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Neuropsychological Phenotypes of 76 Individuals with Joubert Syndrome evaluated at a Single Center

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Contributor's statement page

Angela Summers conceptualized the neuropsychological data analysis, prepared figures, drafted the initial manuscript, and approved the final manuscript as submitted.

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Dr. William A. Gahl, financially accountable investigator of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Abstract

Objectives—Joubert Syndrome (JS) is a genetically heterogeneous ciliopathy characterized by hypo-dysplasia of the cerebellar vermis, a distinct hindbrain/midbrain malformation (molar tooth sign), and intellectual disability. We evaluated the neuropsychological profiles of 76 participants with JS in the context of molecular genetics and clinical covariates.

Methods—Evaluations included neuropsychological testing, structured parental interviews, DNA sequencing, brain magnetic resonance imaging (MRI), electroencephalography (EEG), ophthalmologic examination, and assessment for renal and hepatic disease.

Results—On average, participants manifested Full Scale Intelligence Quotients (FSIQ) in the moderately to profoundly low range (M=64.3±15.3). Of the Wechsler index scores, verbal comprehension was least affected and processing speed was most affected. Receptive language was rated as better than expressive language on the Vineland Adaptive Behavior Scales-Second Edition. Those with abnormal EEG had a significantly lower FSIQ (n=15; M=50.7±12.9) compared to participants with normal EEG (n=39; M=64.7±16.3; p=.004). Participants taking psychiatric medications manifested a lower FSIQ (n=20; M=54.8±13.2) than those not taking them (n=42; M=65.0±17.2; p=.022). These correlations were also present in the *TMEM67*-related JS sub-cohort (n=14). Based on parental assessment, psychiatric and behavioral problems were significantly more common than in the general population for all measures (p<.004 for all).

Conclusions—The majority (65%) of individuals with JS have some degree of intellectual disability. Abnormal EEG is associated with lower neuropsychological function. Processing speed is a weakness, while verbal comprehension and receptive language are relative strengths. These

findings may guide parents, teachers, therapists, and doctors to determine appropriate therapies, accommodations and academic goals for individuals with JS.

Keywords

Joubert Syndrome; neuropsychological function; cognition; EEG; MRI; JSRD

INTRODUCTION

Joubert Syndrome (JS), first described in 1969 [Joubert et al., 1969], is a rare, inherited condition characterized by hypo-dysplasia of the cerebellar vermis in association with a distinct hindbrain/midbrain malformation that results in the appearance of the pathognomonic "molar tooth sign" (MTS) on axial brain magnetic resonance imaging (MRI). The MTS results from a deep interpeduncular fossa and thick, horizontally-oriented superior cerebellar peduncles at the ponto-mesencephalic junction [Gleeson et al., 2004; Maria et al., 1997; Maria et al., 1999] (Figure 1). Typical clinical features observed early in life include hypotonia, abnormal respiratory pattern, abnormal eye movements (including ocular motor apraxia), ataxia, and developmental delay. Variable features include retinal degeneration, ocular colobomas, fibrocystic kidney and liver disease, and polydactyly [Brancati et al., 2010; Joubert et al., 1969; Maria et al., 1999]. This clinical heterogeneity led to the use of the term Joubert syndrome and related disorders, which includes Senior-Løken (retinal degeneration and nephronophthisis) [Løken et al., 1961; Parisi et al., 2004; Senior et al., 1961] and COACH (*c*olobomas, "*o*ligophrenia" for cognitive impairment, *a*taxia, *c*erebellar vermis hypoplasia, and *h*epatic fibrosis) syndromes [Gleeson et al., 2004]. Recently, for simplicity, the term JS is recommended to refer to all participants with the "molar tooth sign" including participants with or without extra-neurological system involvement [Romani et al., 2013]. Therefore, we will use JS to refer to all participants with a MTS, regardless of whether there is an extra-neurological clinical presentation.

The prevalence of JS is between 1/80,000 and 1/100,000, which may be an underestimate due to its under-recognition [Brancati et al., 2010; Parisi et al., 2007]. Pathogenic variants in one of over 30 genes cause JS; inheritance pattern is autosomal recessive, except for one gene, *OFD1*, which is X-linked. Genes associated with JS encode proteins that are required for the normal structure and function of the primary cilium, the sensory antenna of the cell with critical functions in embryogenesis as well as postnatal maintenance of tissues such as retina and kidneys [Gunay-Aygun, 2009; Parisi and Glass, 1993–2016]. An intact primary cilium with normal structure and function is a pre-requisite for fundamental signaling pathways including Sonic Hedgehog (Shh) and Platelet-derived growth factor receptor-alpha (PDGFRα) that are essential for normal brain function. Shh signaling is required for proliferation of cerebellar granule neuron precursors [Spassky et al., 2008] and PDGFRα plays a role in directional neuronal migration [Carter et al., 2012]. Hence, cerebellar hypoplasia and dysgenesis that result in the pathognomonic MTS for JS, are the common downstream effects of defects in the more than 30 distinct JS genes.

Formal neuropsychological assessment of individuals with JS is challenging due to ocular motor apraxia, speech and language disturbance including speech apraxia, impaired vision,

and sometimes, severe cognitive impairment that may interfere with administration and/or interpretation of neuropsychological evaluations [Maria et al., 1999; Poretti et al., 2010; Tavano and Borgatti, 2010]. In addition, the rarity of JS makes it difficult to conduct studies on a large group of individuals to allow statistically meaningful characterization of the neuropsychological findings. The majority of the publications on neuropsychological functioning in JS have heavily relied on caregiver questionnaires. Formal neuropsychological evaluations of small numbers of individuals with JS have shown variable degrees of developmental delay and impaired cognitive functioning [Gitten et al., 1998; Maria et al., 1999; Steinlin et al., 1997; Tavano and Borgatti, 2010; Torres et al., 2001], including rare cases with normal cognition [Holroyd et al., 1991; Poretti et al., 2010; Valente et al., 2005].

Recently, Bulgheroni et al. reported a multi-center study on neuropsychological function in 54 Italian individuals with JS [2016]. The majority of their participants demonstrated scores in the intellectually disabled range. However, their findings suggested that average to above average intelligence may be more common (11%) in individuals with JS than has been previously described in the literature. Additionally, their behavioral/psychiatric data suggested that individuals with JS exhibit more emotional and behavioral problems compared to the general population, although true psychiatric disease was rare.

Here we present the neuropsychological phenotypes of 76 individuals with JS evaluated at the National Institutes of Health (NIH) Clinical Center. We detail cognitive strengths and weaknesses in JS, and present neuropsychological data in the context of the underlying genotype and well-characterized clinical covariates that could influence cognitive functioning, including visual acuity, kidney function, and portal hypertension.

PARTICIPANTS AND METHODS

Participants

All participants were prospectively evaluated at the NIH Clinical Center, between 2003 and 2014, under the protocol “Clinical and Molecular Investigations into Ciliopathies”; (www.clinicaltrials.gov, trial NCT00068224), approved by the National Human Genome Research Institute Institutional Review Board. Participants and/or their parents gave written, informed consent. For recruitment, the study was advertised to individuals with JS and their families by The Joubert Syndrome & Related Disorders Foundation as a natural history study aiming to describe the individual organ system involvement in JS including kidney and liver disease. To minimize ascertainment bias, all travel, lodging and other participation costs, as well as clinical and laboratory evaluations, were sponsored by the NIH. Recruitment was not based on race, gender, or disease severity.

Neuropsychological Evaluation

We administered age-appropriate versions of Wechsler* intelligence scales and we report Full Scale Intelligence Quotient (FSIQ), Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed Index (PSI) scores using standard procedures [Wechsler, 1997; Wechsler, 2002; Wechsler, 2003; Wechsler, 2006;

Wechsler, 2008b; Wechsler, 2011] for participants who were able to complete the requisite portion(s) of a Wechsler IQ test. General Ability Index (GAI), an alternative measure of intelligence that is not strongly influenced by PSI and WMI, was also derived, when possible, using standard procedures [Raiford et al., 2005; Tulsky et al., 2001; Wechsler, 2008a]. Each variable has a mean of 100±15. See Supplemental Methods and Supplemental Table I for explanations of neuropsychological tests and variables.

For participants under 2 years 6 months of age, or those who had sensory, motor, or cognitive impairment(s) that precluded them from completing a Wechsler IQ scale, we administered to their parents the Vineland Adaptive Behavior Scales-Second Edition (Vineland-II) [Sparrow et al., 2005], an informant interview that assesses communication, motor, social, and daily living skills. We report the four Vineland-II subscales and the Vineland Adaptive Behavior Composite (VABC) score. In nine cases, the Vineland-II was administered even though a Wechsler IQ measure was administered. We report the VABC for those whose parents completed a Vineland-II, irrespective of the participant's ability to complete a Wechsler IQ test. The VABC has a mean of 100±15.

FSIQ and VABC share conceptual overlap [2002; de Bildt et al., 2005; Meyers et al., 1979]; thus, we report FSIQ/V, which is the participant's FSIQ when available, or VABC score if FSIQ was not available. Similarly, we report GAI/V, which is a participant's GAI when available, or VABC score if GAI was not available. It is important to note that the Vineland-II is more subjective than Wechsler tests and assesses broader areas of function, such as motor and social skills, that are often outside of what is traditionally known as IQ.

We also specifically characterized individuals who produced FSIQ or FSIQ/V scores ≥70 in an effort to highlight the cognitive strengths and weaknesses observed within this subset of individuals. The Vineland-II includes v-subscale measures of receptive and expressive language. Each v-subscale has a mean of 15±3. In 2010, the Peabody Picture Vocabulary Test-Fourth Edition [Dunn and Dunn, 2007] (PPVT-4; mean of 100±15) was added to the evaluations because we recognized a need to evaluate receptive vocabulary in an objective manner that required minimal speech and/or motor functioning.

Age-appropriate versions of the Child Behavior Checklist (CBCL) [Achenbach and Rescorla, 2000; Achenbach and Rescorla, 2001] were administered to parents to rate their children's behaviors. The CBCL yields scores related to affective, somatic, social, and cognitive issues. Data across age groups (defined by the CBCL as 1.5–5 years and 6–18 years) were combined into one group for scales that overlapped between the age groups. Post-hoc analyses of the scales by age were conducted to elucidate any differences between the younger and older participants.

Molecular Genetic, EEG, Neuroimaging, Clinical, and Biochemical Data Collection

Other evaluations performed at NIH included molecular genetic testing including whole exome sequencing, electroencephalograms (EEG), review of brain MRI, echocardiogram,

*Wechsler scales used in this study included: Wechsler Adult Intelligence Scale – III (WAIS-III), Wechsler Adult Intelligence Scale – IV (WAIS-IV), Wechsler Intelligence Scale for Children – IV (WISC-IV), Wechsler Abbreviated Scales of Intelligence – II (WASI-II), and Wechsler Preschool and Primary Scale of Intelligence - III (WPPSI-III).

abdominal ultrasonography, ophthalmologic examinations (WZ, BB), comprehensive blood and urine biochemistries, and review of past medical records.

The ophthalmologic examinations included assessment of visual acuity and fixation. Best-corrected visual acuity (BCVA) was measured when possible and the Snellen-equivalent acuity recorded. If patient age or cooperation level precluded an adequate measurement of BCVA, a determination of the presence or absence of the following reflexes was documented: 1) fix and follow (FF), 2) central, steady/unsteady and maintained fixation (CSM/CUSM), 3) blink to light (BTL) reflexes. Individuals were determined to have chorioretinal coloboma, retinal degeneration, kidney disease and liver disease based on clinical and laboratory evaluations performed at the NIH Clinical Center [Vilboux et al., 2017].

To evaluate correlations between brain MRI findings and cognitive function, brain MRIs were rated using a 3-point severity score (0=MTS and vermis hypo-dysplasia only; 1=MTS with vermis hypo-dysplasia and other brainstem (infratentorial) abnormalities; 2=MTS with vermis hypo-dysplasia and other infratentorial and supratentorial abnormalities). A brain MRI severity score could not be generated for 13 participants because their MRI images were not available. All 13 of these participants had brain MRI reports describing MTS and 12 of the 13 had gene mutations identified; the remaining participant (Table I, participant 570) had classical clinical features of JS in addition to a brain MRI report describing the MTS.

Please see Supplemental Methods for other details and methods of molecular genetic analysis, neuroimaging evaluations and EEG.

Statistical Analysis

One-way between-subject analysis of variance (ANOVA), paired-samples *t* tests, independent-samples *t* tests, and one-sample *t* tests were performed using SPSS 21 [2012]. All analyses were two-tailed and significance level was set at $\alpha \leq .05$ in order to reduce the amount of type-II error. Effect sizes are reported as partial eta-squared ($\square^2_p$) for between-subjects ANOVAs, Cohen's *d* for paired and independent samples *t* tests, and r^2 for correlations. Descriptive variables are presented as mean±SD.

RESULTS

Participants

Phone interviews with 105 families (comprising 120 individuals with JS) were conducted. Fifteen families could not travel to the NIH Clinical Center in Bethesda, Maryland. The remaining 105 participants from 90 families all underwent week-long clinical evaluations at the NIH Clinical Center. Seventy-nine participants had neuropsychological evaluations at NIH; 21 had MTS, but were unable to complete the neuropsychological evaluation due to scheduling conflicts.

Seventy-six of the 79 participants who had neuropsychological evaluations at NIH are presented in this paper; three participants with Senior-Løken phenotype were excluded

because they did not have MTS on brain MRI. Notably, the intellectual functioning of these individuals was significantly higher (average to above average) than our JS cohort with MTS.

The 76 participants ranged in age from 10 months to 36 years (M=10.2±7.8 years). Thirty-three (43%) were female. Sixty percent of participants acquired the ability to walk independently; of those, the average age that participants began walking was 4.3±2.1 years. Seventy-three percent of participants acquired the ability to speak; of those, the average age of first word(s) was 2.6±1.3 years. Participants were from 66 independent families; eight families had two and one family had three affected siblings (Table I). The causative genes and the main clinical findings including age first walked, age of first word(s), eye, kidney, and liver-related features, as well as brain MRI and EEG results of all 76 participants are detailed in Table I. We identified mutations in 17 JS genes in 73/76 (96%) participants; the most commonly mutated genes were *TMEM67* (n=19; 14 families), *C5orf42* (n=11; 9 families) and *CC2D2A* (n=8; 7 families; Table I, Supplemental Table II).

Ocular motor apraxia was present in 45/56 participants (80%) for whom data were available. Three (4%) were status-post kidney transplantation; 12 (16%) had variable degrees of decreased kidney function at the time of testing. Nine (12%) had portal hypertension, including one who was status-post liver transplantation.

EEG was abnormal in 19/67 (28%) participants who underwent this evaluation (Supplemental Table III). Mild diffuse background slowing was noted in 16, two of which also showed diffuse excess beta activity (one taking ethosuximide, the second taking clonazepam, both known to cause excess beta activity). Two additional participants had diffuse excess beta activity with otherwise normal background activity (one taking no neuropsychiatric medications, the second taking baclofen and clonidine). Diffuse excess bet activity is a non-specific finding with many reported associations, most commonly medication effect. However, these two medications have not been specifically associated with this finding. Five participants had epileptiform findings on EEG, consisting of spikes and/or sharp waves mostly with diffuse or occipitally-predominant localizations. Only two of these five participants had epilepsy (recurrent afebrile seizures), although 7/76 participants (9%) had a history of seizures. Four of 19 (21%) participants with abnormal EEG had abnormal neuroimaging findings in the supratentorial brain including bilateral diffuse pachygyria, focal cortical dysplasia, absence of the corpus callosum splenium, and occipital encephalocele. Seven of 48 (15%) participants with normal EEG had abnormal imaging findings in the supratentorial brain including heterotopia and callosal hypoplasia in two participants, and diffuse polymicrogyria, focal cortical dysplasia, and occipital encephalocele in one participant. Twenty-three participants (29%) were on at least one psychiatric medication (Supplemental Table IV).

Neuropsychological Profile of JS

Table I presents the neuropsychological findings for participants who have FSIQ, Vineland-II, and/or CBCL scores. FSIQ was derived for 32 participants (41%); 12 were too young, 26 had severe physical and/or developmental limitations that precluded comprehensive

evaluation, three had incomplete evaluations due to testing fatigue, and three declined testing due to fatigue from evaluations performed earlier that day.

FSIQ scores ranged from 41 to 95; the average FSIQ was 64.3±15.3 (Table I, *p*Figure 2), representing mild intellectual disability (FSIQ < 70). Five (7%) had a low-average/average FSIQ (80 ≤FSIQ ≤100). The mean GAI was 67.2±16.3 (n=31; Table I, Figure 2). Eight (11%) had a GAI score in the low-average/average range. Both FSIQ and GAI were derived for 26 participants; GAI was significantly higher (=.001, *t*=3.655).

The mean VABC score for those who were not able to complete any part of the Wechsler tests was 58.9±18.7 (n=27). The mean VABC score for all participants, regardless of Wechsler testing, was 60.3±17.3 (n=35; Figure 2).

The average FSIQ/V was 61.7±16.6 (n=62). For the participants who had a FSIQ and VABC score, the difference between the two measures was not significant (n=5; FSIQ M=57.4±21.8, VABC M=68.2±12.9, *p*=.14, *t*=−1.83). The average GAI/V was 63.4±17.3 (n=64). There were only two participants who had a GAI and VABC score, precluding any meaningful analyses.

Wechsler VCI and WMI scores were, on average, in the borderline intellectual functioning range (70 ≤index score ≤79), while PRI and PSI scores were in the intellectually disabled range (Figure 3, Table II).

Vineland-II communication, socialization, daily living, and motor skills subscales were, on average, in the intellectually disabled range (Figure 4).

For those individuals with FSIQ or FSIQ/V ≥70, the Wechsler index scores followed a pattern that appeared similar to that of the overall cohort. VCI (M=90.2±14.9, n=16) and WMI (M=92.4±14.1, n=11) were relative strengths, while PRI (M=82.6±12.2, n=14) and PSI (M=83.1±15.7, n=10) scores were lower. Individuals with JS who produced FSIQ ≥70 were younger (M=8.1±4.1 years, n=14) than those with FSIQ <70 (M=18.8±6.2 years, n=18, *p*<.001; $\square^2_p$=.511). Similarly, individuals with JS with FSIQ/V ≥70 were younger (M=5.9±4.4 years, n=22) than those with FSIQ/V <70 (M=12.5±8.5 years, n=40, *p*=.001; $\square^2_p$=.167). There were no differences in age between individuals who produced a GAI or GAI/V score ≥70 and those who produced scores <70. Individuals with JS who produced a GAI ≥70 were similar in age (14.7±8.5 years, n=16) to those who produced a GAI <70 (17.1±5.3 years, n=15, *p*=.362; $\square^2_p$=.030). Individuals with JS who produced GAI/V ≥70 were similar in age (9.9±9.0 years, n=26) to those who produced a GAI/V ≤70 (M=11.5±7.7 years, n=38, *p*=.469; $\square^2_p$=.010).

Receptive and Expressive Language

The average Vineland-II v-scaled scores have a population mean of 15±3. The receptive language v-scaled score was 9.9±4.4 (−1.7 SD below the normative sample). The average expressive language v-scaled score was 7.3±4.0 (−2.6 SD below the normative sample). Receptive language v-scaled scores were significantly higher than expressive language v-scaled scores (n=35; *p* < .001; Cohen's *d*=.62; Figure 5).

The mean score on the PPVT-4 was 62.6±22.8 (n=30), which is in the low range (the population average score is 100±15). Eight participants had a PPVT-4 score and Vineland-II language scores. The correlation between the PPVT-4 and receptive ($r(6)=.564$, $p=.15$, $r^2=.32$) or expressive language v-scaled scores ($r(6)=.574$, $p=.14$, $r^2=.33$) did not reach statistical significance. The PPVT-4 was significantly correlated with FSIQ ($r(16)=.737$, $p<.001$, $r^2=.54$), FSIQ/V ($r(24)=.783$, $p<.001$, $r^2=.61$), GAI ($r(17)=.669$, $p=.002$, $r^2=.45$), and GAI/V ($r(24)=.733$, $p<.001$, $r^2=.54$).

Correlations between Neuropsychological Function and Other Clinical Features

FSIQ/V scores from participants with a normal EEG (n=39) were compared to scores of those participants with abnormal EEG (i.e., diffuse background slowing; n=15). Participants with a normal EEG had significantly higher FSIQ/V (M=64.7±16.3) compared to those with abnormal EEG (M=50.7±12.9; $p=.004$; $\square^2_p=.146$). Concordantly, GAI/V score was significantly higher in participants with a normal EEG (n=40, M=66.7±16.7) compared to those with an abnormal EEG (n=16; M=53.8±16.1; $p=.01$; $\square^2_p=.113$).

Similarly, the average FSIQ/V score of participants who were taking no psychiatric medications (n=42; M=65.0±17.2) was significantly higher than that of those who were taking one or more (n=20; M=54.8±13.2; $p=.02$; $\square^2_p=.084$). The average GAI/V did not reach statistical significance, but was higher in participants who were not taking psychiatric medications (n=42; M=66.1±18.0) than in those who were taking at least one (n=22; M=58.4±15.0; $p=.09$; $\square^2_p=.046$).

Average FSIQ/V and GAI/V scores were also compared between groups of participants with and without certain clinical findings. Specifically, we examined brain MRI severity score, history of seizures, visual-motor difficulties, decreased kidney function, and portal hypertension. No significant differences between scores of individuals with JS with and without a history of seizures, visual-motor difficulties, decreased kidney function, or portal hypertension were detected. The average FSIQ/V and GAI/V scores were similar among individuals with JS with brain MRI severity scores of 0 (only MTS), 1 (MTS and other brainstem abnormalities) or 2 (MTS and other infratentorial and supratentorial abnormalities). Similarly, chi-squared analyses between individuals with FSIQ/V or GAI/V ≥70 and FSIQ/V or GAI/V <70 did not reveal differences in MRI severity, history of seizures, nor different rates of visual-motor difficulties, decreased kidney function, or portal hypertension.

Neuropsychological Phenotype by Pathogenic Variants in JS Genes

Among the 73 participants whose molecular genetic mutation was identified, *TMEM67*-related JS (n=19) was the most common. Of note, the neuropsychological features of *TMEM67* participants mirrored the cohort overall (Table III). Specifically, abnormal EEG and the use of psychiatric medications were each associated with lower FSIQ/V and GAI/V scores; no other covariates showed any correlation with cognitive functioning. Furthermore, differences between the FSIQ, GAI, VABC, FSIQ/V, or GAI/V scores of participants with and without *TMEM67* pathogenic variants were not detected. The number of participants

with pathogenic variants in other genes was not large enough to run meaningful analyses on those sub-cohorts.

Analysis of the data by comparing patients in three groups based on the severity of their mutations (i.e., 2 missense, 1 missense and 1 null/splice, or 2 null/splice) did not reveal any statistically significant differences in FSIQ, FSIQ/V, GAI nor GAI/V.

When patients were classified into subtypes of JS as proposed by Brancati et al. [2010], there were no statistically significant differences in FSIQ, FSIQ/V, GAI, nor GAI/V scores among the subtype groups.

Neuropsychological Functioning in Siblings

Our cohort included eight families with two siblings and one family with three siblings affected by JS (Table I, participants 271–272, 301–302, 481–482, 500–501, 518–519, 557 and 559, 560–562, 576–577, and 7503–7504). One sibling from one of the sibling pairs had neither a FSIQ, nor GAI, nor VABC score. For the remaining seven families, all of the sibling pairs had either a FSIQ/V and/or GAI/V score within 15 points (1 SD) of one another. One pair had FSIQ/V scores >15 points different (GAI/V scores were <15 different), but both were able to produce FSIQ and GAI scores; furthermore, one sibling had FSIQ and GAI scores that were in the average range. Another sibling pair had GAI/V scores that were >15 points different, but one of the siblings had only a VABC score. The three siblings (560–562) had FSIQ scores of 69, 51, and 56, respectively, and GAI scores of 71, 55, and 64, respectively.

Behavioral Profile of JS

The psychiatric subscales of 45 participants derived from the CBCL are depicted in Figure 6 and Table IV. In the general population, these subscales have a mean of 50±10; scores ≥69 are clinically concerning. One-sample *t* tests revealed that, on average, all of the subscales in our participants were significantly elevated compared to the general population. The summary scales (internalizing problems, externalizing problems, and total problems) have a population mean of 50±10; scores of ≥60 are clinically concerning. Average internalizing problems (struggles within the self, e.g., depression and withdrawal from social contact) and total problems scores were elevated compared to the general population, while no difference in externalizing problems (conflicts with others, e.g., aggression and tantrums) score was detected from the general population (Table IV). There were no statistically significant differences on any of the CBCL scales between those individuals with JS who had FSIQ/V scores ≥70 and those who had FSIQ/V scores <70.

Post-hoc analyses revealed that, in older children (6–18 years), all of the psychiatric subscales and summary scores were significantly elevated compared to the general population. In younger children (1.5–5 years), all of the psychiatric subscales were elevated, compared to the general population, except for oppositional defiant behavior (e.g., persistent irritability towards or defiance of authority). However, none of the summary scales were elevated compared to the general population.

DISCUSSION

The large sample size of this study, coupled with molecular genetic diagnosis and comprehensive clinical evaluations performed prospectively at a single center, allowed us to define the spectrum of neuropsychological function in JS in the context of extra-neurological features and specific genotype. Our results indicated that neuropsychological function in JS varies from extremely low to low-average/average, with the majority (65%) of participants in the intellectually disabled range. These findings are in line with early literature describing neuropsychological functioning in JS, based on a small number of individuals [Gitten et al., 1998; Maria et al., 1999; Poretti et al., 2010; Steinlin et al., 1997; Tavano and Borgatti, 2010; Torres et al., 2001; Valente et al., 2005]. Similarly, the 2016 multi-center Italian study by Bulgheroni et al. reported that the majority of individuals with JS had intellectual disability, although they identified three individuals with JS with above-average intelligence [2016]. In our cohort, the 5 highest FSIQ scores were 95, 88, 85, 85, and 82. We applied the same standard intelligence test (Wechsler IQ scales) to all individuals with JS, while Bulgheroni et al. selected different tests (Leiter-R or Wechsler IQ scales) on a non-random basis, i.e., they chose the test based on the individual's age and clinical presentation. Their approach, although it has advantages clinically, introduces measurement error and, potentially, selection bias. In fact, 5 out of 7 of their participants who performed in the average to above-average range were tested using the Leiter-R. The authors specifically chose the Leiter-R for certain participants 2-21 years of age "with significant attention and communication difficulties." It is possible, therefore, that the use of the Leiter-R in such individuals may have inflated their IQ scores by neglecting to consider the role of verbal expressive and receptive skills in their assessments of intellectual functioning. Future studies could have a sample that employs both Wechsler and Leiter-R more systematically to gauge the extent to which selection bias influences outcome or to determine if the Italian cohort might have included milder cases.

Our data revealed specific strengths and weaknesses of individuals with JS, both in the overall sample and the subset of individuals with cognitive functioning in the borderline to average range. VCI, which measures verbal comprehension and reasoning abilities and is less affected by inattention or gross motor dysfunction, was a relative strength, while PSI, which measures speed of information processing, visual scanning, and visual discrimination, was the lowest index score. PSI is the most sensitive measure of brain dysfunction on the Wechsler measures [Hawkins, 1998]. Various forms of intellectual disability, including those associated with cerebellar malformations, are frequently associated with very low PSI [Steinlin, 2007]. However, PSI relies on motor function, ocular motor function, and vision more heavily than other cognitive measures, especially VCI. In disorders associated with motor and visual impairments, such as JS, PSI may be disproportionately affected by these physical and sensory deficits as compared to a pure cognitive disability. Given that almost all JS participants had relatively slow gross motor function and 79% had ocular motor apraxia, cognitive PSI scores in JS may be artificially depressed. Nevertheless, tests that strongly incorporate gross, fine, and/or visual motor functioning should not be entirely discounted in populations where these deficits are common because they play a major role in daily

activities. Therefore, PSI might be a more precise indicator of an individual's success in certain areas of school and life than other Wechsler scores.

Similarly, GAI, a subset of FSIQ tests, minimizes the influence of motor function because it is only comprised of VCI and PRI tasks. While the GAI scores were only mildly (<5 points) higher than FSIQ scores, this difference was statistically significant. Five points on an IQ test can have a major impact on resources provided to individuals with low IQ scores [Kanaya et al., 2003]. Thus, our findings suggest that both GAI and FSIQ should be considered when evaluating individuals with JS who suffer from motor and visual deficits. Whereas GAI may be a better indicator of an individual's pure cognitive abilities (especially for those with severe physical impairment), FSIQ may offer a more accurate measure of an individual's real-world functioning. Nevertheless, obtaining a GAI is inherently shorter than obtaining a FSIQ, which may make the GAI a more realistic assessment tool when individuals with significant intellectual disabilities are being assessed.

The fact that individuals in our cohort who produced FSIQ, FSIQ/V, and Vineland-II (but not GAI and GAI/V) scores ≥70 were younger than individuals who produced scores <70 is noteworthy. However, given the cross-sectional design of this study, it is difficult to appreciate what is driving this difference. Longitudinal studies may help elucidate if these differences are caused by a plateau in development in individuals with JS, such that as individuals with JS get older, the gap between their development and the development of their age-matched, unaffected peers widens. Or, perhaps, deficits in motor functioning (which affect PSI, and therefore, FSIQ, scores more strongly than GAI scores) drive this observed age difference in cognitive functioning.

When evaluating cognitive function in the context of MRI findings, we did not find a significant difference in cognitive abilities of individuals with only vermis hypo-dysplasia and MTS (score 0), when compared to those with infratentorial (score 1) or supratentorial anomalies (score 2). However, an inverse relationship between cognitive function and the degree of cerebellar vermis hypoplasia was identified when a more detailed brain MRI scoring system was used in a larger neuroimaging study that included a subset of the participants reported here [Poretti et al., 2017]. Furthermore, participants with abnormal EEG results had a significantly lower FSIQ compared to those with normal EEG. Supratentorial brain abnormalities, such as malformations of cortical development, are well-known causes of EEG abnormalities and clinical seizures. The percentage of abnormal neuroimaging findings within the supratentorial brain between participants with (21%) and without (15%) abnormal EEG findings is quite similar. Together, these data suggest that in JS, the presence of supratentorial morphological brain abnormalities do not correlate with diffuse slowing of the EEG background activity or predict lower IQ.

Contrary to the literature describing lower cognitive function in individuals with renal [Ruebner et al., 2016] and liver disease [Stewart et al., 1992], neuropsychological performance was not correlated with presence of kidney dysfunction or portal hypertension in our sample. This lack of correlation may be due to the fact that genes and/or brain abnormalities play a dominant role in cognitive function in individuals with JS, potentially obscuring the relatively minor contribution from kidney and/or liver disease. Alternatively,

as renal and hepatic disease are relatively later manifestations in JS, they may not have had a significant impact on cognitive function in the cohort. Furthermore, we detected no relationship between eye function (ocular motor apraxia), visual acuity, or seizures and cognition. Notably, testing on certain tasks was precluded if the individual's best corrected visual acuity was so impaired that reasonable accommodations could not be made, such as using enlarged stimuli.

Our attempts to analyze the data for correlations within specific JS genes were hampered by the extreme genetic heterogeneity of JS, resulting in small numbers of participants with cognitive data in most gene sub-cohorts. Nevertheless, the neuropsychological functioning in our largest gene-specific group, those with *TMEM67* mutations, resembled the neuropsychological functioning in the remaining participants with other pathogenic variants. Some JS genes are known to cause specific subtypes of JS associated with certain extra-neurological features; retinal degeneration is more likely in *CEP290*-related JS and liver disease is more common in *TMEM67*-related JS [Parisi and Glass, 1993–2016]. However, in parallel to their common effects on brain development that result in structural brain anomalies, all proteins encoded by JS genes appear to influence cognition similarly. Worldwide collaborative studies with larger numbers of individuals with JS with the same causative gene or genetic mutations could illuminate the roles of individual JS genes in cognition. Unfortunately, the rarity of some JS genes may make such studies extremely challenging.

In an effort to elucidate how much of the neuropsychological impairment is determined by the JS genes versus other genes contributing to intelligence, we compared the neuropsychological functioning of affected JS siblings to determine the degree of intrafamilial variability. Most JS siblings in our cohort performed within one standard deviation of each other on the FSIQ, GAI, FSIQ/V and/or GAI/V measures, suggesting that the JS gene and/or environmental factors was a major determinant of neuropsychological function and the contribution of other genes was smaller. The concordance of scores among siblings is not surprising, given the large body of research showing a high correlation of intelligence between siblings without any neurological disorder [Bouchard et al., 1990; Gottfredson, 1998; Neisser et al., 1996]. Nevertheless, JS siblings with discordant intellectual abilities are reported [Poretti et al., 2010], raising the possibility that a rare modifier gene(s) could positively or negatively impact cognition. Given the well-established rates of heritability of IQ in the general population [Bouchard et al., 1990; Gottfredson, 1998; Neisser et al., 1996], future research assessing the IQ of unaffected family members of individuals with JS may further clarify the specific genetic relationship to IQ in JS.

Parents rated receptive language, the ability to demonstrate comprehension of what others say (usually through actions, e.g., following two-part instructions), as less affected than expressive language, the ability to verbally convey meaningful information to others. The Vineland-II scores, consistent with anecdotal observations regarding language abilities in JS [Holroyd et al., 1991; Maria et al., 1999; Steinlin et al., 1997; Tavano and Borgatti, 2010; Torres et al., 2001; Ziegler et al., 1990], suggest that receptive language is a relative strength of individuals with JS. Furthermore, there were moderate correlations between PPVT-4 (receptive vocabulary) and Vineland-II receptive and expressive language scores. While this

relationship did not reach significance, these analyses were limited in power due to the small sample size who had both tests (n=8). These findings may provide some reassurance to parents in knowing that their children may comprehend what others say to them, even if they are not able to reciprocate that communication. Weakness in expressive language skills, common among those with speech apraxia, may potentially result in underestimation of the overall cognitive skills in JS. Bringing this finding to the attention of doctors, teachers, and caregivers of those with JS might result in setting appropriate educational goals as well as improving educational accommodations such as targeted speech therapy.

Our data corroborate the Italian study finding that high rates of behavioral/psychiatric concerns, especially internalizing problems, are observed in individuals with JS, but these rates are relatively low compared to those observed in other developmentally delayed populations. Our participants exhibited more internalizing, rather than externalizing behaviors compared to the general population, which is consistent with findings in children with Down Syndrome [van Gameren-Oosterom et al., 2013]. However, individuals with Autism Spectrum Disorder typically exhibit elevated scores on internalizing, externalizing, and total problems that are higher than those observed in this study [Havdahl et al., 2015]. Parents of participants in our cohort completed a measure of behavioral/psychiatric problems and the data revealed that our participants were more affected by behavioral/psychiatric issues than the general population on 11 of 12 scales. On average, they tended to be more anxious, withdrawn, depressed, inattentive, aggressive, and oppositional than their age-matched peers. Comparisons between individuals who had an FSIQ/V ≥70 and FSIQ/V <70 revealed no statistically significant differences in CBCL scores. Therefore, it appears that behavioral/psychiatric concerns are common in individuals with JS, regardless of their level of cognitive functioning.

Because behavioral expression of these moods/characteristics differs throughout development, the CBCL has two forms based on age. We decided to run subsequent analyses on the behavioral data based on the form that was completed. These analyses revealed that older children with JS (ages 6–18) were elevated on all scales, compared to the general population, while younger children (ages 1.5–5) were not elevated on the oppositional defiant scale nor the summary scales. This suggests that as children with JS get older, they may experience more behavioral/psychiatric issues than they did earlier in life.

Within our cohort, 29% was taking at least one psychiatric medication. While this number is much higher than the national average for both typically developing children (~7%) and adults (~11%) [2011; Jonas et al., 2013a; Zito, 2012], it is much lower than the prevalence of psychiatric medication use in intellectual and developmental disorders (81%) [Deb et al., 2009; Howie et al., 2014; Jonas et al., 2013b; Russell et al., 2011; Zito, 2012]. This relatively low rate of psychiatric medications in individuals with JS may be encouraging to caregivers, indicating that psychiatric and behavioral concerns in JS are much lower than in many other disabilities. The finding that participants taking psychiatric medications had lower scores on neuropsychological testing can be explained in two ways: psychiatric medications may impair cognitive function, or those with impaired cognitive function may have more behavioral/psychiatric issues that require treatment with medications. The current data are insufficient to further understand these findings.

The cognitive difficulties described in this paper parallel those of the Cerebellar Cognitive Affective Syndrome in adults with acquired cerebellar injury [Schmahmann and Sherman, 1998]. Recently, studies have shown that children with pre- and postnatal acquired, as well as hereditary cerebellar diseases, have similar neuropsychological and behavioral phenotypes. Specifically, deficits in attention, verbal memory, executive functioning, visual-spatial functioning, expressive language, internalizing and externalizing problems, and socialization have been demonstrated in these populations [Bolduc et al., 2011; Brossard-Racine et al., 2015; Hanzlik et al., 2015; Lassaletta et al., 2015]. The cognitive and behavioral deficits described in those with JS may thus, in part, reflect the underlying cerebellar dysfunction related to involvement of the hindbrain malformation in the disorder, but other structures may also be involved.

Limitations of this study include the relatively small number of participants within each sub-cohort, such as those with a particular clinical feature or the same causative gene. While we analyzed the relationship between FSIQ/V and GAI/V and numerous clinical correlates, we did not find many statistically significant differences between groups on these measures. Even though the sample size of this study was relatively large compared to other studies assessing neuropsychological function in JS, due to limited numbers in sub-cohorts, the power of our analyses may not have been high enough to detect group differences. The fact that we could only obtain a FSIQ score for approximately 43% of the participants highlights the difficulty of conducting neuropsychological evaluations in individuals with JS. The speech delays and physical and cognitive impairments common in JS frequently hinder the ability to collect sufficient data to obtain an estimated FSIQ. Other studies have found similarly high rates of incomplete neuropsychological assessment [Maria et al., 1999; Poretti et al., 2010; Tavano and Borgatti, 2010]. Whereas Bulgheroni et al [2016] had a higher completion rate of formal testing, they used multiple assessment measures, while we consistently used only Wechsler IQ scales.

CONCLUSION

This paper represents the largest cohort of individuals with JS who have undergone neuropsychological evaluation prospectively in a single center. Our findings demonstrate that processing speed is the weakest cognitive domain in JS, while verbal comprehension appears less affected. We identified an association between lower cognitive function and diffuse slowing of the background activity in EEG, and an association between lower IQ and likelihood of taking psychiatric medications. This study substantiates parental beliefs that individuals with JS are better at understanding language than verbal expression. The *TMEM67* sub-cohort mirrored the neuropsychological profile of the other participants. While our data, in general, reflect the level of functioning in everyday life of individuals with JS, the extent to which physical limitations contribute to overall impairment remains unclear. It is apparent that most individuals with JS will likely require special education and need the assistance of speech, occupational, and/or physical therapists, among other paraprofessionals, and many may benefit from augmentative and assistive communication devices. Our findings on specific weaknesses and strengths in JS will likely enable parents, caregivers, and educators to provide targeted therapy, support, and appropriate accommodations, and help set appropriate educational goals for individuals with JS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ANOVA	analysis of variance
EEG	electroencephalogram
FSIQ	Full Scale Intelligence Quotient
GAI	General Ability Index
JS	Joubert Syndrome
CBCL	Child Behavior Checklist
MRI	Magnetic Resonance Imaging
MTS	Molar Tooth Sign
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
PRI	Perceptual Reasoning Index
PSI	Processing Speed Index
VABC	Vineland Adaptive Behavior Composite
VCI	Verbal Comprehension Index
Vineland-II	Vineland Adaptive Behavior Scales-Second Edition
WMI	Working Memory Index

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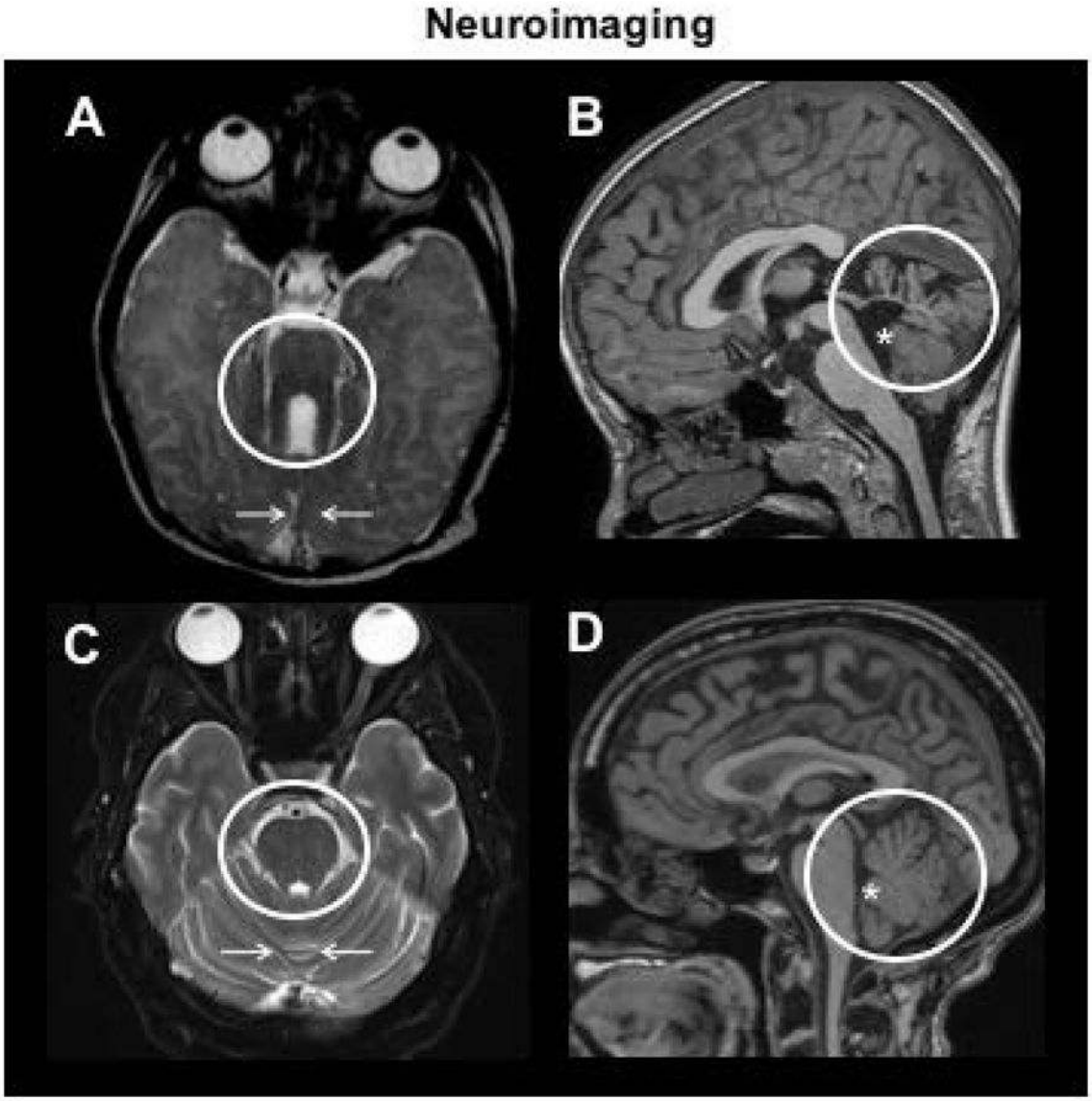

Figure 1.

A. Axial brain MRI obtained at the pontomesencephalic junction showing the "MTS" (circle) and hypoplastic cerebellar vermis (arrows) compared to normal, C. B. Sagittal brain MRI demonstrating hypoplasia and dysplasia of the cerebellar vermis (circle) and enlarged fourth ventricle (asterisk) with rostral displacement of the fastigium compared to normal, D.

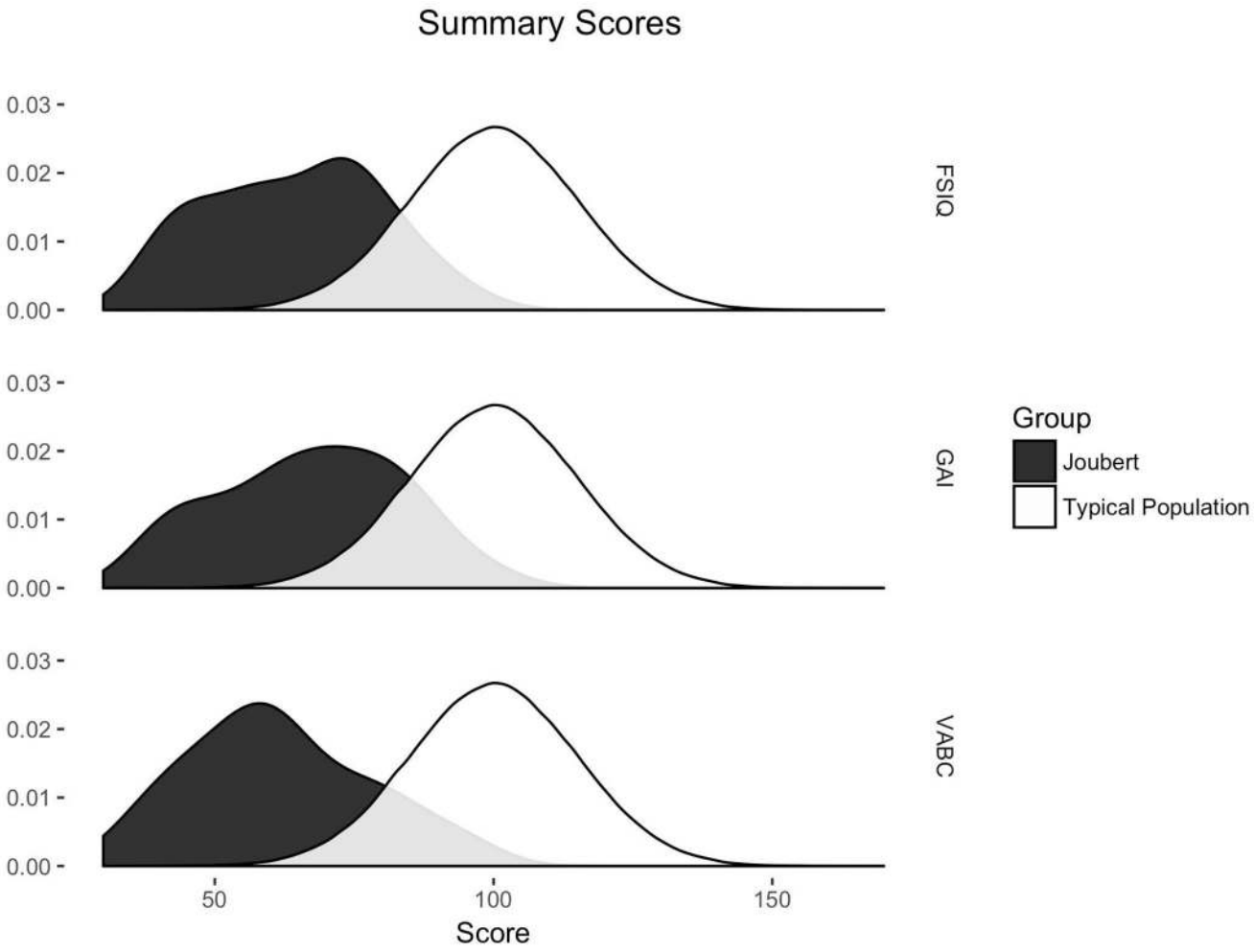

Figure 2.

Density plots depict the bell curve for a typically developing population compared to the distribution of (A) FSIQ (n=32, M=64.3±15.3), (B) GAI (n=31, M=67.2±16.3), and (C) VABC (n=35, M=60.3±17.3) in this JS cohort.

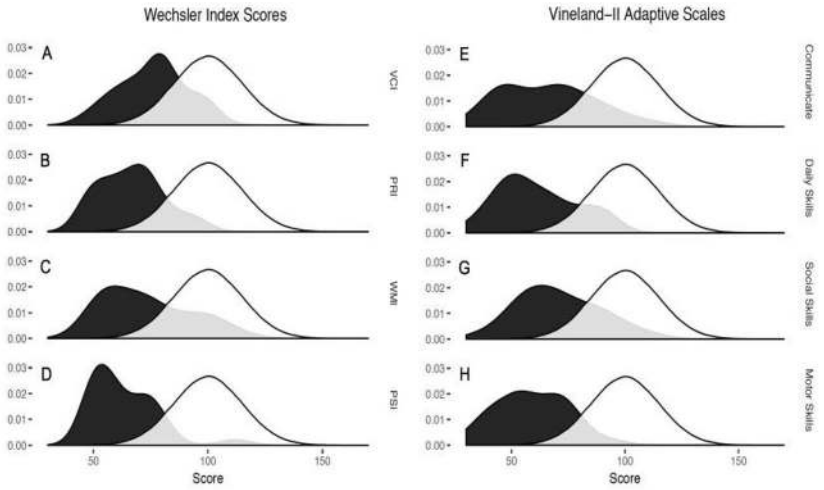

Figure 3.

Density plots depict the bell curve for a typically developing population compared to the distribution of this JS cohort for: Wechsler index scores (A) VCI/verbal comprehension (n=40, M=76.1±14.6), (B) PRI/perceptual reasoning (n=40, M=66.6±13.8), (C) WMI/working memory (n=27, M=73.1±18.7), (D) PSI/processing speed (n=29, M=63.1±14.2) and Vineland-II subscales (E) communication skills (n=36, M=64.4±21.1), (F) social skills (n=35, M=69.4±19.5, (G) daily living skills (n=35, M=60.2±18.1), and (H) motor function (n=35, M=55.1±18.4).

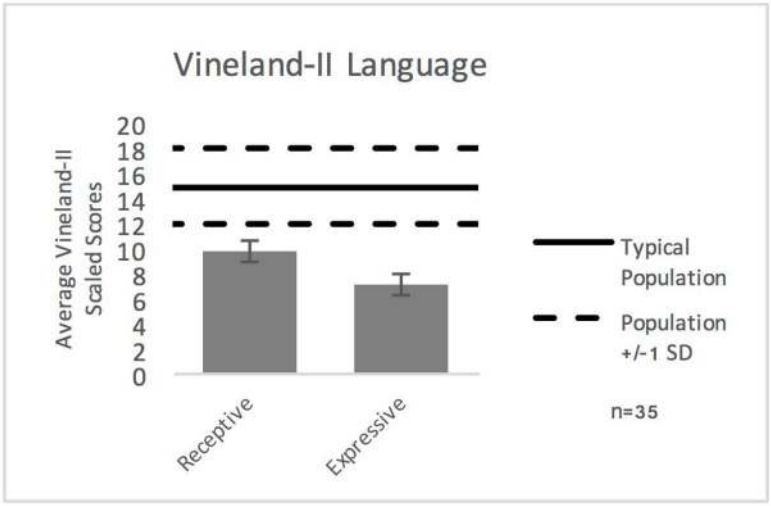

Figure 4.

As measured on the Vineland-II, expressive language is lower than receptive language in individuals with JS, $p<.001$, n=35. However, both are low compared to the general population (M=15±3). Error bars represent ±1 SE.

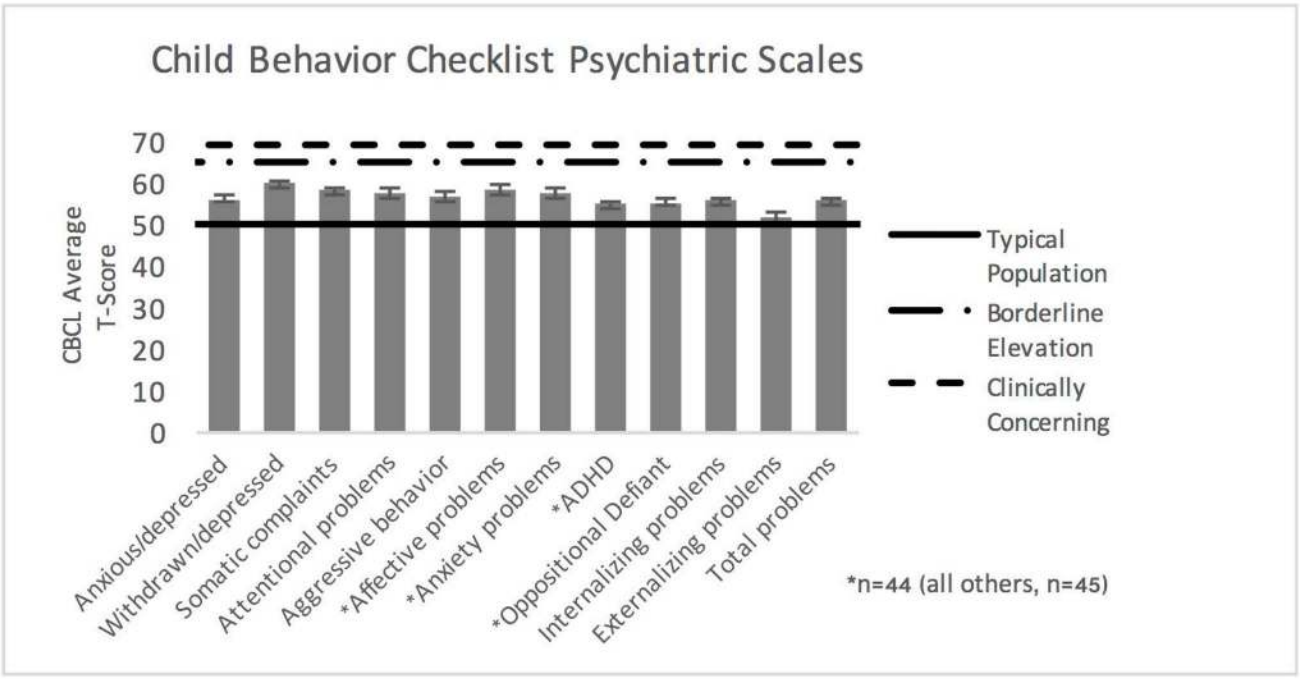

Figure 5.

Rates of behavioral/psychiatric issues are significantly higher in JS than the typical population (M=50, solid line), p<.003 for all scales except externalizing behavior. An individual score of 65–69 is considered borderline (dash-dot line) and a score ≥70 is considered clinically concerning (dashed line). Error bars represent }1 SE.

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TABLE I

Neurocognitive Test Results and Molecular Genetic and Clinical Characteristics of 76 Patients with Joubert Syndrome, organized by causative gene.

NIH Ciliopathy Number	Age at evaluation (sex)	Tests Administered	FSIQ	GAI	Vineland-II	Gene	Age first walked	Age first spoke	Kidney Function (GFR)	Portal Hypertension	Ocular Motor Apraxia	Best Corrected Visual Acuity	Brain MRI severity¶	Abnormal EEG	Seizures	Number of Psychiatric Medications
097	5.3 (M)	WPPSI-III; CBCL	72	NA	NA	TMEM67	6.0	4.0	↓ (28)	No	Yes	20/25	0	No	No	0
216	4.9 (F)	PTI; CBCL	NA	NA	NA	TMEM67	No	No	↓(69)	Yes	NA	FF	1	Yes	Yes	0
238	8.2 (M)	WISC-IV; CBCL	NA	53	NA	TMEM67	3.0	3.5	↓ (38)	Yes	NA	20/40	0	NA	No	0
271[a]	6.7 (F)	WISC-IV	95	99	NA	TMEM67	3.0	0.9	↓ (27)	No	NA	20/25	INA	NA	No	0
272[a]	9.3 (M)	WISC-IV; CBCL*	76	87	NA	TMEM67	2.2	1.2	WNL¥	Yes	NA	20/20	1	No	No	0
301[b]	9.5 (M)	WISC-IV	75	79	NA	TMEM67	2.7	1.1	WNL	No	Yes	20/40	INA	No	No	1
302[b]	5.1 (M)	WPPSI-III	73	NA	NA	TMEM67	3.2	3.5	WNL	Yes	Yes	20/50	INA	No	No	0
303	14.7 (F)	WISC-IV	54	63	NA	TMEM67	5.0	2.0	WNL¥	No	NA	20/25	1	NA	No	0
309	17.4 (M)	WAIS-III	61	71	NA	TMEM67	2.0	1.3	WNL	Yes	Yes	20/25	1	No	No	0
432	36.2 (F)	WAIS-III	60	71	NA	TMEM67	4.0	2.0	↓ (70)	No	Yes	20/63	1	No	Yes	6
459	7.8 (F)	WNV; CBCL	NA	NA	NA	TMEM67	6.0	4.0	WNL	No	Yes	20/70	0	No	No	0
542	11.9 (F)	WISC-IV; CBCL	75	84	NA	TMEM67	4.0	3.0	WNL	Yes	No	20/50	1	No	No	0
545	2.2 (F)	Vineland-II; CBCL	NA	NA	94	TMEM67	No	1.8	WNL	No	No	CSM	1	No	No	0
548	4.5 (M)	Vineland-II; CBCL	NA	NA	37	TMEM67	No	No	WNL	No	NA	BTL	1	Yes	Yes	6
557[c]	6.8 (M)	Vineland-II	NA	NA	39	TMEM67	No	No	WNL	No	Yes	CSM	INA	Yes	No	2
559[c]	16.7 (M)	WISC-IV; CBCL	42	42	NA	TMEM67	8.0	2.5	↓(59)	Yes#	No	20/40	INA	No	No	1
560[d]	29.6 (M)	WAIS-IV	69	71	NA	TMEM67	5.5	1.3	WNL	No	Yes	20/50	INA	No	No	3
561[d]	24.9 (M)	WAIS-IV	51	55	NA	TMEM67	5.0	3.5	WNL	No	Yes	20/30	INA	No	No	1
562[d]	22.9 (M)	WAIS-IV	56	64	NA	TMEM67	7.5	5.5	WNL	Yes	Yes	20/20	INA	No	No	2
458	2.2 (F)	Vineland-II; CBCL	NA	NA	82	C5orf42	No	No	WNL	No	Yes	FF	1	No	No	0
471	8.0 (M)	WAIS-IV; CBCL	74	71	NA	C5orf42	4.0	3.5	WNL	No	NA	20/40	2	No	No	0
481[e]	27.6 (M)	WAIS-IV; Vineland-II	NA	60	NA	C5orf42	No	No	WNL	No	Yes	20/60	1	No	Yes	1
482[e]	24.5 (F)	Vineland-II	NA	NA	20	C5orf42	No	No	WNL	No	Yes	20/40	1	No	No	0
491	19 (M)	WAIS-IV; CBCL	73	77	NA	C5orf42	3.0	4.0	WNL	No	Yes	20/80	INA	No	No	2

NIH Ciliopathy Number	Age at evaluation (sex)	Tests Administered	FSIQ	GAI	Vineland-II	Gene	Age first walked	Age first spoke	Kidney Function (GFR)	Portal Hypertension	Ocular Motor Apraxia	Best Corrected Visual Acuity	Brain MRI severity¶	Abnormal EEG	Seizures	Number of Psychiatric Medications
500[f]	11.8 (F)	WISC-IV; CBCL	NA	NA	NA	C5orf42	No	4.0	WNL	No	No	20/50	INA	No	No	0
501[f]	10.0 (M)	WISC-IV; CBCL	85	85	NA	C5orf42	6.0	3.0	WNL	No	No	20/25	INA	No	No	0
523	2.3 (F)	Vineland-II; CBCL	NA	NA	55	C5orf42	No	No	WNL	No	Yes	CSM	2	No	No	0
528	18.8 (M)	WAIS-IV; CBCL	64	72	NA	C5orf42	9.0	4.0	WNL	No	Yes	20/32	1	No	No	0
534	8.4 (F)	WISC-IV; CBCL	NA	NA	NA	C5orf42	3.5	1.3	WNL	No	Yes	20/30	1	No	No	2
568	14.1 (F)	WISC-IV	43	44	NA	C5orf42	2.3	3.0	WNL	No	No	20/32	0	NA	No	3
364	16.3 (F)	WISC-IV; Vineland-II; CBCL	44	45	65	CC2D2A	10.0	2.0	WNL	No	Yes	20/25	2	Yes	Yes	3
446	3.2 (M)	Vineland-II; CBCL	NA	NA	58	CC2D2A	2.3	2.0	WNL	No	Yes	20/80	2	No	No	0
483	2.3 (F)	Vineland-II; CBCL	NA	NA	95	CC2D2A	No	1.0	WNL	No	No	20/50	2	No	No	0
495	3.5 (M)	WPPSI-III; CBCL	76	NA	NA	CC2D2A	No	1.5	WNL	No	Yes	20/50	1	NA	No	0
565	15.4 (F)	WISC-IV; CBCL	60	64	NA	CC2D2A	5.0	2.0	WNL	No	Yes	20/25	2	No	No	0
575	2.3 (F)	Vineland-II; CBCL	NA	NA	83	CC2D2A	2.3	1.0	WNL	No	Yes	20/300	0	Yes	No	0
576[g]	15.7 (F)	WISC-IV; CBCL	48	47	NA	CC2D2A	2.8	2.5	WNL	No	Yes	20/20	0	No	No	1
577[g]	13.1 (F)	WISC-IV; CBCL	44	40	NA	CC2D2A	3.6	1.5	WNL	No	Yes	20/30	1	Yes	No	0
228	20.9 (F)	WAIS-III	65	76	NA	AHI1	4.0	2.0	WNL	No	NA	20/80	0	Yes	Yes	1
472	5.0 (M)	WPPSI-III; CBCL	NA	NA	NA	AHI1	No	3.0	WNL	No	NA	20/40	0	No	No	0
513	1.9 (M)	Vineland-II; CBCL	NA	NA	61	AHI1	No	No	WNL	No	Yes	FF	1	NA	No	0
517	3.3 (M)	WPPSI-III; Vineland-II; CBCL	73	NA	70	AHI1	No	2.0	WNL	No	Yes	20/300	1	NA	No	0
540	17.9 (F)	WAIS-IV; CBCL	57	60	NA	AHI1	8.0	3.5	WNL	No	No	20/100	INA	No	No	1
574	5.1 (M)	CBCL	NA	NA	NA	AHI1	5.2	2.0	WNL	No	Yes	20/100	0	No	No	0
213	13.2 (F)	WISC-IV; CBCL	NA	NA	NA	CEP290	3.0	3.0	WNL[¥]	No	NA	20/640	2	Yes	No	0
373	4.4 (M)	Vineland-II	NA	NA	61	CEP290	No	3.0	↓(55)	No	NA	20/400	1	Yes	No	0
441	23.5 (F)	WAIS-IV	NA	56	NA	CEP290	5.5	3.0	↓(21)	No	NA	20/250	1	No	No	4
455	6.9 (M)	Vineland-II	NA	NA	41	CEP290	No	No	WNL	No	NA	BTL	2	Yes	No	0
480	0.9 (M)	Vineland-II	NA	NA	74	CEP290	EFA	EFA	WNL	No	Yes	FF	0	No	No	0
552	4.3 (M)	WPPSI-III	NA	NA	NA	CEP290	2.5	1.0	WNL	No	NA	20/100	1	Yes	No	0
368	4.0 (M)	WPPSI-III; Vineland-II	88	NA	87	KIAA0586	2.2	1.0	WNL	No	No	20/30	0	No	No	0

NIH Ciliopathy Number	Age at evaluation (sex)	Tests Administered	FSIQ	GAI	Vineland-II	Gene	Age first walked	Age first spoke	Kidney Function (GFR)	Portal Hypertension	Ocular Motor Apraxia	Best Corrected Visual Acuity	Brain MRI severity¶	Abnormal EEG	Seizures	Number of Psychiatric Medications
443	2.2 (F)	Vineland-II	NA	NA	78	KIAA0586	No	1.2	WNL	No	Yes	CSM	1	No	No	0
494	4.4 (M)	CBCL	NA	NA	NA	KIAA0586	2.0	1.2	WNL	No	Yes	20/40	1	No	No	0
507	4.7 (M)	Vineland-II; CBCL	NA	NA	58	KIAA0586	No	No	WNL	No	NA	20/30	2	NA	No	0
531	13.6 (M)	WISC-IV; CBCL	56	83	NA	KIAA0586	2.2	2.0	WNL	No	No	20/20	0	Yes	Yes	2
579	4.4 (M)	WPPSI-III; Vineland-II; CBCL	NA	NA	64	KIAA0586	No	No	WNL	No	Yes	20/20	0	No	No	0
502	1.5 (M)	Vineland-II; CBCL	NA	NA	76	MKS1	No	No	WNL	No	Yes	20/100	0	No	No	0
510	8.0 (M)	WISC-IV; CBCL	85	82	NA	MKS1	4.0	5.5	WNL	No	Yes	20/25	0	No	No	1
537	2.0 (M)	Vineland-II	NA	NA	63	MKS1	No	No	WNL	No	Yes	CSM	1	No	No	0
573	14.0 (M)	WISC-IV; CBCL	NA	65	NA	MKS1	8.5	3.0	WNL	No	Yes	20/125	1	Yes	No	0
7503[h]	21.0 (F)	WAIS-IV; Vineland-II	NA	NA	54	INPP5E	3.5	4.0	WNL	No	Yes	20/40	0	No	No	0
7504[h]	19.0 (F)	WASI-II; Vineland-II	41	NA	51	INPP5E	4.0	5.0	WNL	No	Yes	20/63	0	No	No	0
396	9.0 (F)	Vineland-II	NA	NA	59	TMEM216	No	No	↓(52)	Yes	Yes	no FF	1	Yes	No	1
408	12.0 (M)	WISC-IV; Vineland-II	41	40	68	TMEM216	4.3	3.0	WNL	No	Yes	20/30	0	No	No	0
518[j]	4.8 (F)	Vineland-II	NA	NA	50	TMEM231	No	4.5	WNL	No	NA	br FF	0	Yes	No	0
519[j]	4.8 (F)	Vineland-II	NA	NA	45	TMEM231	No	4.5	WNL	No	NA	no FF	1	Yes	No	0
466	2.3 (F)	Vineland-II; CBCL	NA	NA	46	CSPP1	No	No	WNL	No	NA	BTL	2	Yes	No	2
452	12.3 (M)	Vineland-II; CBCL	NA	NA	34	OFD1	No	No	WNL	No	NA	no BTL	0	Yes	No	0
360	21.4 (M)	Vineland-II	NA	NA	44	RPGRIP1L	No	No	↓ (33)	No	Yes	20/40	1	No	No	5
474	4.5 (F)	Vineland-II; CBCL	NA	NA	57	TMEM237	No	4.0	↓(52)	No	Yes	FF	1	Yes	No	0
400	4.8 (M)	WPPSI-III; Vineland-II	NA	NA	61	B9D1	4.8	No	WNL	No	Yes	20/50	1	No	No	0
389	7.0 (M)	WISC-IV	NA	93	NA	KIAA0753	2.2	1.3	WNL	No	Yes	20/25	1	No	No	0
449	7.9 (F)	Vineland-II; CBCL	NA	NA	55	CELSR2	No	No	WNL	No	No	20/80	2	No	No	0
358	9.1 (M)	WISC-IV; CBCL	82	84	NA	x	4.0	1.5	↓ (34)	No	NA	CUSM	1	NA	No	0
570	4.7 (M)	Vineland-II; CBCL	NA	NA	47	x	No	No	WNL	No	Yes	CUSM	INA	No	No	3
578	2.3 (F)	Vineland-II; CBCL	NA	NA	78	x	2.0	1.0	WNL	No	Yes	20/100	1	No	No	0

Letters next to participant ID represent siblings. ARD: Advanced Retinal Degeneration; BTL: Blink to light; CBCL: Child Behavior Checklist (age-appropriate form was administered), CSM: Central Steady Maintained; CUSM: Central Unsteady Maintained; EFA: Excluded from analysis because participant was too young to expect achievement of developmental milestone; FF: Fix and Follow (br FF: brief Fix and Follow); FSIQ: Full Scale Intelligence Quotient; GFR: Glomerular Filtration Rate; INA: Image not available for rating by NIH team (MRI report only); MTS: Molar Tooth Sign; NA: no available data; Vineland-II: Vineland Adaptive Behavior Scales -- Second Edition; WNL: Within Normal Limits; x=unknown gene mutation;

*IQ testing and CBCL collected at a different age; + higher scores are associated with lower functioning;

≠status post kidney transplantation;

#status post liver transplantation;

‖0=only vermis hypoplasia and MTS, 1=0+0ther infratentorial anomalies, 2=1+supratentorial anomalies.

Table II

Relationship between Wechsler Index Scores in Subjects with JS

Index Score	n	Mean (SD)	VCI	WMI	PRI	PSI
VCI	40	76.1 (14.6)	-	0.73	0.76	0.62
WMI	27	73.1 (18.7)	-	-	0.60	0.61
PRI	40	66.6 (13.8)	-	-	-	0.71
PSI	29	63.1 (14.2)	-	-	-	-

VCI was significantly higher than PRI and PSI (p<.001), while PSI was significantly lower than VCI (p<.001), WMI (p=.023), and PRI (p=.025).

VCI: Verbal Comprehension Index; WMI: Working Memory Index; PRI: Perceptual Reasoning Index; PSI: Processing Speed Index

TABLE III

Neurocognitive Test Results in *TMEM67*-related JS in comparison to remainder of the cohort

Pathogenic Variant	n	FSIQ Mean ± SD (n)	GAI Mean ± SD (n)	FSIQ+V Mean ± SD (n)	GAI+V Mean ± SD (n)	*p*-value FSIQ +V EEG WNL > FSIQ +V abnormal EEG	*p*-value GAI +V EEG WNL > GAI +V abnormal EEG	*p*-value FSIQ+V no psych. med.> FSIQ+V ≥ 1 psych. med.	*p*-value GAI+V no psych. med.> GAI +V ≥1 psych. med.	*p*-value receptive language > expressive language
TMEM67	19	66.1 ± 13.9(13)	69.9 ± 15.9(12)	64.3 ± 17.5(16)	67.3 ± 19.5(15)	.014	.014	.009	.027	1.00
All other genes	55	63.1 ± 16.4(19)	65.5 ± 16.8(19)	60.8 ± 16.4(46)	62.3 ± 16.7 (49)	.050	.107	.200	.513	<.001

TMEM67 scores mirrored those of all other genes in the cohort.

Table IV

Psychiatric Profiles in JS on the CBCL

Behavioral Feature	Mean (SD)
subscales	
Anxious/depressed	56.0 (8.9)¥
Withdrawn/depressed	59.5 (9.3)¥
Somatic complaints	57.8 (8.8)¥
Attentional problems	57.4 (7.5)¥
Aggressive behavior	56.3 (8.8)¥
Affective problems#	58.1 (9.3)¥
Anxiety problems#	57.2 (9.1)¥
ADHD#	54.5 (5.2)¥
Oppositional Defiant#	55.1 (7.8)¥
summary scales	
Internalizing problems	55.4 (11.9)†
Externalizing problems	51.6 (10.6)
Total problems	55.31 (11.0)□

†elevated ($p = .004$)

□elevated ($p = .002$)

¥elevated ($p < .001$)

#n=44 (for all other analyses, n=45)