is unique in which the higher scores represent "definite dysfunction" and lower scores represent "typical performance" (Miller Kuhaneck et al., 2010).

Preschool Language Scales Fifth Edition© (PLS-5) (Zimmerman, 2011). The PLS-5 is a direct and interactive assessment of expressive and receptive language. The scales are auditory comprehension and expressive language including a combination of both scales together. The PLS-5 scales are represented as standard scores with a mean of 100 and standard deviation of ±15 (Zimmerman, Steiner, & Pond, 2011).

Data Analysis Plan

In-depth case study analyses were used to examine both quantitative data (e.g. standardized outcomes measures) and qualitative data (e.g. semi-structured interviews).

Qualitative data analysis. The constant comparison method was used to code and examine themes from the interview transcripts (Corbin & Strauss 1990). Codes were initially informed by the FXS literature and the PEO theoretical framework, however specific codes & themes were emergent from the data itself. Dedoose software (7.0.23, 2016) is a secure mixed-methods and qualitative data base management and analysis software. Dedoose software was used to code for categories and themes found in the FXS family interviews. The research team incorporated coding meetings to develop the codebook and operational definitions. The research team met to code 25% of the total data by 100% consensus to establish rigor and reliability. After establishing reliability, each researcher coded the remaining transcripts separately. Any codes requiring clarification were revisited by the full team and coded via 100% consensus.

Quantitative Data Analysis. The research team examined three standardized assessment scores for the quantitative analysis. For each standardized assessments, raw scores and standard scores were examined to note the difference between individual raw score gains in performance skills compared to where the child is in relation to the typical norm of standard scores.

Case-Study Analyses. The standardized assessment raw and standard scores were examined in comparison to semi-structured interview data to determine areas of consistency and areas of disconnect regarding improvements in overall function and occupational engagement.

Results

Our research question was: How can semi-structured interviews reveal occupational performance changes in response to medication in a more contextually valid and sensitive manner when compared to traditional standardized outcome measures?

Quantitative Results - Raw scores and standard scores from standardized assessments were used to compare to each other per assessment, per subject at baseline and again at post testing. The MSEL scales are represented as T-scores with a mean of 50 ±10. PLS-5 scales are represented as standard scores with a mean of 100 ±15. The SPM-P scales are based on T-scores with a mean of 50 ± 10, however, it is important to note that the SPM-P scale is unique in that higher scores represent "definite dysfunction" and lower scores represent "typical performance".

Qualitative Results – Baseline and post-treatment semi-structured interviews were listened to and verbatim transcripts read through by all four researchers. The codebook was developed via the constant comparison method (Glaser & Strauss, 1967; Corbin & Strauss, 1990), informed by the FXS literature and the PEO theoretical framework (Law et al., 1996). Codes included key aspects of the FXS phenotype (e.g. communication, anxiety, sensory processing, and behavioral excesses). Three key themes emerged from the coding focused around meaningful family activities and occupations: (1) household communication, (2) community engagement and (3) sensory regulation for participation in meaningful activities / occupations.

Each case has been compiled and presented below; all names are pseudonyms, with analyses of both quantitative and qualitative data.

Participant Demographics

Name	CA Baseline	CA Post	IQ Baseline	IQ Post
Kai	29.6 months	35.6 months	78	78
Isaac	34.7 months	40.7 months	49	49
Derek	34.5 months	40.5 months	52	56
Shiloh	59.4 months	65.4 months	49	56

Table 1 Participant Demographics, Chronological Age (CA) and IQ (MSEL, Early Learning Composite Standard Score X=100±15)

Kai

Kai's chronological age at baseline was 29.6 months and had an IQ of 78. After post treatment, he was reassessed at 35.6 months and his IQ remained at 78. It is important to note that Kai's IQ is more than 1 standard deviation higher than the other three children in this sample and an IQ of 78 is relatively high for the FXS population. His MSEL raw scores post treatment showed some point increases between baseline and post-testing. MSEL standard scores remained unchanged (see Figure 2 and Figure 3). His PLS-5 raw scores showed little or no point increases between baseline and post-testing. PLS-5 standard scores decreased (see Figure 4 and Figure 5). Kai's SPM-P raw scores decreased in majority of the SPM-P scales whereas body awareness remained unchanged and planning and ideas increased between baseline and post-testing. Majority of Kai's SPM-P standard scores decreased whereas body awareness remained unchanged and planning and ideas increased (see Figure 6 and Figure 7).

Kai's family reported both performance skill improvements and positive occupational impacts of sertraline treatment between baseline and post-intervention. Specifically, family

reported improvement in fine motor, gross motor, and speech, whereas Kai may have had difficulty beforehand. Kai's parent said at post-testing,

> The gross motor is coming along quickly as is the fine motor as is the speech. And the other thing too is that of speech generation, expressive language has been tougher for him. We're seeing his ability to maintain his expressive language levels when he's in a more stressful situation. Whereas before we would see a pretty sharp loss.

This quote falls into the themes of household communication and sensory regulation for participation in meaningful activities / occupations as they note the intersection of improved language and occupational engagement in context. Additionally, Kai's family reported being able to perform family occupations, such as going to a birthday party. Kai's family member shared,

> They play loud music and usually by the end of the hour or so he's like 'okay, I'm kind of doneski with this'. It's not like he melts down and freaks out. He's sort of like ok I'm just going to come sit down with momma now.

This example merges the themes of sensory regulation for Kai's management of sound, for participation in meaningful activities / occupations as well as community engagement at a party which he could not attend previously.

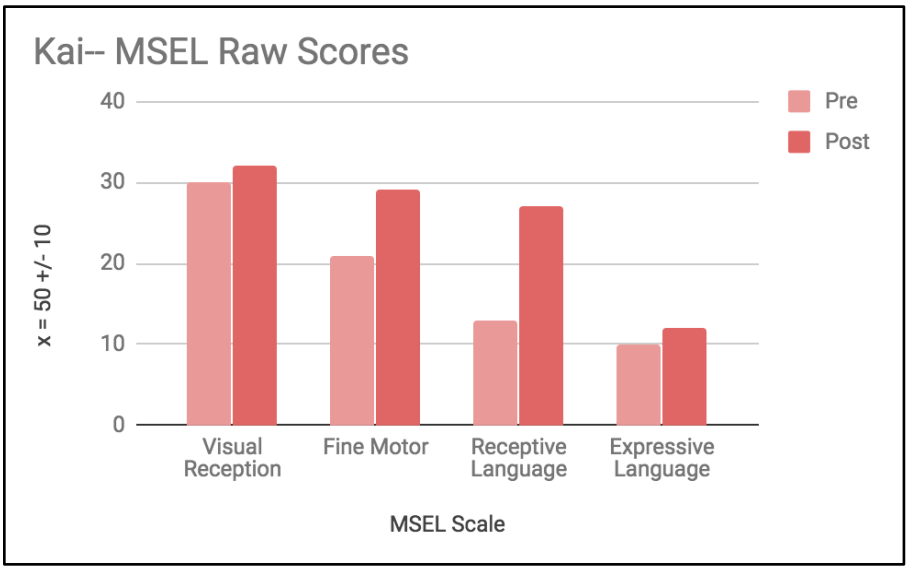

Figure 2 Kai, MSEL, Raw Scores, baseline and post-treatment

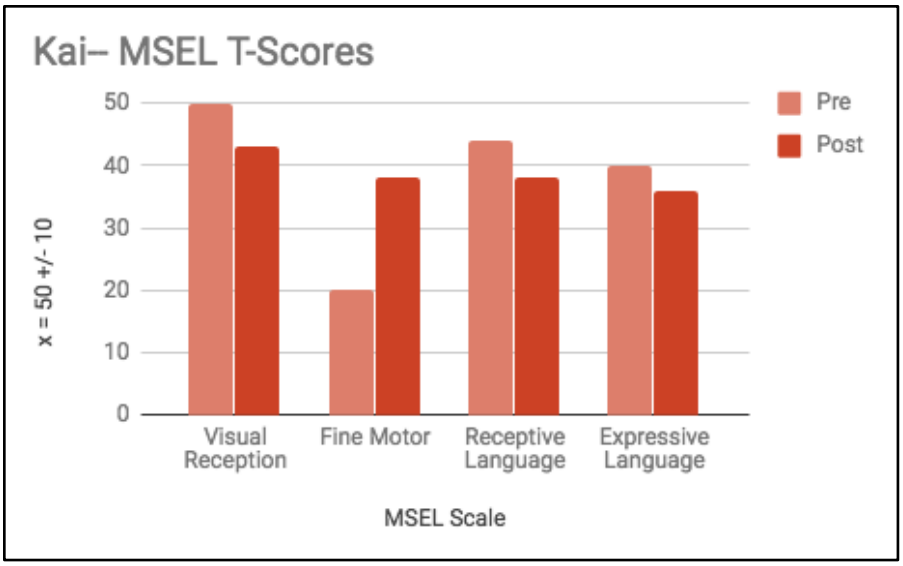

Figure 3 Kai, MSEL, Standard Scores, baseline and post-treatment

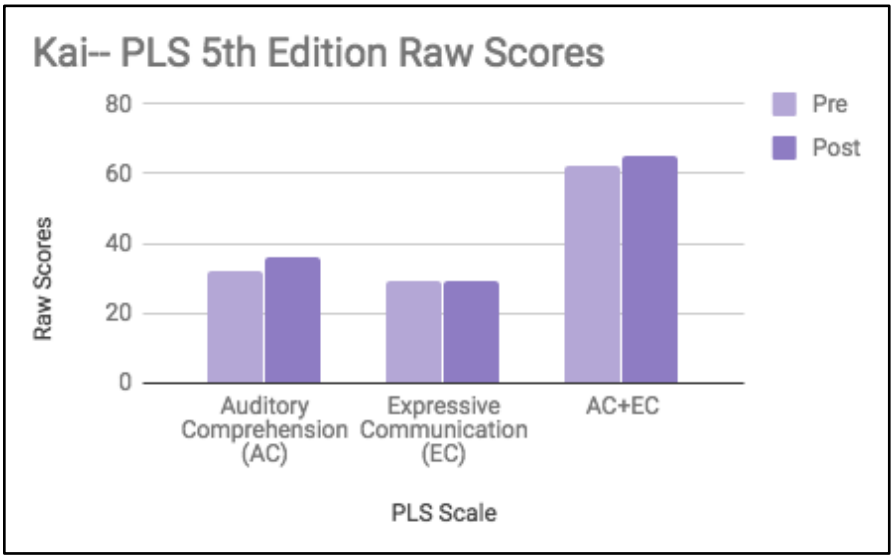

Figure 4 Kai, PLS-5, Raw Scores, baseline and post-treatment

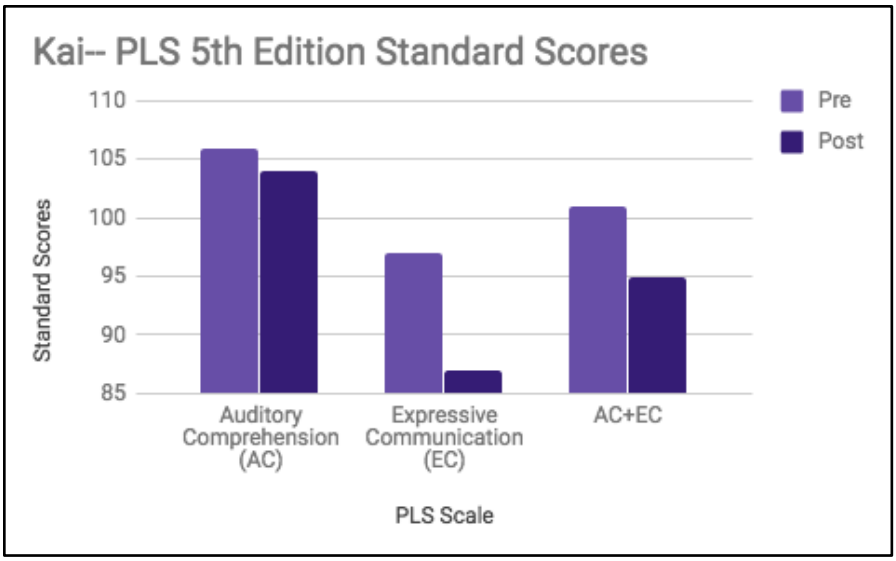

Figure 5 Kai, PLS-5, Standard Scores, baseline and post-treatment

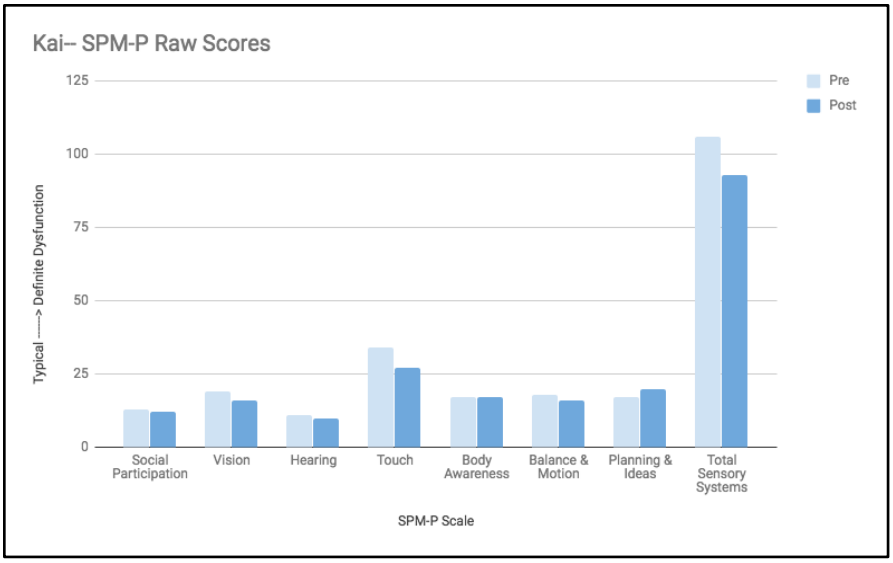

Figure 6 Kai, SPM-P, Raw Scores, baseline and post-treatment

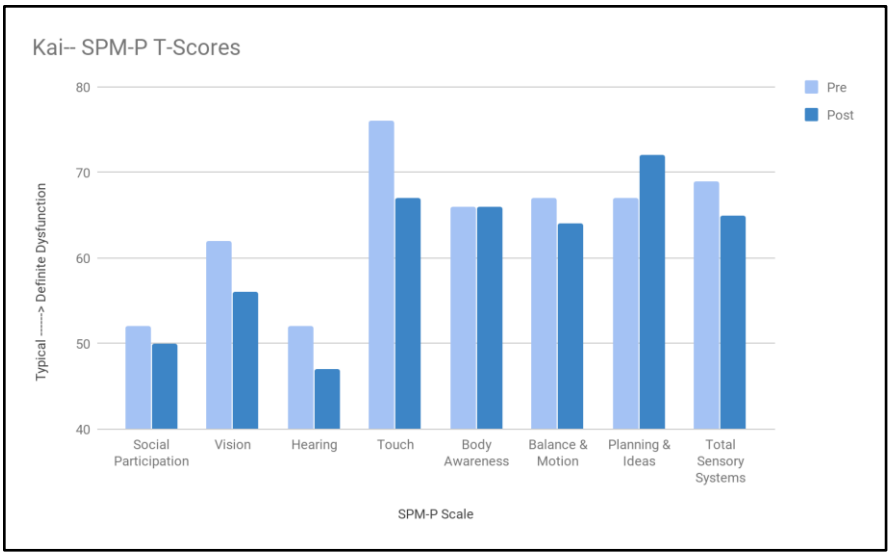

Figure 7 Kai, SPM-P, Standard Scores, baseline and post-treatment

Isaac

Isaac's chronological age at baseline was 34.7 months and he had an IQ of 49. After post treatment, he was reassessed at 40.7 months and his IQ remained at 49. His MSEL raw scores showed some point increases between baseline and post-testing. MSEL standard scores remained unchanged (see Figure 8 and Figure 9). His PLS-5 raw scores showed some point decreases between baseline and post-testing. PLS-5 standard scores decreased between baseline and post-testing (see Figure 10 and Figure 11). Isaac's SPM-P raw scores showed some point increases and decreases across the SPM-P scales while balance and motion remained unchanged. Majority of Isaac's SPM-P standard scores increased whereas body awareness decreased (see Figure 12 and Figure 13).

Isaac's family reported both performance skill improvements and positive occupational engagement changes between baseline and post-testing. Specifically, Isaac's family reported improvement in expressive language and self-regulation whereas Isaac had difficulty beforehand. A family member reported,

> The other thing is they feel like his language is improved. It's not showing so much on the testing...he kind of went from hardly saying anything to really starting to repeat things we say and he started to say more words of his own.

This quote falls into the theme of household communication. Isaac's family specifically notes the difference in his functioning in everyday life in contrast to what is shown in his language test scores. Regarding, Isaac's sensory processing and response to proactive sensory strategies both at home and in other settings, his family reported, "Sometimes it's simple. We have rocking chairs, in their place and our place. And we just sit down and rock with him. He likes the rocking motion sometimes. If you rock with him it will calm him down." This quote falls into the theme of sensory regulation for participation in meaningful activities/occupations as they family is illustrating a calming response to rocking that affords family engagement.

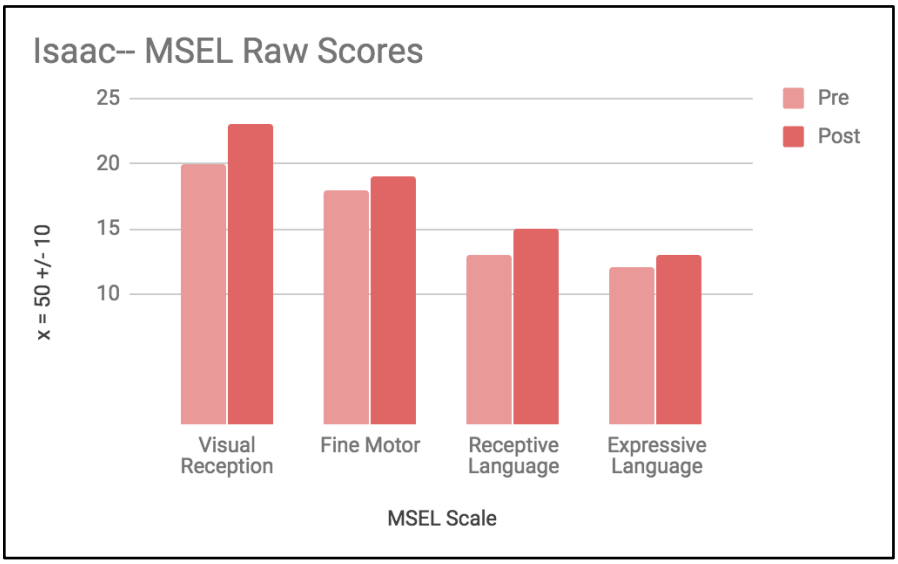

Figure 8 Isaac, MSEL, Raw Scores, baseline and post-treatment

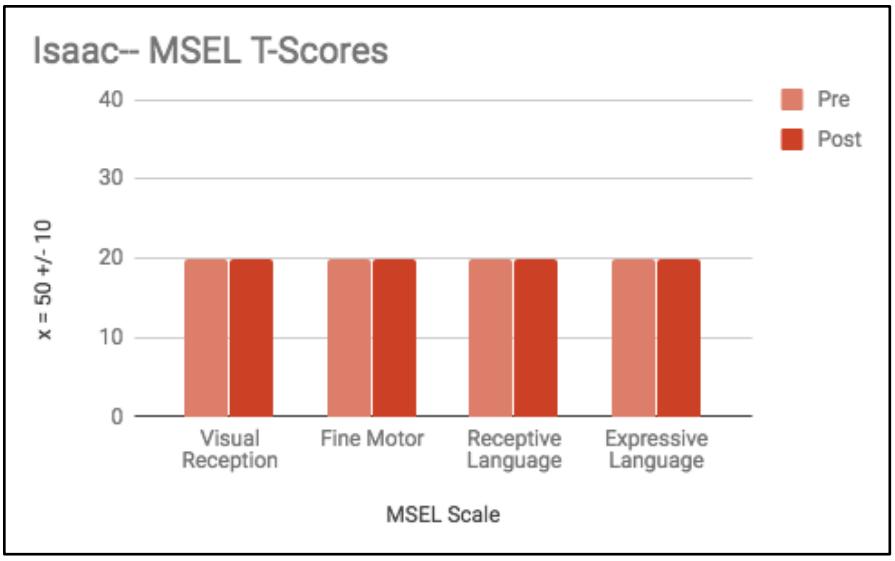

Figure 9 Isaac, MSEL, Standard Scores, baseline and post-treatment

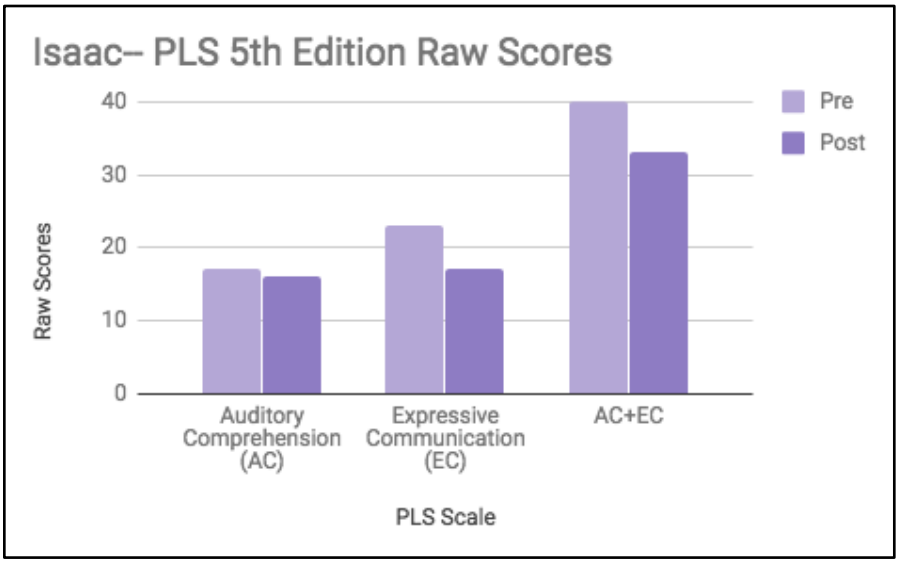

Figure 10 Isaac PLS-5, Raw Scores, baseline and post-treatment

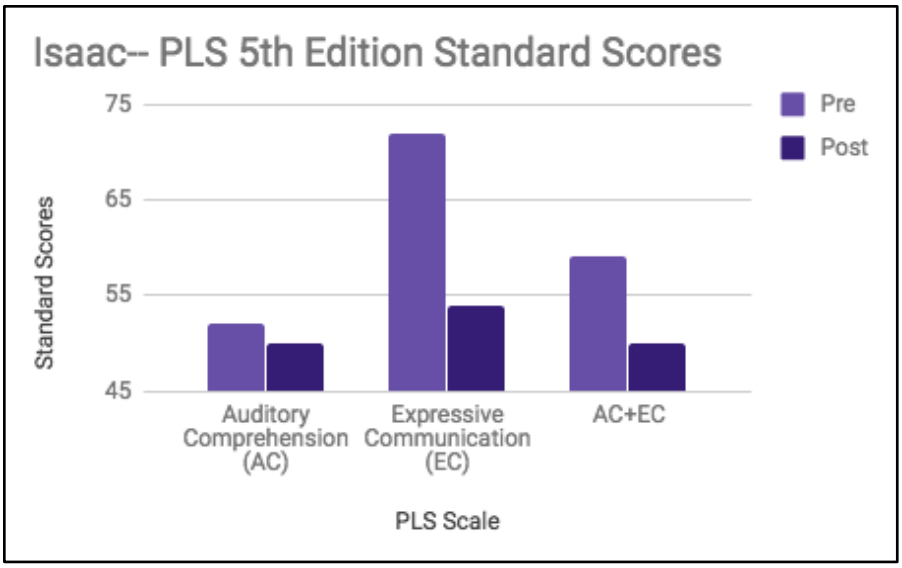

Figure 11 Isaac, PLS-5, Standard Scores, baseline and post-treatment

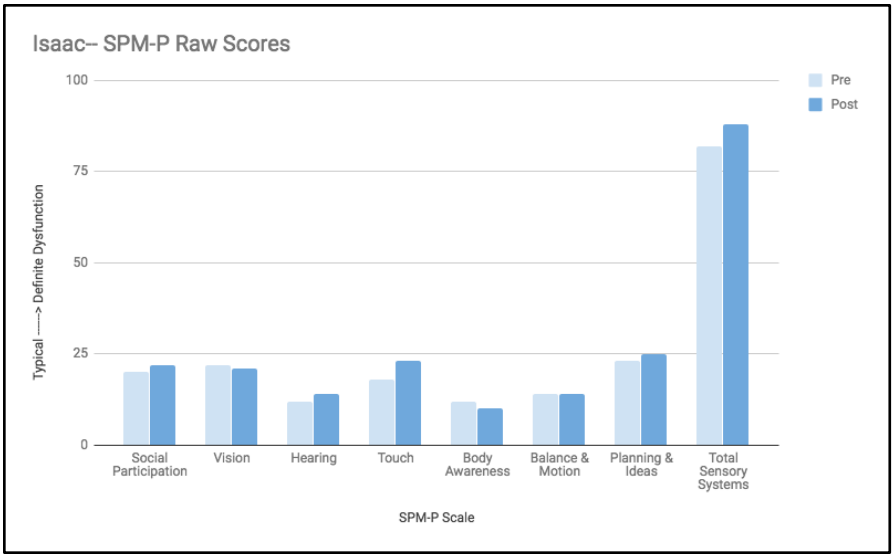

Figure 12 Isaac, SPM-P, Raw Scores, baseline and post-treatment

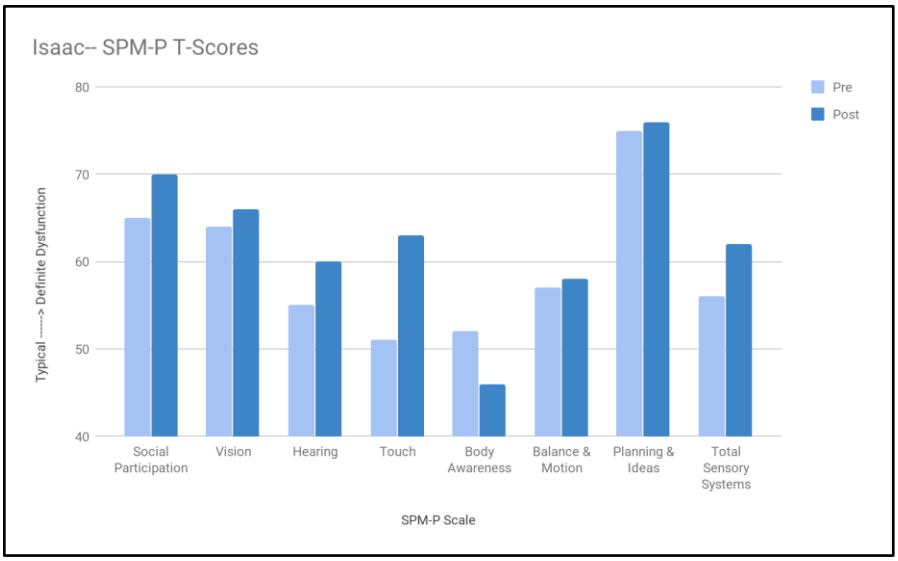

Figure 13 Isaac, SPM-P, Standard Scores, baseline and post-treatment

Derek

Derek's chronological age at baseline was 34.5 months with an IQ of 52. He was reassessed at 40.5 months and his IQ increased to 56. His MSEL raw scores showed some point increases in visual reception, fine motor, and expressive language, and some point decreases in receptive language between baseline and post-testing. MSEL standard scores showed some increase in visual reception and fine motor, some decrease in receptive language, and no change in expressive language (see Figure 14 and Figure 15). His PLS-5 raw scores showed some point increases between baseline and post-testing. PLS-5 standard scores showed some increase in auditory communication and some decrease in expressive communication (see Figure 16 and Figure 17). His SPM-P raw scores showed some point increases in vision, body awareness, and balance and motion, some point decreases in social participation and planning and ideas, and no change in hearing and touch. SPM-P standard scores showed an increase in vision, touch, body awareness, and balance and motion. However, there was a decrease in social participation, and planning and ideas, and no changes in hearing (see Figure 18 and Figure 19).

Derek's family reported both performance skill improvements and positive occupational performance impacts following intervention. Specifically, Derek's family reported improvement in receptive and expressive language, whereas Derek may have had difficulty beforehand. A family member stated, "Yesterday he wanted a yogurt, so he went to the refrigerator and said 'eat' and I opened it up and said 'what do you want?' and he grabbed his yogurt." This quote falls into the theme household communication, as the context afforded clear receptive and expressive communication for Derek. When describing participation in the community and going out to eat as a family, Derek's parent reported,

> We went out to dinner with our neighbors, and took him to a place he has never been before, and through the whole entire dinner at a restaurant, and was fine. He was completely fine. He sat and colored. So we can do more things like that.

This quote falls into the cross sections of both themes of community engagement and sensory regulation for participation in occupations, as he could be engaged and self-regulate at a restaurant.

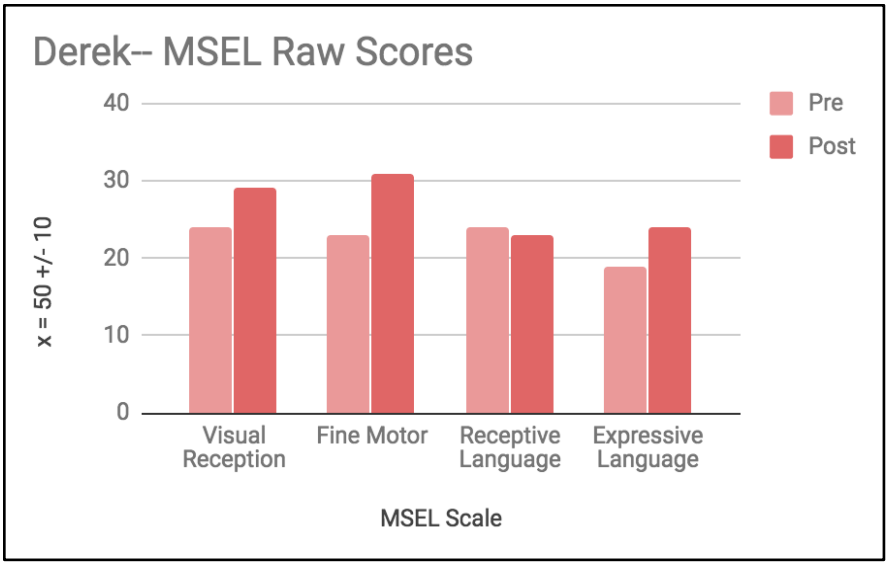

Figure 14 Derek, MSEL, Raw Scores, baseline and post-treatment

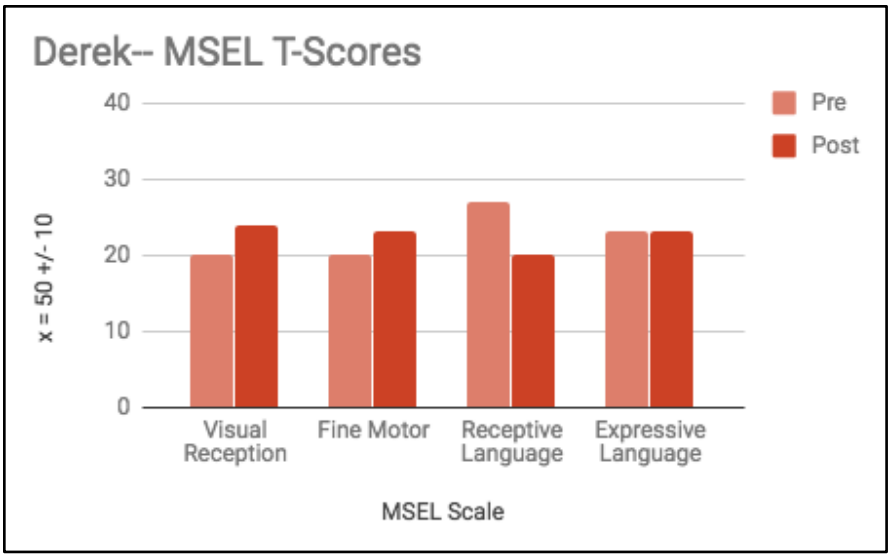

Figure 15 Derek, MSEL, Standard Scores, baseline and post-treatment

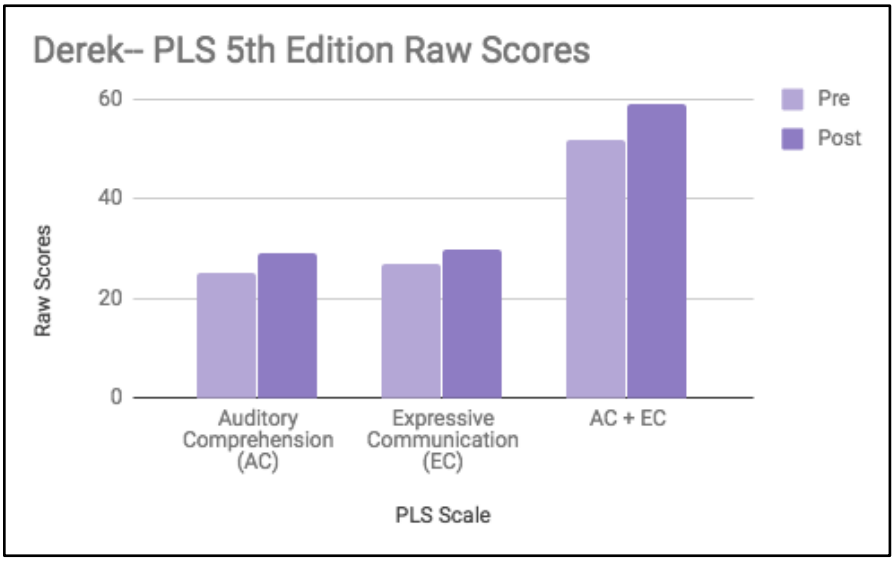

Figure 16 Derek, PLS-5, Raw Scores, baseline and post-treatment

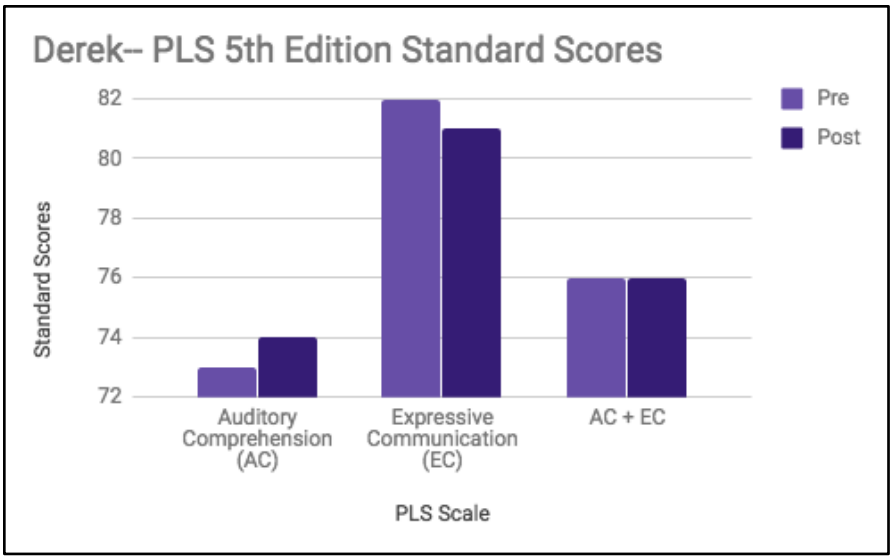

Figure 17 Derek, PLS-5, Standard Scores, baseline and post-treatment

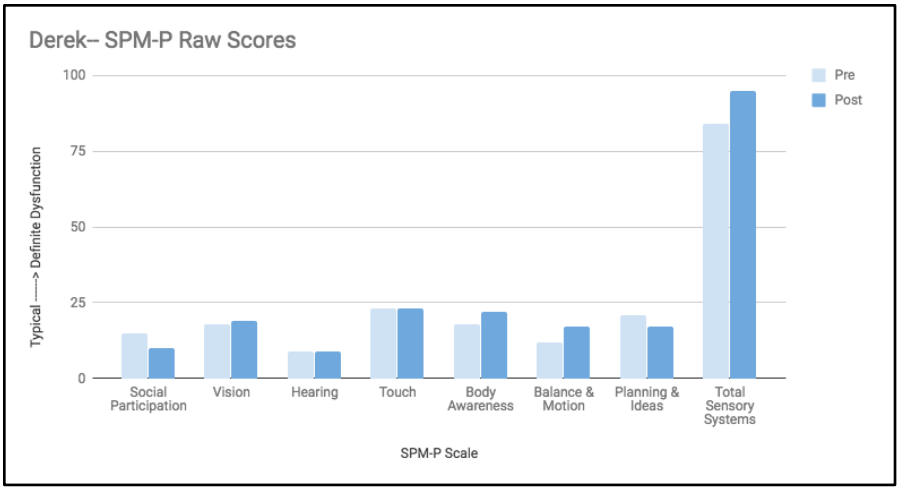

Figure 18 Derek, SPM-P, Raw Scores, baseline and post-treatment

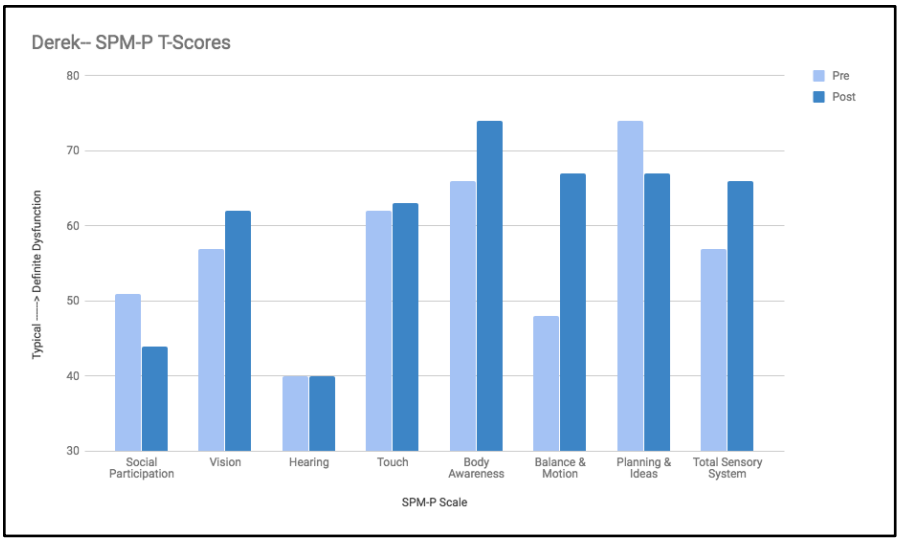

Figure 19 Derek, SPM-P, Standard Scores, baseline and post-treatment

Shiloh

Shiloh's chronological age at baseline was 59.4 months with an IQ of 49. He was reassessed at 65.4 months and his IQ increased to 56. His MSEL raw scores showed some point increases between baseline and post-testing in fine motor, receptive language and expressive language whereas visual reception remained unchanged. MSEL standard scores remained unchanged (see Figure 20 and Figure 21). Shiloh's PLS-5 raw scores showed some point increases between baseline and post-testing. PLS-5 standard scores showed small increase (see Figure 22 and Figure 23). His SPM-P raw scores showed both point increases and decreases between baseline and post-testing. SPM-P standard scores varied in changes where social participation, hearing, and planning and ideas decreased, body awareness, balance and motion increased, and vision and touch remained unchanged (see Figure 24 and Figure 25).

Shiloh's family reported both performance skill improvements and positive impacts on occupational engagement between baseline and post-testing. The family reported specific

improvements in communication and household activities whereas Shiloh may have had difficulty beforehand. Shiloh's parent said,

> He's very good at routine, when he's done with his goldfish crackers he'll bring me the bowl or the cup on the counter in the kitchen. We've started having him set his place at the table. Things like that, chores, he loves to help me mop.

Here, the family is noting the themes of household communication and communication in meaningful family activities. Another example of improved communication was Shiloh's use of pictures as an augmentative and alternative communication system. Shiloh's parent described, "I think he is doing great, if we don't understand what he is saying, show me a picture, show me what you are talking about and he will show you." These quotes fall into the themes of household communication for participation in meaningful activities/occupations.

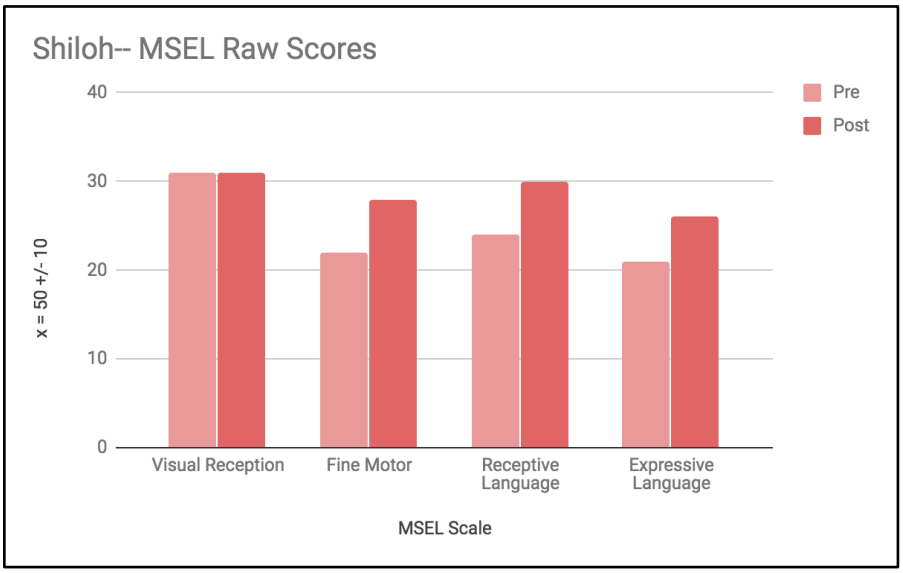

Figure 20 Shiloh, MSEL, Raw Scores, baseline and post-treatment

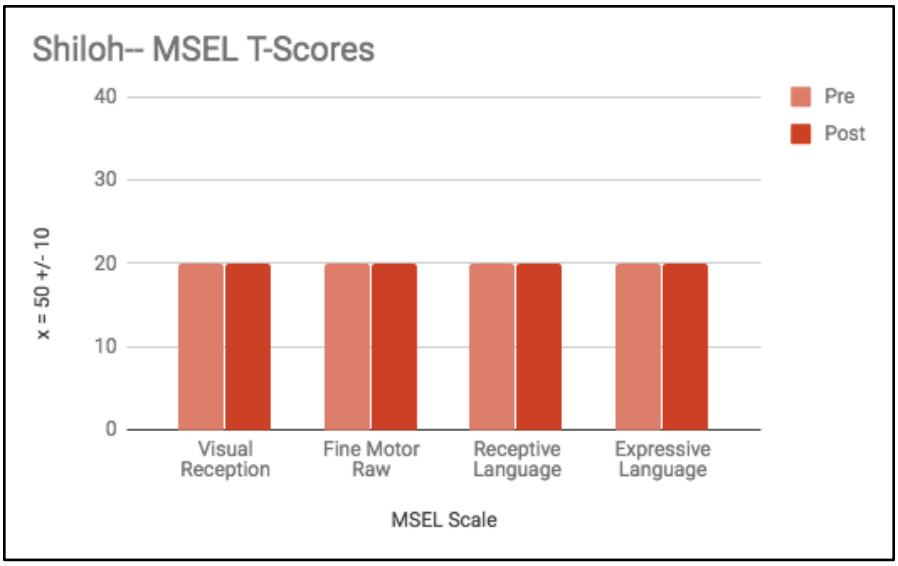

Figure 21 Shiloh, MSEL, Standard Scores, baseline and post-treatment

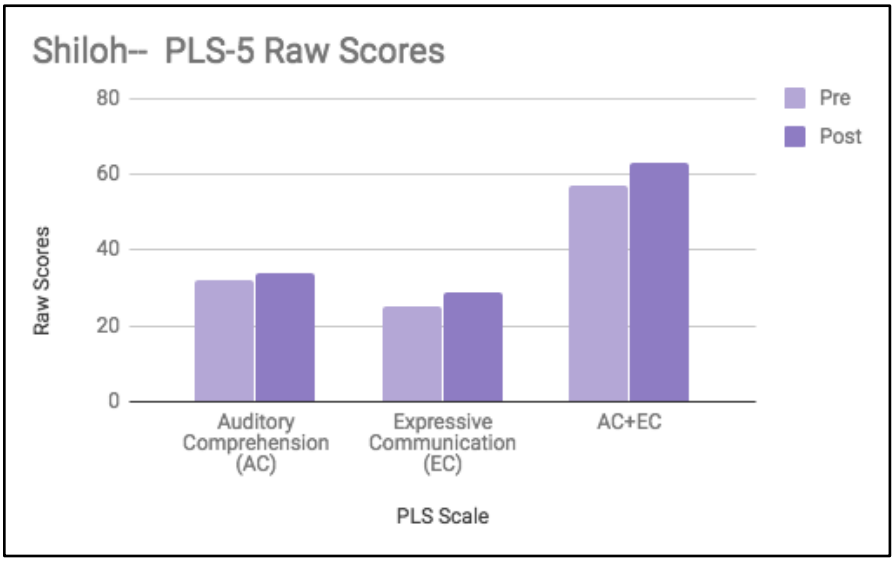

Figure 22 Shiloh, PLS-5, Raw Scores, baseline and post-treatment

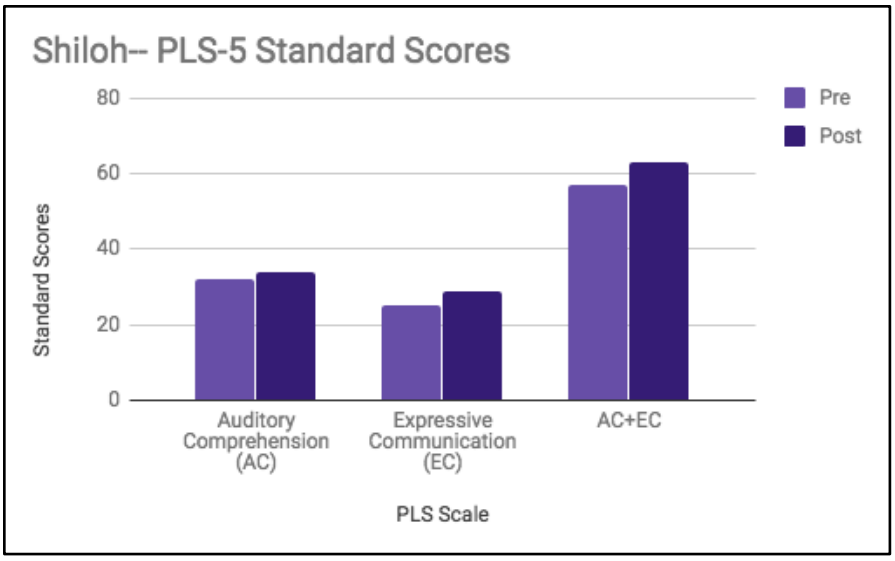

Figure 23 Shiloh, PLS-5, Standard Scores, baseline and post-treatment

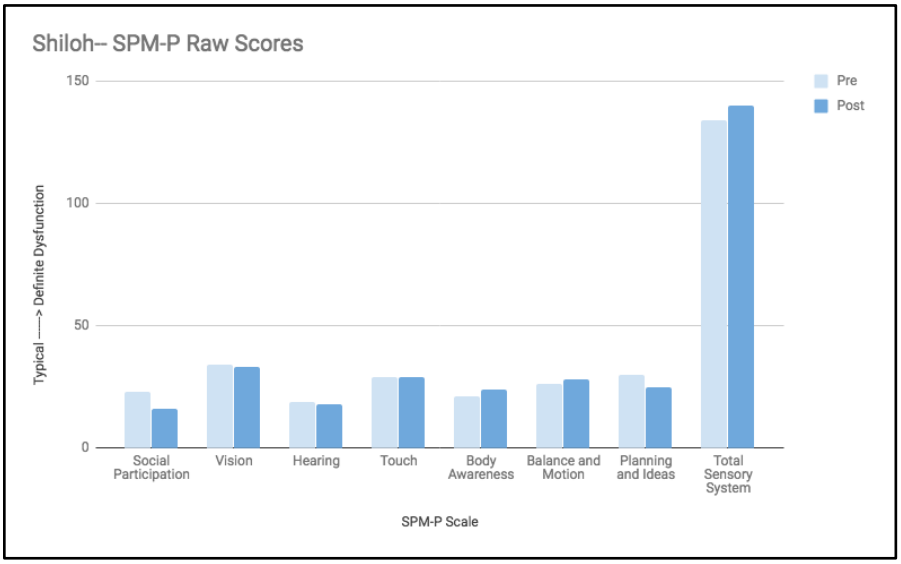

Figure 24 Shiloh, SPM-P, Raw Scores, baseline and post-treatment

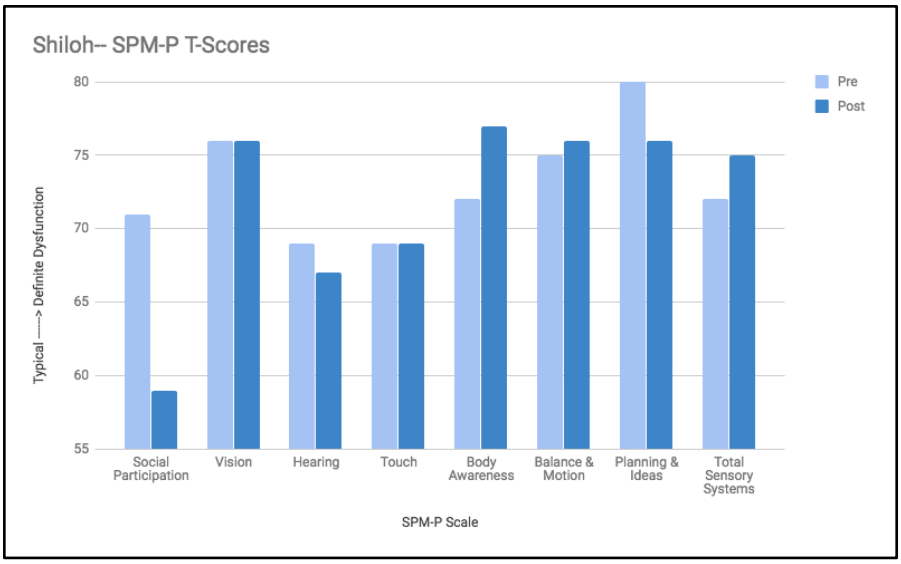

Figure 25 Shiloh, SPM-P, Standard Scores, baseline and post-treatment

Discussion

From the literature, FXS phenotypes are shown to impact the family and child's occupational engagement across contexts. In this study, families with children who have FXS reported positive outcomes of sertraline as stated in the transcribed semi-structured post interviews. Daily occupational engagement and FXS phenotypes such as anxiety, behavior management, self-regulation, social participation, and communication have shown improvement through the qualitative interviews. In the FXS research study completed by Hess et al., (2016) showed no statistically significant primary benefit with respect to early expressive language development. Qualitative data from this study were able to detect improvement in expressive language across all four participants as reported by their family members. The Hess et al., (2016) study further found significant improvements in social participation according to the SPM-P, which aligns with the occupation-based findings here within the semi-structured interviews with family participants. Yet, it is important to note that the semi-structured interviews provided more contextually relevant, occupationally meaningful examples of the social participation and how in some instances these were related to communication and / or sensory regulation improvements, which did not show up as significant in the statistical group analyses. Therefore, traditional standardized assessments, although helpful, demonstrate limited sensitivity to change and do not reflect occupation based improvements in everyday life for children with FXS. Specifically standard scores may not reflect the improvement families are reporting in their occupations and daily life. Semi-structured interviews reveal more contextually relevant changes in occupational performance in response to sertraline treatment in comparison to traditional standardized measures.

The results from participants, Kai, Isaac, Derek, and Shiloh, all illustrate minimal changes in standard scores despite some changes in raw scores. It is important to note that these assessment instruments evaluate many performance skills that can be part of occupational engagement, but not occupations per se. In contrast, when the standardized assessments are compared to the occupation based codes / themes from semi-structured interviews, we find areas of meaning and function as described by the families wherein the children demonstrated improvement.

The PEO (Law et al., 1996) model allowed researchers to not only consider the child living with FXS, but also considered their environments and how families are impacted in their daily occupations. The P (person) focuses on the child with FXS as a whole without other contextual influences and considers both the child and the family living with FXS. The E (environment) focuses on the environments and contexts for the child and family with FXS such as cultural, socioeconomic, physical, and social environment/context. The E in our sample was heavily centered around the home, school and community (e.g. parks, restaurants, grocery store, etc.) based on young children 2-6 years old and families. The O (occupation) focuses on the child and family's lived experience through semi-structured interviews, which reveal their daily life and occupations. This research concluded that the medical model, standardized tests, and clinical trials commonly used in FXS research are limited to only include the P (person) (See Figure 26). Yet, this consideration of the P (person) is limited and out of their typical contexts. In this study, all participants showed minimal gains on standardized assessments after six month post assessment testing and most of the participants had a trend of flat lining in their standard scores. The child's performance skills observed by the examiner during testing were out of context.

Many items/questions on standardized assessments limit the ability for a healthcare professional to understand a full picture of what a child may be capable of in their daily family occupations. It is imperative that practitioners broaden their knowledge about their clients when at the P (person) level. They must consider the data, along with crucial additional information including the child's strengths, interests, and performance capabilities in context. Our results showed that parents were expressing more improvements during the semi-structured interviews, when compared to the standardized assessments across the themes of household communication, community engagement, and sensory regulation for participation in meaningful activities / occupations. Focusing on all aspects of the E (environment), are important because it helps provide the practitioner has a holistic understanding from people that know the client best. The O (occupations) is an important tool in finding out what is meaningful to the family to help better understand their goals, by listening to their lived experiences. In this research, the addition of semi-structured interviews afforded much greater understanding of the P, E and O and thus was a new and occupation based examination of FXS (see Figure 27).

Implications for Occupational Therapy

This study provides supportive evidence for a need for occupation-centered approach to serving children and families with FXS. The OT profession should look beyond assessment scores, particularly standard scores and incorporate qualitative data, as standardized scores alone are not sufficient when evaluating occupational performance of a child with FXS. Standardized scores often do not reflect daily life performance in context as they are more anchored in performance skills. Examining a child’s functioning across contexts provides richer data when obtaining information about a child’s occupational performance and what is meaningful and

important to families. Including family occupations and the impact of living with FXS helps OTs have a better understanding of how to create meaningful and appropriate interventions that contribute to the overall improvement in quality of services.

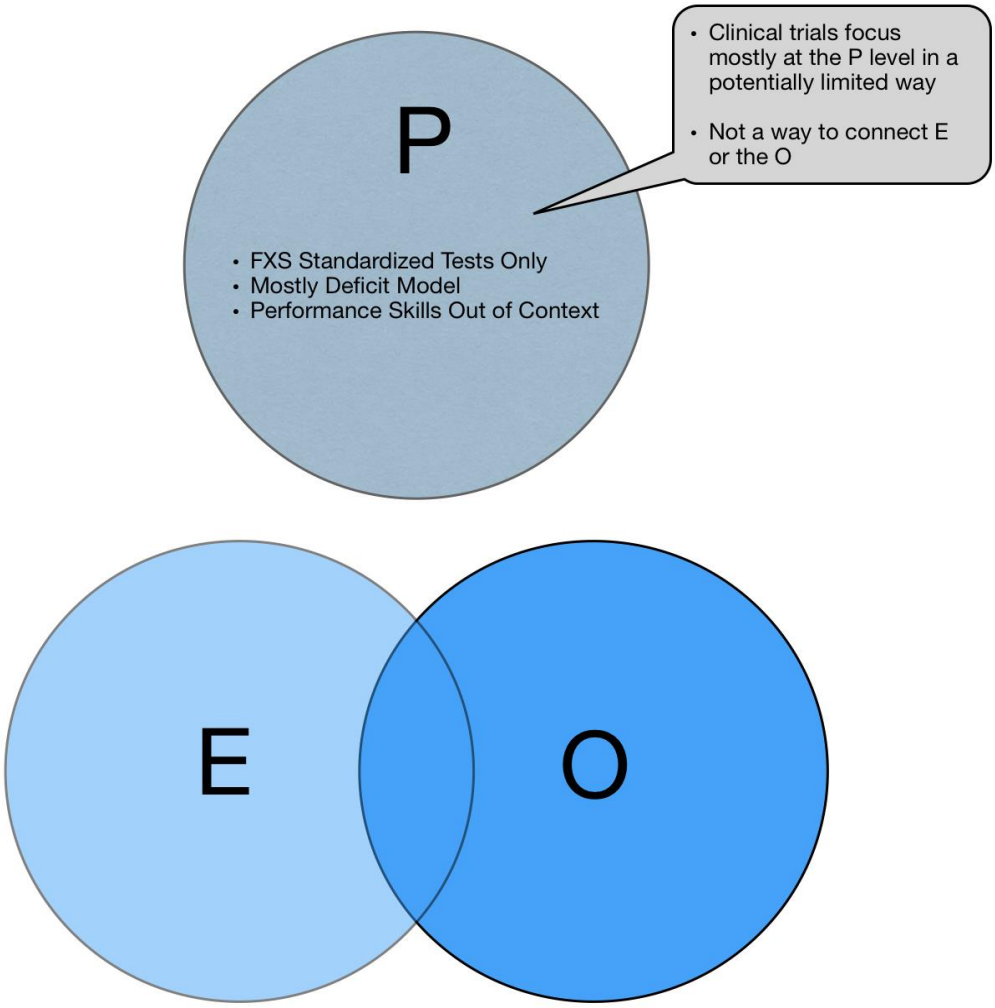

Figure 26 FXS PEO-Medical Model / Clinical Trials, clinical trials focus mainly at the P level, with a limited scope and there is not a way to connect to either the E or the O

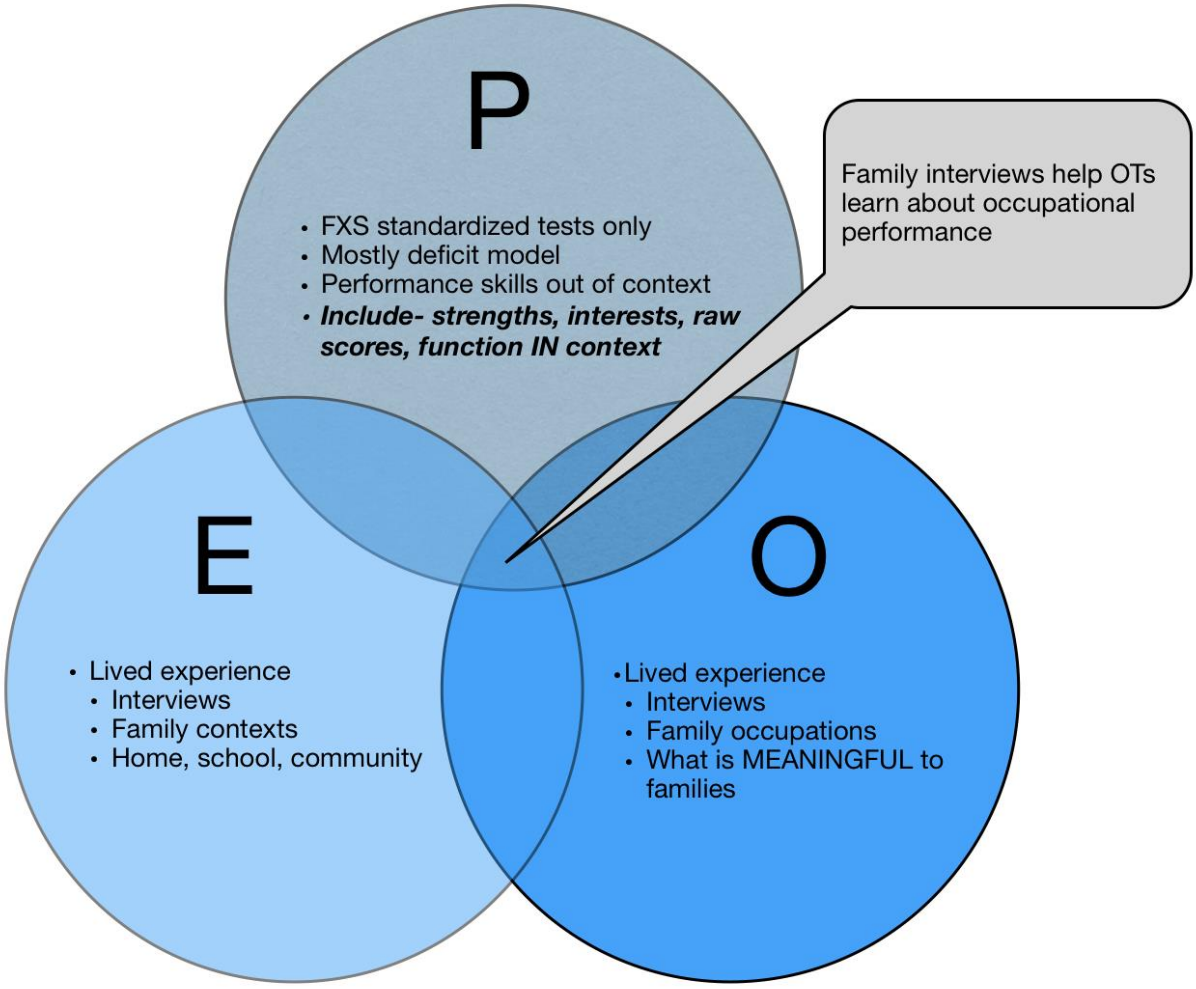

Figure 27 FXS PEO-In Context, family interviews help OTs learn about occupational performance

Limitations

Limitations in this study included the inability to conduct member checks as the study already had taken place at the U.C. Davis MIND Institute. This sample of case studies was deliberately designed to be homogenous; therefore boys were selected from the sertraline treatment group, which may lead to biased results, as the researchers were not blind to group assignment. Even with careful selection to obtain a homogenous sample, we did have one outlier who had a much higher IQ beyond what is typical for boys with full mutation FXS.

Conclusion

FXS is a well-researched topic with many clinical trials, including examination of the effectiveness of sertraline, to treat behavioral symptoms (Hess et al., 2016). Much of the previous literature has been important and informative, yet the research is dominated by the medical model and quantitative outcome measures. There is a dearth of qualitative studies including family voice and context as part of a battery of outcome measures including traditional standardized measures. The goal of this in-depth case study analyses incorporating, mixed methods was to compare and contrast traditional developmental assessments with qualitative semi-structured interviews of family reports about living with FXS and where intervention "improvements" are meaningful, contextually based and occupation focused. Based on the results, traditional standardized assessments have limited sensitivity to change over time for children with FXS, and do not reflect contextually relevant improvements in their daily occupations. Traditional standardized assessments provide a measure of performance skills which don't directly translate to occupational performance per se. Even when certain performance skills improved slightly with a raw score increase, standard scores often were flat lined and this was in direct contrast with family descriptions of improvements and changes over time. In conclusion, the overall message is to thoughtfully examine the lived experiences of those with FXS from an occupation centered lens in addition to standardized assessments in both intervention and research trials to further address meaningful occupational engagement.

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Appendix A

Approval to access FXS database

Permission from Principal Investigator for access to FXS Date base - U.C. Davis MIND Institute

FXS parent interviews

Inbox x

Hess, Laura <laura.hess@dominican.edu> Oct 15 (13 days ago)

to Randi

Hi Randi
I have 2 capstone research groups who will be working on transcribing and analyzing the FXS family interviews that were part of the Sertraline research project. My students have enthusiastically set about their lit reviews and are generating exciting proposals. We are now to the IRB drafting phase here at Dominican.

Would you via response to this email provide us with permission as the PI to access this data? We can then include this as documentation as part of our IRB here.

It has been very rewarding and exciting to teach my students about FXS and have them embark on their research in this area as they become occupational therapists.

Hope this finds you happy and well
take care
Laura

Laura Greiss Hess, PhD, OTR/L
(laura.hess@dominican.edu)
Assistant Professor
Department of Occupational Therapy
Dominican University of California
50 Acacia Ave.
San Rafael, CA 94901
415-482-1906

Randi Hagerman Oct 17 (11 days ago)

to me

Hi Laura, This sounds great and yes you have my permission to do this. I hope all is going well for you. Take care,Randi

Randi J. Hagerman, M.D.
Medical Director of the MIND Institute
Distinguished Professor
Endowed Chair in Fragile X Research

Appendix B

Data Signed Agreement

DTA 2018-0545-D

DATA TRANSFER AGREEMENT

This Data Transfer Agreement ("Agreement") is effective this 16 th day of January, 2018 ("Effective Date"), by and between The Regents of the University of California, on behalf of its Davis campus, having an address at UC Davis Innovation*Access*, Technology Transfer Services, University of California, Davis, 1850 Research Park Drive, Suite 100, Davis, California, 95618-6134 ("Disclosing Party") and Dominican University, having an address 50 Acacia Avenue, San Rafael, CA 94901-2298 (Receiving Party). This Agreement governs the conditions of disclosure and use of the certain de-identified data from the Sertaline in Fragile X Study Data Set, (herein as "Data Set").

The Receiving Party hereby agrees it will:

(1) Safeguard the Data Set against disclosure to others with the same degree of care as it exercises with its own information of a similar nature.

(2) Limit the use or receipt of Data Set to the individuals who require access in order to perform activities permitted by this Agreement.

(3) Use the Data Set for teaching or not-for-profit research purposes only.

(4) Inform the users of the Data Set that they may not:

a. Disclose any data of the Data Set that are individually identifiable, or any information that identifies persons, directly or indirectly, except as permitted under this Agreement;
b. Link the data values with individually identifiable records from any other source;
c. Use the Data Set to learn the identity of any person included in the Data Set or to contact any such person for any purpose;
d. Make statements indicating or suggesting that interpretations drawn are those of the Data Set source;
e. Not re-disclose (i.e. share) the Data Set (or any part), without approval from the Disclosing Party.

(5) Promptly notify Disclosing Party of any use or disclosure of the Data Set of which it becomes aware that is not permitted by this Agreement.

(6) Require any contract employees or its subcontractors or agents that receive or have access to the Data Set to abide by the terms of this Agreement.

(6) Acknowledge the source of the data in all reports based on the Data Set.

THE DISCLOSING PARTY MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE DATA SET WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Receiving Party assumes all liability for claims for damages against it by third parties which may arise from the Receiving Party's use of the Data Set.

The Receiving Party agrees to use the Data Set in compliance with all applicable statutes and regulations.

This Agreement terminates five (5) years from the Effective Date, provided that, either party may terminate this Agreement at an earlier date upon thirty (30) days prior written notice. In the event of such early termination, the obligations of each party under this Agreement shall survive and remain in effect until the date two (2) years from the Termination Date.

Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

This Agreement may be executed in any number of counterparts, including facsimile or scanned PDF documents. Each such counterpart, facsimile or scanned PDF document shall be deemed an original instrument, and all of such counterparts, together, shall constitute one and the same executed Agreement.

IN WITNESS WHEREOF, the parties execute this Agreement as of the above Effective Date.

Disclosing Party

The Regents of the University of California

By: [redacted]
(Signature)

Name: Jan D. Carmikle BC

Title: Senior Intellectual Property Officer

Date:

Read & Acknowledged by Disclosing Party Researcher

By: [redacted]
(Signature)

Name: Dr. Randi Hagerman, Professor

Date: 1/19/18

Receiving Party

Dominican University of California

By [redacted]
(Signature)

Name: Tammi D. Jackson

Title: Vice President of Finance and Administration

Date: 1-18-18

Read & Acknowledged by Receiving Party Researcher

By [redacted]
(Signature)

Name: DR. LAURA GROSS HESS
ASSISTANT PROFESSOR

Date: 1/18/18

Appendix C

Baseline and Post Semi-structured Interview Question Protocol

BASELINE	POST
1. Tell me about (child's name). I especially want to hear stories about the kinds of things you enjoy about (child's name), what his / her gifts and talents are; what his / her strong points are. 2. Tell me about your child's activity level / behavior? Tell me a story about how this may impact you as a family? 3. What do you notice about your child's reactions to sensory input? (moving through space, sound, touch, smelling things, eating). Tell me a story about how this may impact you as a family? 4. Tell me about your child's abilities in communicating with you? Other family members? Other children? Tell me a story about how this may impact you as a family? 5. What interventions are you participating in currently including school and/or therapies (such as OT / speech)? Is there anything you would like to see changed about your child's intervention situation or the way he or she is during intervention / services? 6. What has led you to participate in research that includes a trial of medication? 7. Tell me your feelings about the possibility that your child may get the real medication? Tell me your feelings about the possibility that your child may get the placebo? 8. What are your expectations and/or hopes for this research study? What does participating in this type of research mean to you and your family?	During our first interview we were able to discuss your child's strengths and patterns including behavior, sensory, anxiety and communication and the impact on your family. As a follow up to that conversation, today I would like us to discuss any changes you have seen since beginning the study in these areas and the impact to your family. 1. Let's start with activity level and behavior. What changes if any have you noticed and how has that impacted you as a family. 2. Have you noticed any changes related to anxiety? How has that impacted you as a family? 3. Have you noticed any changes related to sensory processing? How has that impacted you as a family? 4. Have you noticed any changes related to communication? How has that impacted you as a family? 5. Do you think you were given the placebo or the medication? What were you observing / feeling that has led you to wonder whether you had the medication or not? 6. Is there anything you would like to share in terms of your family's involvement in the research study regarding what you have learned thus far and what your hopes are for learning that can come out of the research?

9. What are you hoping will change as a result of this research? What are you hoping to learn? 10. What are your hopes for the potential of the medication and what this may mean for interventions / therapies? Other?	

Appendix D

IRB Approval Letter

DOMINICAN UNIVERSITY of CALIFORNIA 1890

February 5, 2018

Elena Javier
50 Acacia Ave.
San Rafael, CA 94901

Dear Elena:

I have reviewed your proposal entitled *Effects of Sertraline Treatment for Young Children with Fragile X Syndrome: Family Perspectives* submitted to the Dominican University Institutional Review Board for the Protection of Human Participants (IRBPHP Application, #10666). I am approving it as having met the requirements for minimizing risk and protecting the rights of the participants in your research.

In your final report or paper please indicate that your project was approved by the IRBPHP and indicate the identification number.

I wish you well in your very interesting research effort.

Sincerely,

[redacted]

Randall Hall, Ph.D.
Chair, IRBPHP

Cc: Laura Hess