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# Psychotic symptoms in youth with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) may reflect syndrome severity and heterogeneity

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ABSTRACT

*Objective:* In the clinical syndrome Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), obsessive compulsive disorder (OCD) and/or food refusal symptoms have an abrupt-onset (over 48 h) coupled with at least two other specified neuropsychiatric symptoms. We aimed to characterize in detail for the first time, psychotic symptoms experienced by children with PANS as well as the impact of psychotic symptoms on disease severity and course of illness. We inform about the diagnosis of the clinical description: PANS and hope to improve evaluation, treatment, diagnostic validity and future investigation.

*Methods:* Retrospective review of 143 consecutive PANS clinic patient charts meeting inclusion criteria. The Caregiver Burden Inventory, Global Impairment Score, and Children's Global Assessment Scale were used to assess impairment.

*Results:* Visual and auditory hallucinations were each experienced by 36%, of which most (83%) were transient and complex (non-threatening voices or figures). 6.3% and 5.5% of patients experienced delusions and thought disorganization respectively. Those with psychotic symptoms showed statistically significant differences in disease impairment and caregiver burden. There were no differences in time to treatment access or length of illness.

*Conclusions:* Over 1/3 of children with PANS experienced transient hallucinations. They were more impaired than those without psychotic symptoms, but showed no differences in disease progression. This difference may point toward heterogeneity in PANS. When evaluating children with acute psychotic symptoms, clinicians should screen for abrupt-onset of a symptom cluster including OCD and/or food refusal, with neuropsychiatric symptoms (enuresis, handwriting changes, tics, hyperactivity, sleep disorder) before initiating treatment.

## 1. Introduction

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a newly recognized pediatric syndrome characterized by a multitude of behavioral and psychiatric manifestations, the most well-recognized of which are obsessive compulsive disorder (OCD) and/or food refusal. Prior descriptions of the psychiatric manifestations of PANS have been limited, possibly overlooking additional domains of psychopathological manifestation of PANS, such as psychosis. Having observed psychotic symptoms in our PANS clinic population, we conducted this study in order to provide more complete characterization of PANS phenomenology by determining the prevalence and characteristics of psychotic symptoms in PANS.

PANS is a childhood syndrome defined by a precipitous onset and prominent neurological and psychiatric symptoms. Children and adolescents with PANS suddenly develop new neurological symptoms (such as motor tics, choreiform movements, new-onset enuresis, motoric hyperactivity, graphomotor skill deteriorations, cognitive dysfunction, attentional difficulties, sensory amplification, sleep disturbances) and new psychiatric symptoms (including obsessions, compulsions, food refusal, anxieties, mood disruption, behavioral regression). The varied symptoms emerge abruptly, over 24–48 h (Chang et al., 2015; Ferrafiat et al., 2017). A cardinal symptom (obsessions, compulsions, or food refusal) and two other symptoms listed in Table 1 must be present to

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**Table 1**
Pediatric acute-onset neuropsychiatric syndrome (PANS) diagnostic criteria (Swedo et al., 2012).

| | |
|---|---|
| I. | Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake |
| II. | Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset) from at least two of the following seven categories:<br>1. Anxiety<br>2. Emotional lability and/or depression<br>3. Irritability, aggression, and/or severely oppositional behaviors<br>4. Behavioral (developmental) regression<br>5. Deterioration in school performance (related to attention-deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)<br>6. Sensory or motor abnormalities<br>7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency |
| III. | Symptoms not better explained by known neurologic or medical disorder, such as Sydenham's Chorea (SC) |

meet PANS diagnostic criteria (Table 1). The course is characterized by abrupt symptom onsets (flares) with more gradual remissions. To meet PANS criteria, other diagnoses must be ruled out and symptoms must not be better explained by another known neurologic or medical disorder such as Sydenham's Chorea. Antecedent, possibly precipitating, factors may be unknown and need not be specified.

Currently, the PANS diagnosis is made using a clinical description: PANS' consensus research diagnostic criteria (Chang et al., 2015). PANS has no specific biomarker. Due to the multiplicity of symptom combinations that could qualify a child or adolescent for the clinical diagnosis (as is the case in most psychiatric diagnosis) and due to the fact that different infections or other stressors may precede syndrome onset, PANS patients likely comprise a heterogeneous group. Clinical symptom presentations may meet diagnostic criteria for one or more other disorders if PANS is not considered. A recent study found that 5% of 136 youth with OCD in an OCD specialty clinic fit the clinical description of PANS (Jaspers-Fayer et al., 2017).

In addition to symptoms specified in the criteria, 14–37% of PANS patients describe psychotic symptoms (Murphy et al., 2012; Frankovich et al., 2015; Calaprice et al., 2017).

In general, more individuals experience psychotic symptoms than have or develop psychotic disorders. Psychotic experiences are more common in those with drug misuse, exposure to stress or traumatic events and those with family histories of mental illness and are generally transient. However, a review and meta-analysis assessing the relationship of psychotic experiences and disorders found that 7.4% of those with experiences later developed psychotic disorders, supporting the possibility of a psychosis-proneness persistence in some (Linscott and van Os, 2013). Children with psychotic symptoms, in general, may have poorer prognoses. Studies suggest that individuals who develop psychosis under age 15 demonstrate more severe psychotic symptoms and impairment later (Lin et al., 2016). Children with a combination of psychotic-like experiences, speech or motor delay or abnormality, and social, emotional or behavioral problems, too, are at increased risk for schizophrenia and schizophreniform disorders (Laurens and Cullen, 2015). Two studies suggest that children with a history of another, similar neuropsychiatric disorder to PANS, Sydenham chorea, may have a 9 times greater relative risk of developing schizophrenia (Wilcox and Nasrallah, 1988; Teixeira et al., 2006).

Psychotic symptom frequency in PANS has been presented in studies that used small clinical samples (Murphy et al., 2012; Frankovich et al., 2015) or a retrospective parent survey (Calaprice et al., 2017). In this study, we sought to describe the type, frequency, and duration of psychotic symptoms in patients with PANS and the relationship of those psychotic symptoms to illness severity in a larger sample of clinician-diagnosed patients by reviewing parent report, clinician assessment, and using child psychiatrist reviewers. Intrigued by our clinical experience, we aimed to examine the prevalence and characterize the quality of psychotic symptoms. We also hoped to understand whether the illness impact differed between those with and without psychotic symptoms. We hypothesized from clinical experience that:

1. Children with PANS experience psychotic symptoms more often than children in the general pediatric population
2. Psychotic symptoms in children with PANS are transient
3. Children with psychotic symptoms have more severe PANS impairment.
4. Psychotic symptoms in PANS correlate with disease progression and duration.

## 2. Method

The Stanford Panel on Human Subjects Institutional Review Board (IRB) approved this study under protocols IRB 26922 and 28533 and in accordance with the latest version of the Declaration of Helsinki. Informed written consent from adult participants and written assent from minor participants were obtained after the nature of the research was fully described and before any data were collected. Data was stored in a secure database.

### 2.1. Sample

We reviewed the clinical electronic medical records (EMR) of 152 consecutive patients seen in the Stanford University PANS clinic between September 1, 2010 and March 31, 2017 who met strict diagnostic criteria for PANS or Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS) (Chang et al., 2015; Frankovich et al., 2015; Swedo et al., 2012). PANDAS is PANS with documented antecedent Group A Streptococcal infection and with tics and/or OCD symptoms as the cardinal symptom(s) (Swedo et al., 1998). To be evaluated in our clinic, all patients must have been referred by their pediatrician, live locally, have had an abrupt-onset neuropsychiatric change within 3 months and, per the referring physician, demonstrate symptoms consistent with the PANS diagnostic criteria.

Patients underwent psychiatric and medical evaluation per the PANS Evaluation Guidelines (Chang et al., 2015). Evaluation included gathering, collating and reviewing all available medical, psychiatric, psychological, educational and other therapy (dietary, occupational therapy, physical therapy, etc.) records. At entry to the clinic, all patients' caregivers completed an electronic questionnaire (the PANS questionnaire) that queries current/historical reports of psychiatric symptoms, somatic symptoms, general medical symptoms, symptom onset, symptom severity, infectious exposures, medical history, past treatments, and family history (Leckman et al., 1989; Murphy et al., 2012). Caregivers also completed a Children's Yale-Brown Obsessive Compulsive Checklist and Scale (Scahill et al., 1997), the Yale Global Tic Severity Scale (Leckman et al., 1989), the Caregiver Burden Inventory (CGBI) (Novak and Guest, 1989; Farmer et al., 2018), and a rated Leikert 100-point Global Impairment score. Patients were examined by a clinical team including a primary care provider, a child psychiatrist, and a pediatric rheumatologist using standard history, review of systems, and physical and psychiatric examinations. When symptoms were endorsed, practitioners followed up with queries and examination based on DSM symptom diagnostic descriptions to further characterize them. Before the diagnosis of PANS was made, the clinical team considered differential diagnoses (including OCD, eating

disorders, anxiety disorders, cognitive disorders, tic disorders, mood disorders, trauma, and psychotic disorders) that could better explain the heterogeneity of symptoms seen in each patient. Laboratory and other evaluations were obtained as directed by clinical presentation and diagnostic guidelines. Given the young age of the patients coming into the clinic, urine drug screens were not routine. The PANS Diagnostic Guidelines, specify that symptoms must not be "better explained by a known neurologic or medical disorder, such as Sydenham chorea", and notes that while symptoms overlap with a variety of psychiatric disorders, the "the acuity of onset and simultaneous presentation of these symptoms differentiate PANS from these psychiatric conditions" (Chang et al., 2015).

To evaluate only patients with psychotic symptoms in the context of PANS and not PANS patients with premorbid psychotic symptoms, we excluded records with noted pre-morbid psychotic symptoms and records where time of psychotic symptom onset could not be defined. If the psychotic symptoms appeared likely to be related to another known condition (e.g. febrile illness with hallucinations, substance-induced psychosis), the record was also excluded. The clinical histories and presentations from families and children with a mean age of 10.9 years (SD 4.0) at psychotic symptom onset did not suggest necessity for urine toxin screening. If it was an older child (i.e. an adolescent) and substance use was suspected from clinical exam, or parent/patient report, a urine drug screen was obtained. If the screen was positive and the psychotic symptoms were classified as substance-induced psychosis, the patient's record was then removed from the final cohort group.

### 2.2. Measures

At each visit to the clinic, all patients' caregivers completed the PANS questionnaire, the Children's Yale-Brown Obsessive Compulsive Checklist and Scale (Scahill et al., 1997) (to assess OCD symptoms), the Yale Global Tic Severity Scale (to assess tic symptoms), the Caregiver Burden Inventory (Novak and Guest, 1989; Farmer et al., 2018), and a rated Likert 100-point Global Impairment score. At each subsequent visit, caregivers completed PANS questionnaires that excluded past and families histories.

The clinical team completed the Children's Global Assessment Scale (CGAS) (collection started in 2017) at clinic entry and at each subsequent visit (Schorre and Vandvik, 2004; Shaffer et al., 1983). To describe where the patient was in the course of the PANS disease, at each visit clinicians recorded whether or not the patient was in a "flare". Following rheumatologic convention, we defined a flare as "reflecting a cluster of symptoms, signs, and impacts of sufficient intensity and duration to require consideration of (re)initiation, change, or increase in therapy" (Bartlett et al., 2015).

### 2.3. Record review

A research assistant (EN) conducted the initial medical record review using a keyword navigational search method (Table 2). The initial medical record review was followed by an expert consultative review to determine the presence or absence of psychotic symptoms, type of psychotic symptoms, psychotic symptoms after a medication change, and details of the medication change. The consultative review included at least one of the patient's treating clinicians, a child and adolescent psychiatrist with expertise in OCD (MT) and an additional child and adolescent psychiatrist (MS).

The cohort group experiencing psychotic symptoms included those with hallucinations and/or thought disturbances (delusion or disorganization). If the patient's EMR mentioned any keyword listed in Table 2 and review with the treating clinicians and the OCD expert indicated that the patient did experience a clearly documented first experience of psychotic symptom during the course of their PANS, then the patient was identified as having a psychotic symptom concurrent with PANS. We defined hallucinations as perceptions in the absence of identifiable, external stimuli (Chaudhury, 2010). We defined delusions as fixed false beliefs that resist change despite the presence of counterevidence and that are not better explained by OCD or anxiety (Dudley et al., 2016). We defined thought disorganization as any of the following observable behaviors or speech patterns: flight of ideas, clang association, tangentiality, distracted speech, perseveration, derailment, thought blocking, poverty of thought, loose association, incoherent speech, and nonsensical statements (Cummings, 1988; Gaebel and Zielasek, 2015).

**Table 2**
Keyword search terms.

| Psychotic Symptom | Keywords |
|---|---|
| Psychosis | Psychosis/psychotic<br>Internal stimuli |
| Hallucinations | Hallucination/hallucinate<br>AH/VH, VH/AH, AH, VH<br>Voices |
| Delusions | Delusion/delusional<br>Grandiosity/grandiose<br>Paranoia/paranoid<br>Persecute/persecutory |
| Thought Disorganization | Flight of ideas<br>Poverty of thought<br>Loose association<br>Derail/derailment<br>Tangential/tangentiality<br>Clang/clang association<br>Pressured speech<br>Incoherent/incoherence<br>Nonsense/nonsensical<br>Perseverate/perseveration<br>Distract/distractible speech |

### 2.4. Cohort denominator group

#### 2.4.1. No psychotic symptom group

Patients without a clearly documented instance of psychotic symptoms were categorized as having no psychotic symptoms associated with PANS. Seven patients in this group lacked data for Caregiver Burden Inventory (CGBI), Global Impairment score (GI), and Children's Global Assessment of Functioning (CGAS) and were excluded from those analyses involving disease severity variables.

#### 2.4.2. Timing of first experience of psychotic symptom for analysis

We determined the timing of new psychotic symptom onset from the medical record review. We used the family's reported date as the date of the psychotic symptom onset. When not reported precisely, we adopted the conventions of a) if onset was reported as occurring in between two clinic visits, we coded the visit date in which the experience was reported as the onset date, b) if onset was reported as an age, we coded the patient's birthdate as the onset date, and c) if onset was reported in the form of a year only, we coded January 1st of that year as the onset date. In two cases psychotic symptom and PANS onset occurred in the same year, but it was unclear which onset occurred first. We included these cases in the primary analysis and excluded them in a sensitivity analysis. We also collected onset and resolution dates for all subsequent episodes.

#### 2.4.3. Course of psychotic symptoms

We coded psychotic symptom course as either single episode, episodic, or continuous/chronic/unclear. We defined single episode course as psychotic symptoms that distinctly began and resolved within a one-month period without any further recurrence. We defined episodic course as psychotic symptom episodes that were multiple and distinct, each with a clear beginning and remission from symptoms. We defined continuous/chronic/unclear course as symptom episodes without clear

beginnings or remissions.

### 2.5. Statistical analysis

SAS Statistical Analysis Software program (Cary, North Carolina, U.S.A.) was used to run statistical analysis. We did not adjust for multiple comparisons in any of our analyses because this study was exploratory in nature.

To test for differences in demographic and disease characteristic variables, we used unadjusted tests of association. We used t-tests to compare normally distributed continuous variables and Wilcoxon rank-sum tests to compare non-normally distributed variables. We used chi-square tests to compare categorical variables.

To test for differences in disease impairment between patients with history of psychotic symptoms and patients without psychotic symptoms, we employed mixed models with repeated measures, in which the outcome variable was disease impairment and predictors were: flare status (yes/no), psychosis (ever had psychotic symptoms/never had psychotic symptoms), time (years since first clinic appointment), and two interaction terms (psychosis*flare and psychosis*time). Flare status is a time-changing variable; psychosis is not time changing. The psychosis variable indicates whether patients with psychotic symptoms have higher disease impairment scores. We included the information of whether the patient was in a disease flare as a predictor because past analyses have shown that being in a disease flare is strongly associated with disease severity and so could, theoretically, act as a confounder if the groups had different probabilities of being in a flare. (Alternatively, different probabilities of being in a flare could be part of the pathway through which one group had higher impairment than another group).

We used a random intercept because patients enter the PANS clinic with varying degrees of disease severity. We used variance components correlation structure because it gave the lowest Akaike information criterion correction (AICC) value. We illustrate our mixed models results in Table 3, which shows median disease severity scores separately by psychotic symptoms group and flare and remission. Medians are calculated by averaging score within patient separately by disease and flare, so this figure does not show changes over time.

To test our third hypothesis evaluating psychotic symptoms in PANS as a marker of disease progression, we first compared the time lag between PANS symptom onset and first PANS clinic appointment between groups. The distribution of time-to-appointment was right-skewed, so we evaluated differences between groups using a Wilcoxon rank-sum test. Second, we evaluated the hypothesis that the risk of psychotic symptoms development increased throughout the PANS course by comparing the length of time patients with psychotic symptoms had been ill with PANS to the length of time patients without psychotic symptoms had been ill. We used a Wilcoxon rank-sum test because the time variable was right-skewed. Since this was an exploratory study, we did not correct for multiple comparisons.

Two cases specified same year for psychotic symptoms onset and PANS symptom onset; therefore, it was unclear whether psychotic symptoms preceded PANS symptom onset. After review, treating clinicians believed the psychotic symptoms were a component of the PANS symptom onset during the same year. These patients were included in the cohort group and analysis. We then excluded these patients in a sensitivity analysis.

## 3. Results

One hundred fifty-two records were reviewed for psychotic symptoms associated with PANS. 9 cases were excluded from the initial 152 patient set yielding 143 patients in the final cohort (denominator) group with clearly documented presence of or absence of psychotic symptoms during the course of PANS (Fig. 1).

Forty-nine of 143 patients (34%) were females and 94 of 143 patients (66%) were males. The mean age of PANS onset was 8.5 years (SD = 3.6), 7.8 years (SD = 3.5 years) for girls and 8.7 years (SD = 3.8 years) for boys. Most patients (97 of 143, 68%) identified themselves as Non-Hispanic white. Patients presented to the clinic about two years after PANS symptoms began at age 10.7 years (SD = 3.9 years). Most patients (100 of 143, 70%) had a relapsing/remitting course of illness (Table 4).

### 3.1. Psychotic symptoms were common

Fifty-three of 143 patients (37%) experienced psychotic symptoms during the course of their illness. Six patients first developed psychotic symptoms after a medication change (Table 5). Psychotic symptoms remitted or were episodic in 43 of 53 patients (81%). Most patients who experienced psychotic symptoms had their first onset of psychotic symptoms during the first year of PANS illness (Fig. 2).

There was no statistically significant differences between patients with a history of psychotic symptoms and those without psychotic symptoms in terms of sex, age at PANS symptom onset, age at PANS clinic presentation, length of time to treatment access and course of illness. There was also no statistically significant difference between groups in terms of course of illness (p = .1) (Table 4).

**Table 3**
Results of a mixed model comparing disease severity scales in disease flares and across time in patients with and without psychotic symptoms (n = 137 patients).

| Disease severity variable | Intercept[a] | Flare[b] | Group[c] | Flare*Group[d] | Time[e] | Group*Time[f] |
|---|---|---|---|---|---|---|
| CBI (0–96) n = 1291 CBIs | 19.7 (15.4–24.1) | 7.5 (5.5–9.5)* | 18.1 (11.7–24.6)* | −0.5 (−3.2 to 2.1) | −2.4 (−3.7 to −1.0)* | 0.0 (−1.7 to 1.7) |
| GI (0–100) n = 1894 GIs | 23.0 (18.6–27.5) | 14.4 (12.0–16.9)* | 10.7 (3.9–17.6)* | 0.2 (−3.1 to 3.5) | −3.9 (−5.3 to −2.6)* | −0.5 (−2.3 to 1.3) |
| CGAS (100-1) n = 489 CGAS | 81.4 (75.9–86.8) | −13.6 (−17.0 to −10.2)* | −12.8 (−21.0 to −4.7)* | 1.2 (−3.3 to 5.7) | 0.3 (−2.2 to 2.7) | −0.2 (−3.5 to 3.1) |

Abbreviations: CBI = Caregiver Burden Inventory; GI = Global Impairment; CGAS = Child Global Assessment Score.

[a]Intercept effect estimate is the estimated value of disease severity variable for no psychotic symptom group at first measurement.

[b]Flare effect estimate is the estimated change in disease severity variable when a patient with no psychotic symptoms is in a flare compared with remission when group and years in clinic are held constant.

[c]Group effect estimate is the estimated difference in disease severity variable when in the psychotic symptom group compared with the no psychotic symptom group when flare status and years in clinic are held constant.

[d]Flare*Group effect estimate is the estimated difference in the effect of flare on disease severity variable between the psychotic symptom group and the no psychotic symptom group. If the confidence interval crosses zero, then the interpretation is that there is no difference in the effect of flare between groups.

[e]Time effect estimate is the estimated change in disease severity variable predicted by an additional year of treatment by the Stanford PANS clinic. This estimate is for the no psychotic symptom group.

[f]Group*Time effect estimate is the estimated difference in the effect of time between the psychotic symptom group and the no psychotic symptom group.

*indicates that the 95% confidence interval does not cross 0. (There are no stars for intercept because it is impossible for this 95% CI to cross 0).

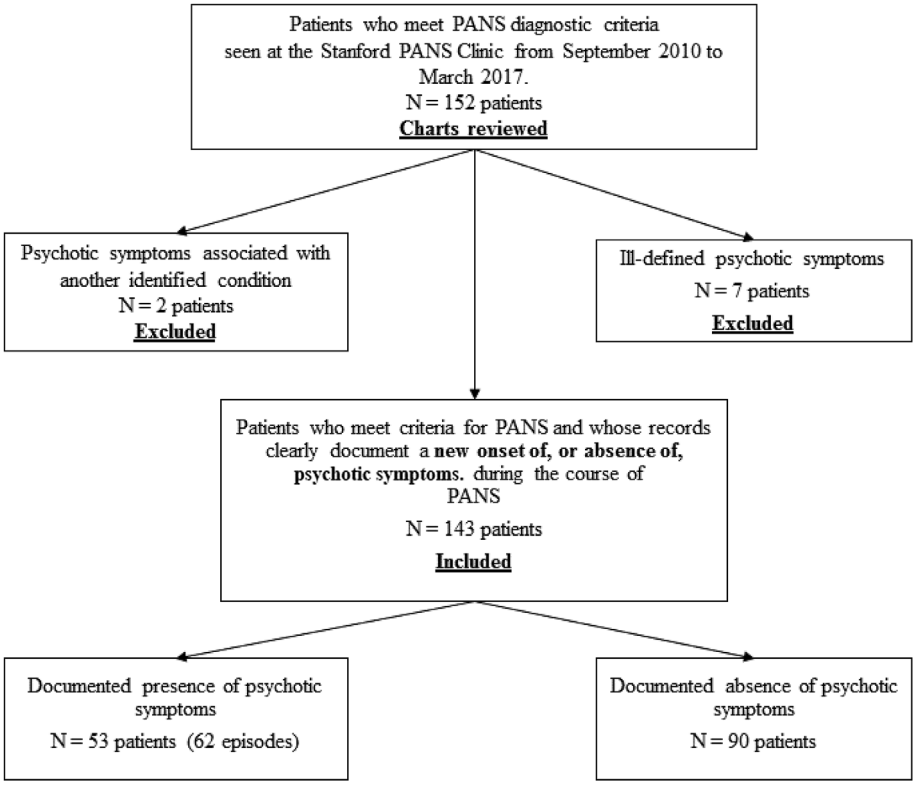


**Fig. 1.** Patients included and excluded in cohort group.

### 3.2. Most psychotic symptoms were transient hallucinations

The most common psychotic symptom was hallucinations: 52 of 143 patients (36%) ever experienced hallucinations. Fewer patients experienced delusions (9 of 143, 6.3%) or thought disorganization (8 of 143, 5.5%). Some patients experienced multiple psychotic symptoms, but others experienced only hallucinations (43 of 143, 30%) or only thought disorder (1 of 143, 0.7%) (Table 5).

The types of hallucinations reported include auditory, visual, or other (gustatory, olfactory, tactile). Auditory and visual hallucinations were equally common (37 of 53 patients who experienced any psychotic symptom, 70%). Other sensory hallucinations were less common (9 of 53 patients, 18%). Of the auditory hallucinations, only one patient heard pejorative or threatening voices. The majority of patients with well-described auditory hallucinations had non-pejorative, non-threatening auditory hallucinations (19 of the 37 patients who experienced auditory hallucinations, 51%). Some auditory hallucinations were not categorized due to limited descriptions of the hallucinations in the EMR (16 of 37 patients who had auditory hallucinations, 43%).

The auditory and visual hallucinations varied in complexity.

**Table 4**
Demographic variables in patients with psychotic symptoms and patients without psychotic symptoms. All patients have been diagnosed with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

| | Cohort Group N = 143 | Psychotic symptoms N = 53 | No psychotic symptoms N = 90 | p-value[a] | p-value (sensitivity analysis) |
|---|---|---|---|---|---|
| Age in years at PANS Symptom Onset, mean (SD) | 8.5 (3.6) | 8.8 (4.0) | 8.3 (3.4) | .50 | .47 |
| Age in years at PANS Clinic Presentation, mean (SD) | 10.7 (3.9) | 11.2 (4.0) | 10.4 (3.8) | .24 | .23 |
| Months from PANS symptom onset to first psychotic symptom, median (IQR) | | 7.3 (0.3–36.6) | N/A | | |
| Age in years of first psychotic symptoms, mean (SD) | | 10.9 (4.0) | N/A | | |
| Male N (%) | 94 (66%) | 31 (58%) | 63 (70%) | .16 | .19 |
| Race/ethnicity N (%) | | | | .76 | .76 |
| Non-Hispanic White | 97 (68%) | 39 (76%) | 58 (64%) | | |
| Black | 0 | 0 | 0 | | |
| Asian | 4 (3%) | 1 (2%) | 3 (3%) | | |
| Hispanic or Latino | 22 (15%) | 9 (17%) | 13 (14%) | | |
| Other/unknown | 20 (12%) | 4 (8%) | 16 (18%) | | |
| PANS Disease course N (%) | | | | .10 | .09 |
| Single Episode | 10 (7%) | 5 (9%) | 5 (6%) | | |
| Relapsing/Remitting | 100 (70%) | 31 (58%) | 69 (77%) | | |
| Chronic/Static (> 9 mo) & Progressive | 33 (23%) | 17 (32%) | 16 (18%) | | |
| PANS Disease course N (%) collapsed | | | | .10 | .09 |
| Not chronic/static | 110 (77%) | 36 (69%) | 74 (82%) | | |
| Chronic/static | 32 (23%) | 16 (31%) | 16 (18%) | | |

Variables with a skewed distribution are reported as median (IQR) whereas variables with a normal distribution are reported as mean (SD).
[a] p-value is for statistical tests comparing the sensory disturbance group with the no sensory disturbance group.

**Table 5**
Type and frequency of psychotic symptoms in Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

| | Prevalence of symptoms (n = 143 patients) | Frequency of symptoms with illness (n = 47 disturbances)[a] | Frequency of symptoms after medication (n = 15 disturbances)[a] | Frequency of symptoms in all disturbances (n = 62 disturbances)[b] |
|---|---|---|---|---|
| **Any Disturbance** | 53/143 (37%) | 47/143 (33%) | 15/143 (10%) | |
| **Perceptual Disturbance** | | | | |
| Hallucinations | 52/143 (36%) | 46/47 (98%) | 15/15 (100%) | 61/62 (98%) |
| Auditory | 37/143 (26%) | 34/47 (72%) | 10/15 (67%) | 44/62 (71%) |
| Visual | 37/143 (26%) | 32/47 (68%) | 10/15 (67%) | 42/62 (68%) |
| Other (gustatory, olfactory, tactile) | 9/143 (7%) | 9/47 (19%) | 0/15 (0%) | 9/62 (15%) |
| Auditory + visual | 24/143 (17%) | 21/47 (45%) | 6/15 (40%) | 27/62 (44%) |
| Auditory + visual + other | 6/143 (4%) | 6/47 (13%) | 0 (0%) | 6/62 (10%) |
| **Thought Disturbances** | | | | |
| Delusions | 9/143 (6%) | 6/47 (13%) | 4/15 (27%) | 10/62 (16%) |
| Thought Disorganization | 8/143 (6%) | 6/47 (13%) | 2/15 (13%) | 8/62 (13%) |

[a] 9 patients had existing disturbance followed by exacerbation or re-occurrence of disturbance after medication change. They contribute 1 disturbance to each column.
[b] 9 patients are double counted in this column per the explanation in[a] (above).

Auditory hallucinations were simple in 2 of 37 patients (5%), complex in 28 of 37 patients (76%), and uncategorized in 7 of 37 patients (19%). Visual hallucinations were simple in 4 of 37 patients (11%), complex in 23 of 37 patients (62%), and uncategorized in 10 of 37 patients (27%) (Table 5).

### 3.3. Those with psychotic symptoms were more severely ill

Patients who experienced psychotic symptoms demonstrated statistically significant more severe PANS illness both during disease flares and in disease remission, as reported by clinicians on the Child Global Assessment Scale and by caregivers on the Caregiver Burden Inventory (CGBI) and the Global Impairment (GI) Scales than patients without psychotic symptoms (Fig. 3).

Each group demonstrated statistically significant improvement in illness severity over one year of treatment. The groups did not differ in the amplitude of this improvement.

### 3.4. Psychotic symptoms did not mark a longer time to treatment access

The time between PANS onset and entry into a multidisciplinary PANS clinic did not distinguish the group with psychotic symptoms from the group without in terms of time between PANS onset and entry into a multidisciplinary PANS clinic (p = .4) for diagnosis and/or treatment.

Due to limitations on available data (frequency of flares) we could not accurately assess the mean number of flares in each group.

## 4. Discussion

### 4.1. Summary of results

We aimed to discover the type, frequency, and duration of psychotic symptoms in this clinical population and assess their association with syndrome severity. Psychotic symptoms were notably common in our PANS sample; more common than reported in other psychiatric disorders (OCD, eating restriction, tic disorder, and mood disorders). (For example, OCD: 1.7% (de Haan et al., 2009), eating disorder: 13% (Hudson and Pope, 1984), Tourette disorder: [schizophrenic disorders 1.8% and psychosis 0.9%] (Groth et al., 2017), mood disorder: 10.2% (Ulloa et al., 2000)). The incidence is resembling that found by other investigators and exceeding that expected in the general population

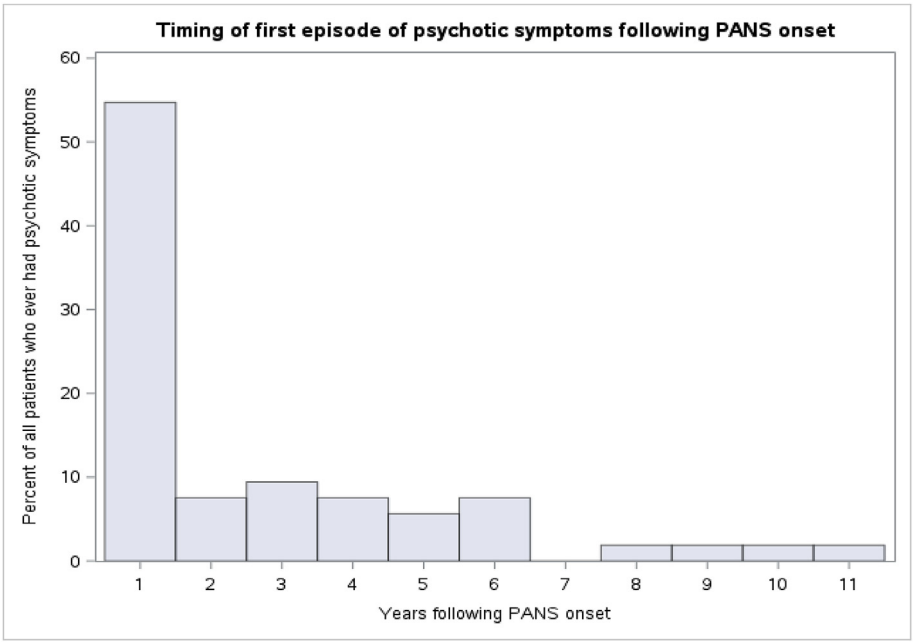


**Fig. 2.** Timing of psychotic symptom onset following PANS illness. Most patients had first onset of psychotic symptoms within the first year of PANS illness.

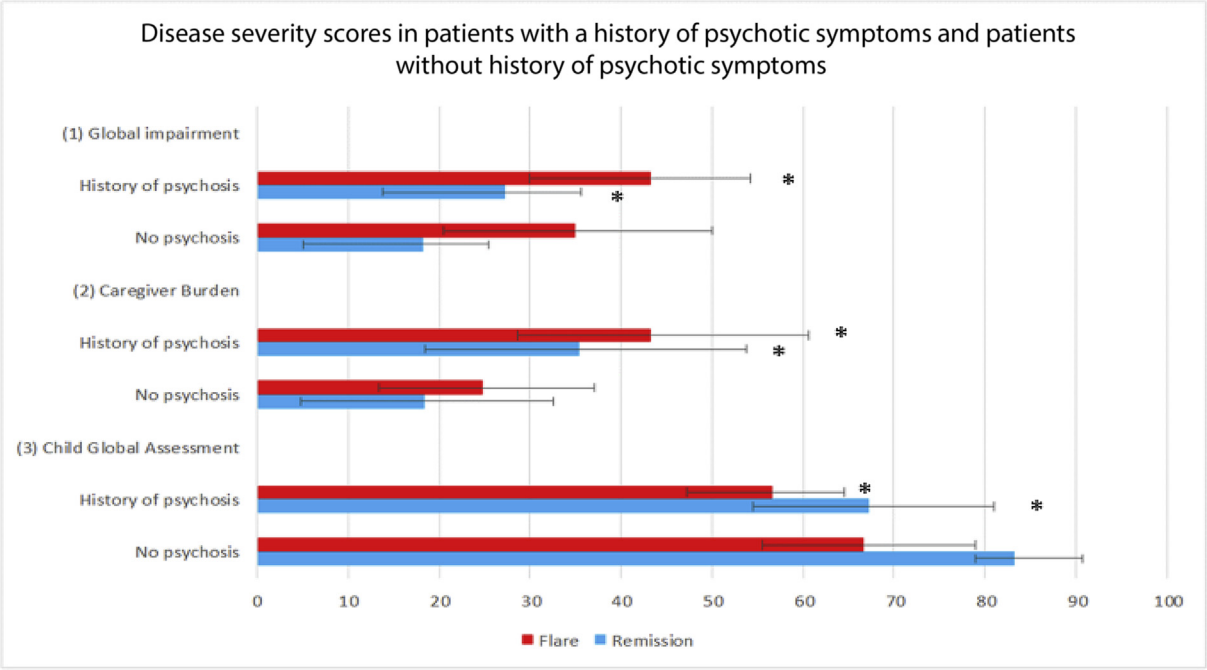


**Fig. 3.** Disease severity in patients with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) with and without psychotic symptoms.
Patients with psychotic symptoms had higher global impairment, poorer functioning (child global assessment), and higher caregiver burden scores than patients without psychotic symptoms both during periods of flare and remission. This figure summarizes results from a mixed model with repeated measures, which takes into account time and correlations within individual.
* indicates that the 95% confidence interval does not cross 0.

(Linscott and van Os, 2013). Over 1/3 of patients reported hallucinations; less than 10% demonstrated thought disorders. Auditory and visual hallucinations were equally common and generally were complex (voices, music, faces, figures). In 83% of patients, symptoms remitted. Parent and clinician-rated measures reported that throughout the course of the illness observed, those with psychotic symptoms were statistically and clinically significantly more severely ill. Contrary to our predictions, those with psychotic symptoms did not have a longer time between onset and access to treatment nor a longer duration of PANS illness. Thus, it did not appear that psychotic symptoms manifestation evolved as a function of the disease worsening over time.

Understanding more about psychosis may help us understand PANS psychopathology. Psychotic symptoms are not uncommon in the general population and occur in many psychiatric conditions. Seven percent of the population reports having psychotic experiences (hallucinations and delusions); 80% of those transiently and most diagnostically nonspecific (Linscott and Van Os, 2013). Auditory hallucinations have been reported in 17% children aged 9–12 years (Laurens and Cullen, 2015; and Os et al., 2008). Many childhood disorders present with psychotic symptoms, including 62 congenital disorders alone (Lauterbach et al., 2008). Psychotic symptoms occur in pediatric psychiatric disorders including, but not limited to, brief psychotic disorder, delusional disorders, schizophrenia, other specified schizophrenia spectrum disorders, mood disorders, post-traumatic stress disorders, and substance induced disorders. Some PANS patients may meet diagnostic criteria for brief psychotic disorder or a schizophrenia spectrum disorder if not considering PANS an exclusionary condition. Psychotic symptoms are also seen in other neuropsychiatric disorders: rheumatic fever (Sydenham chorea), Parkinson's disease, Lewy body dementia, lupus cerebritis, delirium, delirium tremens, alcoholic hallucinosis, and various substance- and pharmacological induced disorders (Benros et al., 2014; Bergink et al., 2014; Lautenschlager and Förstl, 2001).

Evidence supports potential associations between psychotic symptoms and infection and in autoimmunity in infection-mediated neurologic disease, such: neuro-syphilis and Herpes simplex virus type 2 encephalitis and in post-infectious, immune-mediated Sydenham chorea. (Jarius et al., 2015; Munjal et al., 2017; Zheng et al., 2011). In pediatric antibody-associated encephalitidies (such as antiNMDAR encephalopathy and Hashimoto's encephalopathy), psychotic symptoms may emerge alongside the characteristic symptoms of cognitive and memory impairment, behavioral changes, seizures, autonomic dysregulation and abnormal movements) (Kahn, 2017; Pon et al., 2017). Psychotic symptoms also occur in other autoimmune diseases: multiple sclerosis, systemic lupus erythematosus, antiphospholipid syndrome, and neuro-Behçet Disease. First episode psychosis, too, has been associated with increased markers of inflammation, autoimmunity, and infection (Benros et al., 2016; Bocchio-Chiavetto et al., 2018; Kopczynska et al., 2017; Orlovska et al., 2017; Yee et al., 2017; Scott et al., 2018).

### *4.2. Proposed neural substrate for pathogenesis of psychotic symptoms in PANS*

Evidence also supports an association between psychotic disorders and the striatum. Psychosis is well known in the degenerative basal ganglia diseases: Parkinson's, Lewy body dementia and Huntington's (Rosenblatt and Leroi, 2000). The striatum is the major gateway for information flow into the basal ganglia and is implicated in the pathogenesis of schizophrenia (Howes et al., 2011; Yoon et al., 2013, 2014), bipolar disorder (Jauhar et al., 2017) and stimulant abuse (Ljeberman et al., 1990). Basal ganglia abnormalities have been found in Sydenham chorea, whose symptomatic overlap with PANS includes the presence of psychotic symptoms. Striatal findings in Sydenham's chorea have included antibodies that bind to basal ganglia antigens (Church et al., 2002) and enlarged caudate nucleus, one of the major components of the striatum, compared to controls (Giedd et al., 1995).

While the precise nature of the neural mechanisms causing psychotic symptoms in patients with PANS remains unclear, the best available evidence also suggests that the basal ganglia, and in particular

the striatum, are the neural substrate (Giedd et al., 2000; Kumar et al., 2015). Caudate nucleus enlargement, which resolved with illness resolution, has been reported in PANDAS (Giedd et al., 2000). Some evidence suggests that an autoimmune response triggered by molecular mimicry in PANDAS occurs in the striatum (Lotan et al., 2014). A recent PET study using a marker of microglia activation found it concentrated in the caudate nuclei more in patients with PANDAS and Tourette Syndrome than in healthy subjects (Kumar et al., 2015). Another recent study demonstrated elevated binding to striatal cholinergic interneurons of antibodies from serum of subjects with PANDAS which resolved in parallel with symptom improvement after treatment with intravenous immunoglobulin (Frick et al., 2018). The studies implicating immune-mediated basal ganglia and striatal involvement in PANS′ etiology are consistent with considerations about the basal ganglia and striatum's role in pathogenesis of other psychotic disorders.

Our finding of psychosis in PANS might be anticipated both when considering the area of the brain affected proposed for PANS' pathogenesis and considering the pathogenesis of psychosis. The striatum has been identified as a common neural substrate for psychotic symptoms in a variety of illness with varying etiologies (neurologic, psychiatric, and autoimmune) as noted above and for PANS.

### 4.3. PANS diagnosis validity

While not this study's aim, our study adds to information addressing questions about PANS syndrome's diagnostic validation and toward viewing PANS as a heterogeneous syndrome. PANS consensus diagnostic criteria were born out of concerns about the diagnostic validity of: PANDAS, a subtype of PANS (Chang et al., 2015; Rosenblatt and Leroi, 2000; Swedo et al., 2012). PANS′ construct validity, or utility and appropriate treatment have been debated (Swedo et al., 2010; Schrag et al., 2009; Gilbert et al., 2018) The lack of consistent laboratory findings, concern over lack of clear delimitation from other disorders, insufficient longitudinal and treatment studies, and insufficient family/genetic evidence have stood in the way of its being accepted as a valid diagnosis, according to 5 criteria proposed by Robins and Guze (Robins and Guze, 1970).

Our finding that a portion of our sample has transient psychotic symptoms adds to knowledge of PANS by further characterizing PANS presentations, strengthening its clinical description. Our findings that those with psychotic symptoms were 1.) more severely ill throughout their PANS course and 2.) did not have longer times to diagnosis or a longer duration of illness suggest that, in addition to the heterogeneity of possible antecedents, there is heterogeneity of presentation, prognosis and outcome in PANS.

### 4.4. Limitations

Retrospective record review research risks poor data reliability and validity. We reviewed EMRs for noted psychotic symptoms obtained by parent or child report and upon mental status evaluation. Accurately quantifying internal, subjective experience, especially in children, can be fraught with possibilities for error (Courvoisie et al., 2001). Children may under-report hallucinations because of reluctance and incomprehension. Some children, in our experience, often do not remember aspects of a PANS flare. Distinguishing sleep-related experiences from day-time hallucinations, and distinguishing demanding, intrusive obsessive directives from hallucinatory "voices" may be difficult for the child, parent and interviewer. Parents may or may not be aware of the child's psychotic symptoms or may call anxiety, agitation or other severe symptoms "psychotic." We hope that our extensive experience with pediatric psychiatry and pediatric OCD minimized potential error. The skill of the clinician and familiarity with the child, as well as the completeness of examination and charting in light of the number and severity of other PANS symptoms in any one visit could affect reliable retrospective assessment of psychotic symptoms. These factors may have affected the reliability of our data collection. Having multiple data extractors and case-by-case review of charts improves our confidence in our review validity as does the similarity of our findings with those of other PANS investigators. A prospective study with PANS patients could improve focus and reliability of data collection.

## 5. Conclusion

Transient complex auditory and visual hallucinations were equally common in patients with PANS. Hallucinations were largely non-pejorative and non-threatening. Patients with PANS and psychotic symptoms had more functional impairment, higher caregiver burden, and more severe PANS symptoms, but were not distinguished from other patients with PANS by age, sex, age of onset or latency to treatment. The presence of psychotic symptoms was not associated to the time to diagnosis nor duration of illness, suggesting that psychotic symptoms do not mark disease progression, but rather, disease heterogeneity.

### 5.1. Clinical practice implications

Physicians who identify new psychotic symptoms in pediatric patients should consider PANS in their differential diagnoses, along with considering psychiatric, autoimmune, rheumatological, infectious, and toxic disorders.

If PANS is suspected, and ongoing antecedent infection is identified, treating that can hasten recovery and thereby improve the clinical course (Cooperstock et al., 2017). Emerging evidence also suggests that treating inflammation may be beneficial (Frankovich et al., 2017). Identification of the syndrome as PANS may prevent administration of ineffective and adverse-effect associated psychopharmacological treatments, while psychiatric and supportive therapies are always indicated (Thienemann et al., 2017).

Further research is needed to understand fully the mechanisms causing, and the most effective therapies for treating psychotic symptoms in PANS. Further characterizing the course of disorder and its heterogeneous antecedents, further examination of heterogeneous symptom clusters, and further characterizing markers and treatment responses may also help in understanding heterogeneity in PANS syndrome and PANS' possible relationships, similarities and differences from other neurological, psychiatric and autoimmune disorders.

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## Conflicts of interest

None declared.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.11.013.

## Appendix. Psychosis Characteristics after Medication Change

| Patient (sex, Age in Years) | Race/ Ethnicity | Medication (dosage) | Purpose | Type of Psychosis | Duration of Disturbance (days) | Remit (Y/N) |
|---|---|---|---|---|---|---|
| #1 (M, 9) | Caucasian | *Sertraline (unknown) | OCD/ARFID/ED | AH, VH | Unknown | Y |
| #2 (M, 15) | Caucasian | *Alprazolam (unknown) | Panic | AH | Unknown | Y |
| #3 (M, 15) | Hispanic/ Caucasian | Mycophenolic acid (1500 mg BID) | Immunosuppression (steroid sparing agent) | AH, VH, Delusion | ~30 | Y |
| #4 (M, 11) | Caucasian | *Lorazepam (unknown) | Anxiety | VH | < 1 | Y |
| #5 (F, 3) | Caucasian | *Combination Fentanyl and Midazolam (unknown) | Emergency room Procedure | Hallucination | < 1 | Y |
| #6 (M, 3) | Caucasian | *Amantadine taper (100 mg BID tapered to 100 mg QD) | Off Label ADHD | VH, Delusion | < 1 | Y |
| #7 (M,15) | Other | *Ketamine withdrawal (30 mg 2x) | Anesthesia lumbar puncture | AH, VH, thoughts of insertion, paranoid delusion | ~60 | Y |
| #8 (M, 8) | Caucasian | Aripiprazole taper (30 mg, 20 mg, 10 mg) | Mood stabilization. | AH | 120 | Y |
| #9 (M, 10) | Caucasian | Mycophenolic acid (500 mg BID) | Immunosuppression (steroid sparing agent) | AH,VH, and tactile | 5 | Y |
| #10 (M, 10) | Hispanic | Prednisone (30 mg BID 5x days) | PANS flare | AH, | 7 | Y |
| #11 (M, 11) | Caucasian | *Ketamine (7.5 mg) | Anesthesia, Abdominal pain and KUB | AH, VH | 19 | Y |
| #12 (F, 6) | Caucasian | *Lorazepam (0.5–1.5 mg IV prn) | Agitation or Anxiety | AH | 14 | Y |
| #13 (M, 14) | Caucasian | *Fluoxetine (10 mg QD) | Paranoia | mania (AH. VH, paranoid, delusions) | 15 (months) | Y |
| #14 (F, 7) | Caucasian | Mycophenolic acid and/or sedation withdrawal (300mg/m2 BID) and/or (propofol, fentanyl dexmedetomidine & midazolam) | PANS flare and sedation | AH, VH, tactile | ~42 | Y |
| #15 (F, 6) | Caucasian | Prednisone (50 mg QD x 5 days) | PANS flare | VH | 6 | Y |

*Medication was prescribed outside of the PANS Clinic.
Patient # 1–6 first developed psychotic symptoms after a medication change.
Patient # 7–15 had previous psychotic symptoms in the course of their illness and exacerbation or reoccurrence of psychotic symptoms after a medication change.

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