Neurodevelopmental risks for Bipolar Disorder

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Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee of the
Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2014

ABSTRACT

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This dissertation aims to add to the growing literature on the risks and mechanisms in early life that may be associated with later bipolar disorder (BP), expanding the understanding of when and why divergences from typical developmental course occur in BP, if they do. To do so, it utilizes prospectively obtained, serologically documented prenatal biomarkers and clinically documented prenatal and perinatal risk factors, as well as premorbid measures of neurocognitive functioning, in a well-defined birth cohort followed up for BP. This offers a unique opportunity to test some of the evidence as to whether BP is a neurodevelopmental illness. The first paper is a systematic literature review of the neurodevelopmental hypothesis of BP. This review focuses on three developmental time points: prenatal and perinatal exposures, premorbid and prodromal symptom development, and neurocognitive functioning prior to onset. The second paper focuses on two specific putative prenatal and perinatal risk factors for BP: T. gondii and oxytocin to induce labor. The third paper assesses cognition, using both the BP case-control study and the full birth cohort to assess risks for BP and the potential that cognitive impairment reflects a mediator or endophenotype of later BP. Taken as a whole, the findings suggest support for the neurodevelopmental hypothesis of BP and indicate some potentially specific risks for BP.

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Dedication:

This work is dedicated to those men and women drawn into the criminal justice system because of mental illnesses of all types. My work on behalf of those on death row or facing capital trials set me on the course of trying to better understand how mental illness shapes neurodevelopment and alters some people's life trajectory.

I have many people to thank for help with this dissertation, but especially Alan S. Brown who guided the research, helped my thinking and writing when I got stuck, and has mentored my work since I began at Columbia. Similarly, the rest of my dissertation committee was critical in helping me think about the issues and presentation of these data (Sharon Schwartz, Bruce Link, Jennifer Manly, and Cheryl Corcoran). Sharon Schwartz played another essential role as well, as a mentor who pushed my epidemiologic thinking and through her work with the Psychiatric Epidemiology Training program at Columbia. PET has been the intellectual home for me that I hoped it would be when I applied.

Many people have had to listen to me through this process and I deeply appreciate their willingness and assistance. Ahtoy Won Pat-Borja more than any other person has helped me to think through this dissertation at every step and in every way. Sean Bolser listened, suggested, thought with me, throughout the five years that this process has stretched. And my family, which instilled by example and by encouragement the commitment to life long searching for knowledge and to the idea that searching should always hold at its core a dedication to social justice.

Introduction and overview

Bipolar disorder (BP) and schizophrenia (SZ) are serious mental illnesses which disrupt and impair social, behavioral, familial, and occupational functioning, being among the largest contributors to years lost to disability globally (Vos, Flaxman et al. 2012). Although diagnostically specific, BP and SZ are frequently hypothesized to be closely related, sharing phenotypic symptoms, genetic, and environmental risks, and perhaps constituting different specific manifestations of similar etiologies. Both conditions are often viewed as neurodevelopmental diseases, despite the evidence underlying this hypothesis being stronger for SZ than for BP. Whether BP is a neurodevelopmental disease, and whether conceptualizing it as such helps to elucidate the causes, mechanisms, trajectories, and possibilities for prevention, is a complex question and the answers remain elusive.

The neurodevelopmental approach to the origin and course of SZ and BP holds promise for better outcomes because it searches for the causes and mechanisms which result in illness later in life, opening the potential for earlier and more effective intervention and prevention. As suggested by Insel, the neurodevelopmental approach identifies stages of disease progression, each of which may offer specific types of intervention and prevention (Insel 2010). Another way to ask this question is: during which periods do the divergences from typical developmental course occur, and why have they occurred? The neurodevelopmental hypothesis suggests that the divergences may begin before conception and that the risk for them continues through illness onset, at least. For each symptom cluster which constitutes the diagnostic criteria for illness, the timing and mechanism of divergence offers the potential for prevention or remediation. In order to identify the interventions and preventive steps that might work, further research on the antecedent risks, mechanisms, and causes is needed. This is especially true for BP, about which many fewer rigorous, population based studies have been conducted. Because of neurodevelopmental and symptom similarities, one potential approach to better understanding BP is to use the evidence and hypotheses developed to understand SZ, and test whether the purported etiologies and mechanisms are similar, or not, to BP.

A number of competing hypotheses about the relationship between BP and SZ have been proposed (Trede, Salvatore et al. 2005, Craddock and Owen 2010, Demjaha, MacCabe et al. 2012, Derks, Allardyce et al. 2012). Craddock and Owen have argued that the Kraepelinian dichotomy, which

postulated BP and SZ as categorically distinct forms of psychosis, is not supported based evidence of the similarities in genetic risk and pathogenic mechanisms; they articulate a dimensional disease hypothesis that would consider SZ and BP along a psychotic disorder spectrum, more similar than distinct, but clinically differentiated nonetheless (Craddock and Owen 2010). They suggest that the differences along this psychosis-mood continuum are idiosyncratic individual variation rather than associated with a causal mechanism. Demjaha, MacCabe and Murray, offer a similar view of the underlying genetic risk shared by both illnesses which supports the relationship between the conditions; they go on, however, to suggest that the disorders diverge because of additional genetic and environmental exposures which more substantially impair neurodevelopment for those who later develop SZ than those who develop BP (Demjaha, MacCabe et al. 2012). The distinction in this formulation from Craddock and Owen's is that the variation is identifiable beyond the normal individual idiosyncratic manifestation of disease.

In contrast to these views of BP and SZ being diagnoses along a psychotic disease continuum, Derks et al., using latent class analysis, report quite good class specificity for SZ, but symptom heterogeneity for BP, suggesting the illnesses are distinct, but that the BP category may be less discrete. They suggest this heterogeneity may explain the overlap of genetic risk for SZ and BP (Derks, Allardyce et al. 2012). In further support of categorization, a recent editorial by Carpenter summarized a clinician/researcher view of these disorders, stating: "The modest progress made to date has not been sufficient to redefine the classification landscape based on neurobiology, biomarkers, or distinctive phenomenology. One winces when an overlap is claimed based on similar ratings on a particular test at a single assessment, because this simplistic analysis overlooks the remarkable distinctions in form and content between these disorders" p961 (Carpenter 2013).

Nevertheless, the comparative lack of research on the antecedents of BP makes such hypotheses difficult to parse; with limited evidence regarding the risks, mechanisms, and phenotypic specificity of BP, it is not possible to know how BP relates to SZ. For instance, despite significant attention to putative shared genetic risks (Consortium 2013), evidence suggests pleiotropic effects of genes relating to psychiatric illnesses (Sivakumaran, Agakov et al. 2011). Along with the direct causal hypothesis of environmental risks, these pleiotropic genetic effects which may result in distinct diagnoses support the need more complete and complex investigation of the environmental risks and the

interactions between genetic and environmental risks. This is particularly important for BP, about which less is known regarding the antecedent risks.

BP is characterized by significant changes in mood, and defined by (hypo)mania interspersed with major depressive episodes (Goodwin, Jamison et al. 2007). Manic episodes are distinct periods of abnormal and persistent elevated, expansive, or irritable moods. The symptoms of mania may include: grandiosity, irritability, paranoia, racing thoughts, greater energy, decreased need for sleep, pressured and excessive speech, thought disorder, distractibility, and impulsivity (Goodwin, Jamison et al. 2007). Major depressive episodes in BP are similar to those in unipolar affective disorder, marked by alterations of mood, cognition, and behavior. Suicide attempts are common in BP (Jamison 2000). These mood alterations disrupt social and occupational functioning, and frequently necessitate hospitalization. BP is associated with a substantial burden for patients, family members, and society, being the sixth-leading cause of time lost to disability or death (Simon 2003).

The studies which follow utilize prospectively obtained, serologically documented prenatal biomarkers and clinically documented pre- and perinatal risk factors, as well as premorbid measures of neurocognitive functioning, in a well-defined birth cohort followed up for BP. This offers a unique opportunity to test some of the evidence as to whether BP is a neurodevelopmental illness.

Study Methods

The Child Health and Development Study (CHDS) is a large, representative birth cohort, containing 19,044 live births, which included nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (Kaiser) in Alameda County, California between 1959 and 1966. (van den Berg 1979, van den Berg, Christianson et al. 1988). This cohort has been followed prospectively, with prenatal serologic samples obtained during pregnancies, perinatal measures obtained during routine medical care, childhood cognitive assessment performed at ages 5, 9-11, and 15-17 on subsets of the birth cohort, and psychiatric diagnoses confirmed in adulthood. Using a nested case-control design to obtain all BP cases and matched controls from the CHDS birth cohort, this research investigates the relationship between serologically obtained prenatal exposures and birth complications, early childhood cognition, and onset of BP. Previously, this birth cohort has been

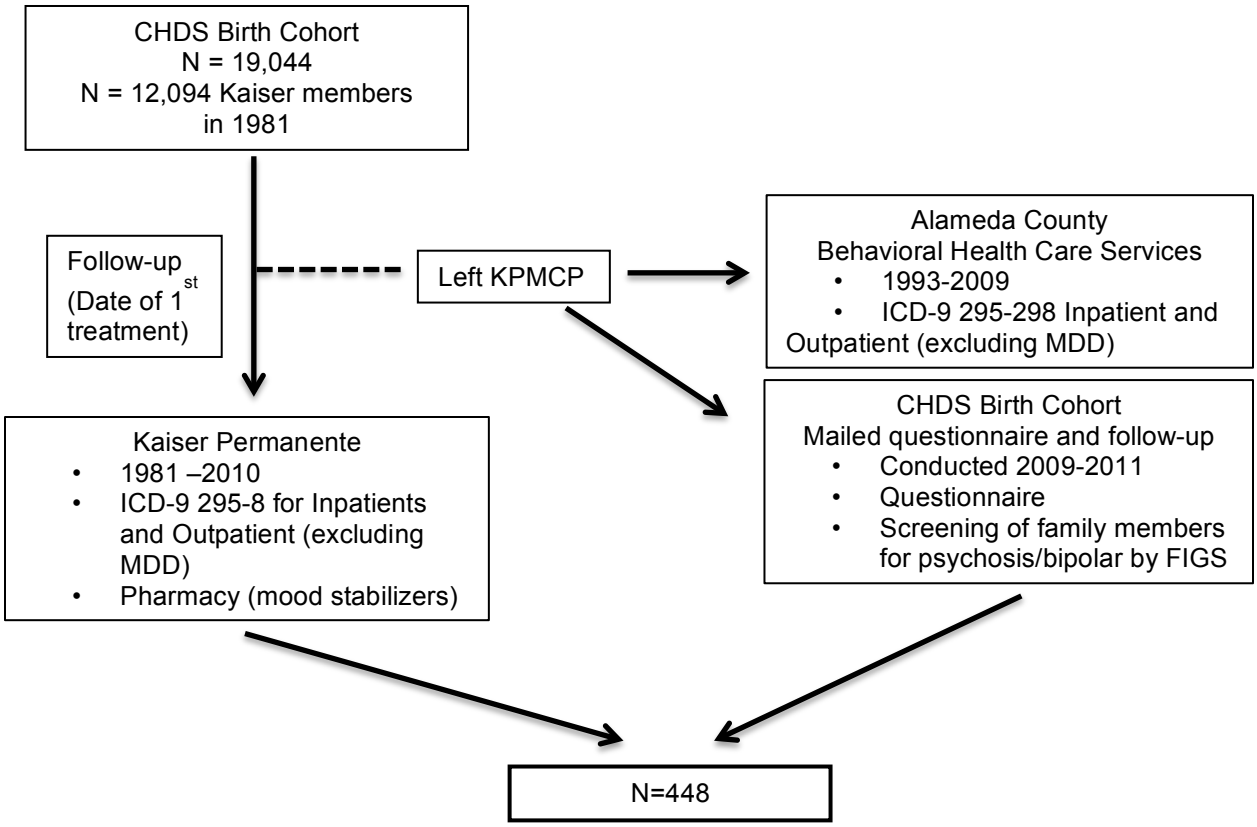
extensively studied for prenatal and other early developmental risk factors for SZ, which supports the unique quality of the data and offers an unusual opportunity for studying BP (Susser, Schaefer et al. 2000).

Case Identification

People with potential DSM-IV BP, which included BP I, BP II, BP NOS, and BP with psychotic features, were ascertained by screening procedures which used data from three sources: Kaiser's electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailing to the entire living CHDS birth cohort (mothers and children). This approach sought to maximize ascertainment of individuals with BP. CHDS cohort members who belonged to Kaiser when first treated would have been ascertained from this source. Subjects who left Kaiser prior to the first treatment of BP and who did not have other health insurance, but who still lived in Alameda County, would likely have been treated by ABHCS and therefore ascertained. Subjects who were not ascertained by these two approaches were ascertained by a mailed survey to the entire cohort.

The ascertainment process identified 448 subjects who potentially met the criteria for BP and psychotic disorder.

Chart 1: Ascertainment of potential cases from all sources



Ascertainment of Kaiser subjects

Subjects with potential BP (and other psychotic disorders) were identified by screening Kaiser inpatient and outpatient databases. Computerized record linkages between CHDS and Kaiser identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of Kaiser members regardless of the hospital at which treatment is received. This covered the period from 1981-2010. Those with discharge diagnoses of ICD-9 295-298 from the Kaiser inpatient database were considered as potential BP subjects. A database of outpatient treatment was introduced in 1981, but did not contain searchable codes for diagnoses until 1995. Potential BP cases from the outpatient database were considered to screen positive if they received ICD-9 diagnoses of 295-298 excluding unipolar major depressive disorder. Case ascertainment also used the Kaiser outpatient pharmacy database, which commenced in 1992. Cases screened positive based on prescriptions for mood stabilizing medications used in the treatment of BP (lithium, carbamazepine, valproic acid). Before contacting subjects who were currently enrolled in Kaiser, the subject's treating psychiatrist was contacted, informed about the study, and asked to approve contact with the subject to seek his/her consent to participate.

Any subjects identified by these methods were invited to participate in the study, receiving a letter to the most recent address, and those who did not refuse contact by returning a postcard, were contacted to arrange an appointment for a diagnostic interview. Up to several repeat appointments were scheduled for subjects who failed to attend the interview. Extensive efforts were made to locate individuals who were no longer living at the most recent listed address, including Department of Motor Vehicles records, telephone directories, and contacting the subjects' parents or siblings from CHDS or Kaiser files. Mortality records, reverse directories, jail searches, and visits to previous addresses were also used as necessary.

Ascertainment by Alameda County Behavioral Health Care Services (ABHCS)

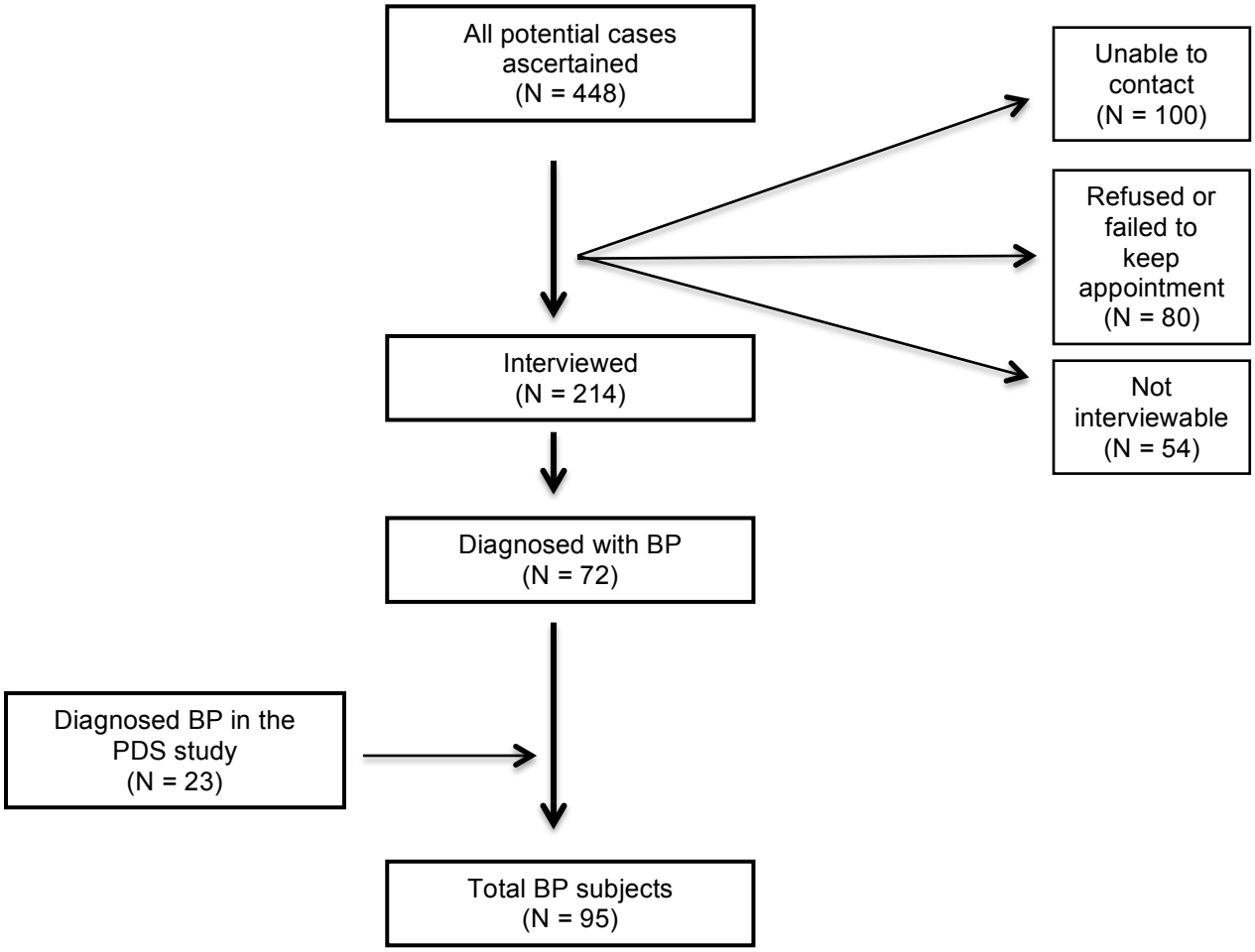
Outpatients with potential BP were also ascertained by electronic record linkage between the CHDS and ABHCS identifiers. The ABHCS database included treatment from 1993-2009. These subjects screened positive based on ICD-9 outpatient diagnoses of 295-298, excluding unipolar major depressive

disorder. Procedures for finding and recruiting these potential subjects were similar to those described above for ascertainment by Kaiser.

Ascertainment of CHDS birth cohort by mailed questionnaire and follow-up

The third method of ascertainment was initiated by letters mailed to all living mothers (N=6,971) and cohort members (N=13,009) with known addresses in the entire CHDS cohort (excluding families in which potential cases had already been identified in the Kaiser and/or ABHCS) along with a questionnaire on mental and physical health. This was conducted from 2009-11. Questionnaire respondents who reported “mental health problems” in an eligible cohort member (including the respondent him or herself) were contacted by a trained Kaiser study interviewer who administered the Family Interview for Genetic Studies (FIGS) to screen for possible BP or psychotic illness in the cohort member. If the FIGS indicated at least one bipolar and/or psychotic symptom (delusions/hallucinations), then the cohort member was considered to have screened positive, and was invited to participate in the diagnostic interview. If the respondent (mother or sibling) described symptoms in a birth cohort member, the respondent was asked if he or she would be willing to have the study contact the affected family member about participation in the study. If the respondent agreed, the affected cohort member was contacted by letter and invited to participate.

Chart 2: Ascertainment of cases



Diagnostic protocol

Accurate diagnosis of BP is critical to understanding its causes. A number of prior studies have suffered from poor diagnostic specificity of BP, grouping a number of illnesses into catch-all categories such as “affective disorders.” The current research benefits from the careful diagnostic assessment and inclusion of confirmed cases of BP.

A total of 214 subjects (48% of those ascertained) were interviewed using the Structured Clinical Interview for DSM-IV TR (SCID). The reasons that some subjects were not interviewed were: 100 could not be contacted, 80 refused or failed to keep the appointment, and 54 who could not be interviewed because he or she had died, were incarcerated, permission from the physician could not be obtained, or because the person was too psychotic or mentally disabled.

Study interviewers had a minimum of a master’s degree in a mental health field and were trained to reliability on the SCID. DSM-IV-TR diagnoses including diagnostic qualifiers representing subtypes of BP were systematically assigned by consensus of three experienced clinicians (psychiatrists/Ph.D. psychologist), based on review of the SCID and medical records. This yielded 72 BP cases. Among those interviewed, consensus diagnoses of non-BP disorders were also assigned: there were 61 cases of SZ and other schizophrenia spectrum disorders, 62 cases of major depressive disorders, and 19 cases with other diagnoses. These non-BP categories were not included in the present study. Although unipolar major depressive disorder was not included in the screening procedure, the diagnostic protocol enabled us to exclude subjects with database diagnoses of BP and/or psychotic disorders who were found instead to have unipolar depressive disorder in accord with structured research criteria.

Comparing the interviewed to those not interviewed demonstrates few differences (Table 1). Although both maternal and paternal age differ, the amount of difference in mean age is 2 years for fathers and 1 year for mothers. Similarly, gestational age differs by 4 days. These differences are likely statistically but not clinically significant. No differences exist on the exposures of interest for this study.

Table 1: Characteristics of potential case subjects interviewed and not interviewed.

Characteristics	Potential cases interviewed (N=214)	Potential cases not interviewed (N=234)	P value
Maternal age, mean years (SD)	27.7 (6.7)	26.5 (6.5)	0.055
Paternal age, mean years (SD)	32.2 (7.7)	30.1 (7.5)	0.007
Maternal race, N (%)			0.479
White	119 (55.9)	118 (51.1)	
Black	76 (35.7)	87 (37.7)	
Other	18 (8.4)	26 (11.2)	
Maternal education, N (%)			0.750
Less than high school	47 (24.2)	52 (25.2)	
High school graduate	76 (39.2)	86 (41.8)	
Some college/college graduate	71 (36.6)	68 (33.0)	
Gestational age, mean days (SD)	282.5 (17.7)	278.6 (19.5)	0.027
Any maternal psychiatric history, N (%)			0.731
Yes	21 (10.1)	25 (11.1)	
No	188 (90.0)	201 (88.9)	
Maternal smoking			0.476
Yes*	81 (46.0)	83 (42.4)	
No	95 (54.0)	113 (57.7)	
Exposure to gestational influenza			0.832
Exposed	13 (6.4)	13 (5.9)	
Unexposed	190 (93.6)	207 (94.1)	
Childhood Raven number tested (mean)	105 (-0.2)	97 (-0.11)	0.497
Childhood Peabody number tested (mean)	107 (96.68)	97 (97.79)	0.624
Induced labor			0.909
Induced	7 (3.4)	7 (3.4)	
Not induced	98 (48.0)	92 (45.1)	

*current smoking or smoked until current pregnancy

Nevertheless, as with all longitudinal studies, loss to follow-up potentially biases this study. The ascertainment process was conducted to capture as many potential cases as possible and every effort was made to locate and interview each. While few meaningful demographic differences were observed, it is not possible to calculate the extent to which bias from loss to follow-up might be having an effect or the direction of that hypothetical effect. It is important to note, however, that the prevalence of BP cases identified in this study comports with the national and international rates (Merikangas, Akiskal et al. 2007, Merikangas, Jin et al. 2011), providing some confidence that few cases have been missed. Moreover, because of the extensive contemporaneous documentation and longitudinal follow-up, information about the exposed in the full cohort makes direct assessment of potential bias in ascertainment testable. This is an important strength of this study.

Ascertainment from PDS I study

Additional cases of BP had been ascertained through Kaiser records by an earlier study (Prenatal Determinants of Schizophrenia I, PDS I) and were included in the present study (Susser, Schaefer et al. 2000). Although the purpose of PDS I was to identify SZ and other schizophrenia spectrum disorder cases, BP cases were also diagnosed by interview in that study. The protocol for the PDS I included the same electronic linkages with the Kaiser inpatient, outpatient, and pharmacy databases, and utilized the same ICD-9 diagnostic codes (295-298). Ascertainment covered the period from 1981-1998. The only other differences in the screening methods are that the PDS I did not include review of pharmacy records for treatment with mood stabilizers, and the PDS I included a second screening step, which involved psychiatrist review of abstracted data from inpatient/outpatient records for symptoms of psychosis. The Diagnostic Interview for Genetic Studies (DIGS), rather than the SCID, was used for interviewing potential subjects in the PDS I. There were 23 BP cases diagnosed in the PDS I study.

In total, then, 95 people with BP were diagnosed following ascertainment from all sources and clinical interview.

After complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Kaiser.

Control Selection

In order to ensure that controls would have been equally likely (as their matched cases) to be ascertained if they had been treated for BP in Kaiser or ABHCS, controls were matched to cases on membership in Kaiser (for cases ascertained through Kaiser records) or residence in Alameda County (for cases ascertained through ABHCS or by CHDS mailing survey) in the year the case was first treated as reported in the SCID. For Kaiser, membership in the plan at that time was used for control matching, since cohort members would have been documented in Kaiser databases if they sought care for BP. The DMV was used to ensure place of residence at the time of diagnosis for cases treated by ABHCS and those identified from the mailed survey, since these subjects would have been the population at risk for

treatment at same time. The vast majority of the subjects who received the mailing were Alameda County residents.

Control matching criteria included: date of birth (+/- 30 days), sex, and availability of maternal archived sera (for serologic studies). A maximum of an 8:1 ratio of controls to cases was achieved, as it represented the maximum number of controls that could be successfully matched to cases on all criteria and to maximize statistical power.

Exclusion criteria (prior to matching) were: all of the CHDS cohort members who screened positive for BP or psychotic disorders, but did not have BP (N=376) and siblings of cases; potential controls who belonged to Kaiser at the time of case ascertainment were excluded from the control pool for cases identified from ABHCS or the cohort mailing; and siblings of selected controls were excluded from further control selection, so that all controls were independent observations, each representing a single family or pregnant woman.

This protocol yielded 754 matched controls. As can be seen below in table 2, cases and controls differ on maternal race, with fewer white controls and more "other" controls. As expected, cases and controls differ on having a family history of psychiatric illnesses.

Table 2: Demographic comparison of cases and controls

	Bipolar Cases (N = 94)	Controls (N = 746)	P value
Maternal age at child's birth, Mean (SD)	27.3 (6)	28.0 (6)	0.32
Maternal education, N (%)			0.85
< High school	18 (21)	128 (19)	
High school graduate	32 (37)	271 (39)	
Some college or college graduate	36 (42)	293 (42)	
Maternal race, N (%)			0.07
white	64 (69)	425 (58)	
African-American	24 (26)	215 (29)	
other	5 (5)	92 (13)	
Paternal education N (%)			0.51
< High school	12 (14)	134 (20)	
High school graduate	26 (32)	192 (28)	
Some college or college graduate	44 (54)	350 (52)	
Paternal race, N (%)			0.14
white	55 (70)	387 (59)	
African-American	19 (24)	189 (29)	
other	5 (6)	79 (12)	
Maternal psychiatric history (any), N (%)	24 (25)	132 (18)	0.07
Birthweight in grams, Mean (SD)	3374 (21)	3289 (17)	0.17
Gestational age in days, Mean (SD)	281 (16)	280 (14)	0.33

The decision to exclude siblings and those who screened positive from the pool of people eligible to be controls, may have made the controls healthier than they otherwise should have been. It is unlikely that this had a significant effect because the matching process and very large birth cohort makes selection of any particular member of the cohort as a control unlikely. Not surprisingly, those who screened positive but do not have BP, differ from the controls, as can be seen in Table 3, on a number of outcomes of interest. Those who screened positive perform more poorly on cognitive testing, have lower maternal education, and are more likely to be African-American. They are also somewhat, although not statistically significantly, more likely to have been exposed to oxytocin and to gestational influenza.

Table 3: Comparing percent exposed for 376 screened positive but not BP and potential controls:

	Exposed / ascertained	Exposed / potential control	Exposed percent of total cohort	p-value
Oxytocin to induce	0.056 %	0.041 %	0.0011 %	0.15
Gestational flu	0.061 %	0.043 %	0.0012 %	0.098
Maternal race, African American	0.451 %	0.241 %	0.0078 %	0.0001
Maternal education, some college or college graduate	0.335 %	0.431 %	0.0069 %	0.0001
Raven (N = number tested)	165	6894		.0073
PPVT (N = number tested)	167	6835		.001

One way to estimate how much, or if, this mattered for the study results, is to assume that ten percent of the excluded subjects had met the matching criteria and been selected, ignoring the matching process, and assuming a simple equal probability of being selected. These assumptions overestimate the approximately six percent of the cohort who met criteria to be controls, as well as overestimating the probability that any single individual would be selected because the matching criteria limited the probability for most cohort members. Nevertheless, these assumptions are conservative in the sense of being likely to over-weight the importance of the exclusion. These assumptions would have added approximately 35 subjects to the control pool for possible selection, making the total number of controls 781.

Using the population prevalence rate of each exposure and outcome, this would add 7 people with less than high school graduation, 13 who completed high school, and fifteen with some college or a college degree; it would add 23 white, 8 African-American, and 4 people of other race/ethnicity to the controls; for oxytocin to induce labor, which has a population prevalence of 0.0415 in this birth cohort, it

would increase the number of exposed controls by 2 people; and for gestational influenza, with a population prevalence of 0.0432, it would increase the number of exposed controls by 2 people.

Because T. gondii was measured by testing of maternal sera as described below, it was not possible to calculate the population prevalence precisely for this birth cohort because only sera for cases and selected controls were analyzed. Seroprevalence of T. gondii antibody in controls was estimated at 18 percent for the selected controls in the case-control study which would add six exposed controls. Based on chi-square comparisons of these hypothetical adjustments, none of the changes in the numbers of exposed controls alters the observed effects.

Summary of background and significance

Despite being identified as distinct but related conditions, research on the antecedent risks for SZ has been more substantial than the antecedents of BP. Further investigation of BP and its putative causes, onset, and course has the potential to improve the understanding of similarities and differences between SZ and BP, and to identify mechanisms and potential etiologies, all with the aim of improving prevention and intervention. Whether BP is most appropriately considered a neurodevelopmental disorder remains debated, as does the exact nature of the onset and course of illness. Yet, the accumulating evidence tends to support the hypothesis that it is neurodevelopmental, has premorbid and prodromal phases, and likely has antecedent risks. Additional testing of this hypothesis, using more rigorous methodological designs, has the potential to advance the understanding of an illness which has significant social and personal costs, making the studies which follow a unique and significant contribution to understanding BP.

Prior studies from the CHDS birth cohort

Ideally, testing of the neurodevelopmental hypothesis of BP requires a longitudinally followed birth cohort with prenatally and perinatally obtained evidence of potential risks, as well as continual follow-up testing during the developmental period and confirmed diagnosis in adulthood. Few, if any, prior studies have had such complete data available. The CHDS was an NIH-sponsored study of nearly 20,000 pregnancies in women enrolled in the Northern California Region of the Kaiser Permanente Medical Care Plan (van den Berg 1979). Pregnancy, labor and delivery, and child development data were obtained

prospectively. In addition, prenatal maternal serum specimens were obtained during each trimester and stored frozen for later use. The relationship between elevated T. gondii IgG antibody titer and risk for SZ was examined previously in the CHDS (Brown, Schaefer et al. 2005). That study ascertained cases from computerized records, chart review, and diagnostic interview, similar to the method used in this study. Maternal sera were assayed using the same technique as well. Seventy-one case subjects were identified and controls were matched on availability of sera, date of birth, and enrollment in the health plan. Controlling for maternal age, the only covariate found to potentially confound the association, the adjusted odds ratio for SZ for those with a high IgG titer compared to the reference group (reference group: IgG titer <1:16) was 2.61 (95% CI: 1.00, 6.82, p=.051). There was no association between moderate IgG antibody titer and risk of SZ (Brown, Schaefer et al. 2005).

A comprehensive neuropsychological assessment was administered to subjects identified as having developed SZ in the CHDS and who were recruited into the Developmental Insult and Brain Anomaly in Schizophrenia Study (DIBS). The DIBS investigated early developmental risks for later cognitive impairment in SZ. A total of 50 subjects were administered the comprehensive neuropsychological battery (Brown, Vinogradov et al. 2009). Maternal infection, including T. gondii, was found to be associated with impaired adult cognitive performance, specifically with measures of executive functioning (Brown, Vinogradov et al. 2009). This study suggests a relationship between prenatal infection and cognitive impairment observed in adults with SZ. The DIBS neuropsychological testing was also analyzed in a trajectory model, using the CHDS Peabody Picture Vocabulary Test (PPVT) administered at ages 5 and 9-11 to examine the course of cognitive functioning over 33 years. This study found a ten point difference in the early childhood PPVT, with those who would later develop SZ performing more poorly than the matched controls. In adulthood, the gap in performance was wider, with those who had developed SZ scoring 15 points below the controls (Kremen, Vinogradov et al. 2010). This study supports the utility of examining the early childhood test battery administered in the CHDS with later development of psychiatric illnesses.

Birth complications, while extensively studied, have not been examined in the CHDS in relation to SZ or BP, or as antecedents to childhood neurocognitive deficits.

Previous studies in the Prenatal Factors and Bipolar Study (PFB)

The proposed study uses data obtained in the NIH-sponsored PFB. Previously, a number of findings have been published utilizing this study. First, gestational exposure to clinically diagnosed maternal influenza has been shown to raise the risk of offspring BP by nearly fourfold, and nearly sixfold for BP with psychotic features (Parboosing, Bao et al. 2013). In addition, using maternal serum drawn during pregnancy to directly quantify maternal influenza, the association between gestational influenza and later life BP with psychotic features was fivefold and the association with BP without psychotic features was non-significant (Canetta, Bao et al. 2014). This result is similar to the findings in the CHDS cohort that maternal influenza during the first half of pregnancy increases the risk of SZ by a factor of three (Brown, Begg et al. 2004).

Paternal age has also been found to increase the risk for SZ, including in the CHDS (Brown, Schaefer et al. 2002). A study in the PFB found no increased risk for BP associated with paternal age, controlling for maternal age (Brown, Bao et al. 2013). Treating paternal age as a continuous variable, no association was observed with BP (OR=1.00, 95% CI=0.97-1.04, p=0.83), and this did not meaningfully change when controlling for maternal age (OR=1.03, 95% CI=0.98-1.08, p=0.29). One prior study found maternal age associated with an increased risk of BP, although it became attenuated when controlling for paternal age (Menezes, Lewis et al. 2010). This was also tested in the PFB. Again, no association was observed between maternal age and BP (OR=0.98, 95% CI=0.95-1.02, p=0.31), and controlling for paternal age did not alter this result (OR=0.96, 95% CI=0.90-1.02, p=0.16).

Finally, maternal smoking was also analyzed in the PFB for its potential association with BP (Talati, Bao et al. 2013). Smoking during pregnancy was associated with a twofold increased risk for BP for offspring (OR=2.03; 95% CI 1.20-3.45; *p*= 0.01), and this finding was essentially unchanged when adjusting for a number of potential confounders, including maternal history of psychiatric illness, maternal alcohol use during pregnancy, and offspring birth weight.

Conclusion

What follows are three papers. First, I present a systematic literature review of the neurodevelopmental hypothesis of BP. This review focuses on three developmental time points: prenatal and perinatal exposures, premorbid and prodromal symptom development, and neurocognitive functioning prior to onset. The second paper focuses on two specific putative prenatal and perinatal risk factors for BP: T. gondii and oxytocin to induce labor. The third paper assesses cognition, using both the BP case-control study and the full CHDS cohort to assess risks for BP and the potential that cognitive impairment reflects a mediator or endophenotype of later BP.

These studies aim to add to the growing literature on the risks and mechanisms in early life that may be associated with later BP, expanding the understanding of when and why divergences from typical developmental course occur in BP, if they do. As with any small set of studies, they will not fully answer the question of whether BP should be thought of as a neurodevelopmental illness. Negative findings do not rule out the possibility of early life divergences, just as positive findings are not enough to opine that the divergences are causal of later life BP. Nevertheless, treatment interventions to shift the course of illness, and prevention of illness, may all be better informed and targeted, even if incrementally, based on the elucidation of specific risks and mechanisms for later life BP, and that is the aim of these studies.

Paper 1: Systematic literature review of the neurodevelopmental origins of bipolar disorder

The neurodevelopmental hypothesis posits that altered, pathological, or delayed maturation of the developing brain, long before the manifestation of disease, shifts the neurodevelopmental trajectory, followed by later life onset of psychiatric illness (Oneal and Robins 1958, Fish, Shapiro et al. 1965, Nasrallah and Weinberger 1986, Murray and Lewis 1987, Meyer and Feldon 2010, Catts, Fung et al. 2013, Millan 2013). Determining whether BP is best conceptualized as a neurodevelopmental illness has implications for prevention, identification, and treatment. The neurodevelopmental approach holds promise for better outcomes not simply because it searches for the causes and mechanisms which result in illness, but also because it proposes an understanding of the disease course. Writing about SZ, Insel recently suggested that the neurodevelopmental approach identifies stages of disease progression, each of which may offer specific types of intervention and prevention (Insel 2010). Delays in treatment, misdiagnosis, certain treatments (such as antidepressants which may worsen the course of BP), and a high risk of suicide during early phases of the illness, are each worsened by delays in illness identification (Howes and Falkenberg 2011). If the neurodevelopmental hypothesis is supported, it suggests that earlier identification and intervention may be possible, targeting the specific points of disease progression prior to onset.

Determining whether BP is a neurodevelopmental disease necessarily requires rigorously identifying and differentiating its symptoms from related or similar conditions. BP is characterized by significant changes in mood, and defined by (hypo)mania interspersed with major depressive episodes (Goodwin, Jamison et al. 2007). Manic episodes are distinct periods of abnormal and persistent elevated, expansive, or irritable moods. The symptoms of mania may include: grandiosity, irritability, paranoia, racing thoughts, greater energy, decreased need for sleep, pressured and excessive speech, thought disorder, distractibility, and impulsivity (Goodwin, Jamison et al. 2007). Major depressive episodes in BP are similar to those in unipolar affective disorder, marked by alterations of mood, cognition, and behavior. Suicide attempts are common in BP (Jamison 2000). These mood alterations disrupt social and occupational functioning, and frequently necessitate hospitalization. BP is associated with a substantial burden for patients, family members, and society, being the sixth-leading cause of time lost to disability or death (Simon 2003).

International studies suggest that the mean pooled prevalence of BP for six to twelve months is approximately .8%, with significant regional differences (Ferrari, Baxter et al. 2011). Lifetime prevalence in the United States is estimated at 1.0% for BP I and 1.1% for BP II (Merikangas, Akiskal et al. 2007). The onset is typically in the late teens to early twenties (Goodwin, Anderson et al. 2008), although some studies have found a second age period of increased occurrence between ages 45 and 54 (Kroon, Wohlfarth et al. 2013). Most people with BP experience more than one episode, with the average duration of manic and depressive episodes ranging from 4 to 13 months (Goodwin, Jamison et al. 2007).

To investigate the strengths and weaknesses of the neurodevelopmental hypothesis of BP, a systematic literature was undertaken. This systematic literature review examines whether BP should be considered a neurodevelopmental disease similar to how SZ is predominantly viewed. Priority was given to papers which use epidemiological approaches, with preference given to population based studies. Inclusion criteria were that the paper was written in English and that diagnostic criteria were clearly defined. Particular focus has been given to the prenatal and perinatal exposures which have been suggested to be associated with psychotic disorders, as well as the measures of cognitive and behavioral abilities across time.

Searches were conducted in PubMed and Web of Knowledge databases for papers which address the neurodevelopmental hypothesis of BP using search terms related to BP. In combination and singly, the searched terms included: bipolar disorder, neurodevelopment, manic depress*, psychosis, affective disorder, neuropsych*, cognition, trajectory, prenatal, perinatal, obstetric complication, prodrome, and premorbid. This produced 2,414 titles, and following deletion of duplicates and review of titles and abstracts, 386 papers were considered for inclusion. Additional abstracts were reviewed after identification of papers from the reviews and some additional search terms (e.g., oxytocin, T. gondii, influenza, parental age, famine, clinical high risk) were hand-searched to check for studies which might have been missed. Fifty-seven population based studies were included, with additional reviews, meta-analyses, patient and clinical studies reviewed for specific questions which arose from, or are unanswered by, the population based studies.

This review considers four areas relevant to the neurodevelopmental hypothesis: prenatal and perinatal risks; whether symptoms mark a distinct period of premorbid and prodromal functioning; whether

those at high risk and first episode have diagnostically specific symptoms; and whether cognitive processes differ from people without BP.

Overview of literature review

In recent years, a great deal of attention has focused on the question of whether or not BP is neurodevelopmental, prompting many meta-analyses and reviews focused on potential prenatal, perinatal, cognitive, genetic, molecular, and epigenetic roots of BP (Torrey, Miller et al. 1997, Buka and Fan 1999, Quraishi and Frangou 2002, Tsuchiya, Byrne et al. 2003, Murray, Sham et al. 2004, Krabbendam, Arts et al. 2005, Daban, Martinez-Aran et al. 2006, Robinson and Ferrier 2006, Scott, McNeill et al. 2006, Torres, Boudreau et al. 2007, Arts, Jabben et al. 2008, Goodwin, Martinez-Aran et al. 2008, Bora, Yucel et al. 2009, Kurtz and Gerraty 2009, Tenyi, Trixler et al. 2009, Bora, Yucel et al. 2010, Bora, Yucel et al. 2010, Pukrop and Klosterkotter 2010, Skjelstad, Malt et al. 2010, Beblo, Sinnamon et al. 2011, Bora, Yucel et al. 2011, Howes and Falkenberg 2011, Howes, Lim et al. 2011, Lewandowski, Cohen et al. 2011, Mann-Wrobel, Carreno et al. 2011, Sole, Martinez-Aran et al. 2011, Brietzke, Mansur et al. 2012, Depp, Mausbach et al. 2012, Fusar-Poli, Deste et al. 2012, Fusar-Poli, Howes et al. 2012, Gigante, Bond et al. 2012, Arango, Fraguas et al. 2013, Bourne, Aydemir et al. 2013, Lim, Baldessarini et al. 2013, Martin and Smith 2013, Narayan, Allen et al. 2013, Noto, de Souza Noto et al. 2013, Olvet, Burdick et al. 2013, Samame, Martino et al. 2013). These reviews and meta-analyses are discussed below.

Many of these reviews include studies with disparate diagnostic or outcome criteria, small samples, and methodological limitations. As is often the case, many of the studies of putative risks for BP are cross-sectional or patient derived samples. Yet, a number of population based studies have been conducted as well (Gershon, Hamovit et al. 1987, Lasch, Weissman et al. 1990, Brown, Susser et al. 1995, Machon, Mednick et al. 1997, vanOs, Jones et al. 1997, Hultman, Sparen et al. 1999, Brown, van Os et al. 2000, Jones and Tarrant 2000, Cannon, Caspi et al. 2002, Reichenberg, Weiser et al. 2002, Mortensen, Pedersen et al. 2003, Zammit, Allebeck et al. 2004, Tiihonen, Haukka et al. 2005, Pedersen and Mortensen 2006, Laursen, Munk-Olsen et al. 2007, Osler, Andersen et al. 2007, David, Zammit et al. 2008, Kravariti, Reichenberg et al. 2009, Khashan, McNamee et al. 2011, Mortensen, Pedersen et al.

2011, Jansen, Magalhaes et al. 2012, Sorensen, Saebye et al. 2012, Class, Abel et al. 2013, Haukvik, McNeil et al. 2013, Seidman, Cherkerzian et al. 2013). These studies are also discussed below.

Review of the neurodevelopmental hypothesis for BP

Historically, BP has been thought to be related closely to SZ, as noted above, and as the neurodevelopmental hypothesis of SZ has become increasingly accepted, a similar hypothesis has been applied to BP. For instance, a study focused on early identification and treatment of SZ suggested four areas in which to asses risk of SZ based on literature reviews: cognitive deficits, affective disturbance, school failure, and social isolation (Cornblatt, Lencz et al. 2003). Whether these same areas of risk would be observed in BP, or whether a different set of risks during the developmental period should be considered, are analyzed based on a systematic literature review on the putative developmental origins of BP.

BP and SZ are similar in a number of ways, and are frequently hypothesized to be related across numerous causes and phenotypic symptoms (Murray, Sham et al. 2004, Demjaha, MacCabe et al. 2012, Hall, Smoller et al. 2012). These similarities may suggest that both conditions are neurodevelopmental, particularly because the evidence supporting the neurodevelopmental hypothesis of SZ is strong. As recent research suggests, the symptom overlap between BP and SZ is quite high and the conditions can be difficult to differentiate (Tamminga, Ivleva et al. 2013).

First, the age of onset and population prevalence are quite similar (Kessler, Berglund et al. 2005), and the premorbid and prodromal periods are often marked by significant neurodevelopmental and clinical symptoms (Sanches, Keshavan et al. 2008, Skjelstad, Malt et al. 2010, Howes, Lim et al. 2011). Similarly, cognitive impairment is observed premorbidly in both illnesses (Tiihonen, Haukka et al. 2005, Goodwin, Martinez-Aran et al. 2008, Hill, Harris et al. 2008, Urfer-Parnas, Mortensen et al. 2010, Sorensen, Saebye et al. 2012). These impairments have been documented in the prodrome (Olvet, Stearns et al. 2010), as well as at first episode psychosis (Hill, Reilly et al. 2009, Zanelli, Reichenberg et al. 2010, Dickerson, Stallings et al. 2011), and during the course of the illness (Quraishi and Frangou 2002, Bearden, Woogen et al. 2010), although likely in different domains and with lesser severity in BP than in SZ (Seidman, Cherkerzian et al. 2013).

Second, these disorders share a number of important symptoms, with mood symptoms common in SZ (Hausmann and Fleischhacker 2002, Siris 2005) and psychotic symptoms common in BP (Ohayon and Schatzberg 2002, Merikangas and Lamers 2012). Third, and perhaps related to, or resulting from, the overlap in symptomatology, familial aggregation between SZ spectrum disorders and BP has been observed (Van Snellenberg and de Candia 2009, Dean, Stevens et al. 2010). The illnesses share common genetic risks (Bramon and Sham 2001, Lichtenstein, Yip et al. 2009, Gejman, Sanders et al. 2011), and have some similar abnormalities in grey and white matter brain structures (Pol, van Baal et al. 2012). Offspring of a parent with SZ or schizoaffective disorder are at a substantially increased risk for BP (Mortensen, Pedersen et al. 2003), and offspring of a person with BP, at an increased risk of SZ (Van Snellenberg and de Candia 2009, Dean, Stevens et al. 2010). Finally, treatment with antipsychotic medications can be effective for both conditions (Brugue and Vieta 2007, Lieberman 2007, Lieberman and Stroup 2011).

Neurodevelopmental hypothesis of BP

Four major areas of evidence which are often cited to support the neurodevelopmental hypothesis of psychiatric illness are reviewed: prenatal and perinatal risks for later illness, prodromal phase symptoms of illness, first episode and onset symptoms of illness, and neurocognitive markers of illness.

Prenatal and perinatal risks for BP

Population based studies which examine specific, rather than global or aggregated, prenatal and perinatal exposures, suggest significantly increased risks for BP (see Table 4). Gestational exposure to clinically diagnosed maternal influenza has been shown to raise the risk of offspring BP by nearly fourfold, and nearly sixfold for BP with psychotic features (Parboosing, Bao et al. 2013). In addition, using maternal serum drawn during pregnancy to directly quantify maternal influenza, the association between gestational influenza and later life BP with psychotic features was fivefold and the association with BP without psychotic features was non-significant (Canetta, Bao et al. 2014). Assessing affective disorder more generally, Sacker et al found an increased risk of illness in a population based birth cohort (N = 32),

based on maternal self-report of influenza during pregnancy (Sacker, Done et al. 1995), as did Machon et al in a population based ecological study of Helsinki births during an influenza epidemic (Machon, Mednick et al. 1997). This association was also observed in the CHDS birth cohort study of SZ,

Table 4: Specific prenatal and perinatal population based studies of BP risk

Author/year	Sample size (N)	Study type	Specific prenatal or perinatal risk	Results	Significance
Sacker et al (1995)	32 Affective disorder	British births during March 3-9, 1958, registry based	Gestational influenza: maternal report	Increased risk of Affective disorder	Maternal self-report
Machon et al 1997)	19 Affective disorder	Helsinki births during 1957 influenza epidemic, registry based	Gestational influenza: ecological exposure	Increased risk of Affective disorder with 2nd semester exposure to influenza compared to controls	Ecological support for a second trimester effect of influenza
Parboosing et al (2013)	92 BP, 722 controls	Population based birth cohort, nested case-control	Gestational influenza: medical record based	Increased risk of BP from gestational influenza exposure at any time during pregnancy fourfold increase in risk of BD (OR = 3.82; CI: 1.58, 9.24); and an almost 6 times increased risk of BP with psychotic features (OR = 5.74; CI: 1.52, 21.7)	All trimester exposures increase risk
Canetta et al (2014)	85 BP, 170 controls	Population based birth cohort, nested case-control	Gestational influenza: maternal sera based	Increased risk of BP with psychotic features (OR = 5.03; CI: 1.38, 18.38), but not with BP (OR = 1.26; CI: 0.65, 2.44)	Association with BP with psychotic features
Talati et al (2013)	79 BP, 654 controls	Population based birth cohort, nested case-control	Gestational exposure to maternal smoking	Increased risk of BP associated with maternal smoking during pregnancy (OR = 2.03; CI: 1.20, 3.45)	Maternal smoking assessed prospectively at time of pregnancy
Done et al (1991)	10 BP	British population based study, births March 3-9, 1958	Preterm birth or small for gestational age	Increased risk of Affective disorder for shorter gestational time	10 BP cases not analyzed, risk is for 32 Affective disorder cases
Laursen et al (2007)	814 BP	Danish population based study, registry based	Preterm birth or small for gestational age	Increased risk of BP 5.32 times (CI: 2.75, 10.72) for smallest 10% before week 37	Results adjusted for age, calendar time, sex, family psychiatric history, maternal age
Nosarti et al (2012)	217 BP Affective	Swedish population based study, registry based, births 1973-85	Preterm birth or small for gestational age	Increased risk of BP 2.7 times (CI: 1.6, 4.5); for those born 32-6 weeks. 7.4 times (CI: 2.7, 20.6) for less than 32 weeks	Results adjusted for Apgar score, birthweight, sex, parity, maternal age and education, family psychiatric history
D'Onofrio et al (2013)	N for BP not reported; 3,300,708 births	Swedish population based study, registry based, births 1973-2008	Preterm birth or small for gestational age	Increased risk of BP/psychotic disorders for continuous measure of earlier preterm birth	Linear relationship: as number of weeks in utero increased, risk decreased
Disanto et al (2012)	14,569 BP, 3545 Parkinson's patient controls	British hospital data, retrospective patient study	Season of birth	Increased risk of BP for those born in January	
Brown et al (1995)	122 Affective disorder	Dutch population based study, registry based, births 1944-6	Gestational exposure to extreme famine	Increased risk of BP for those exposed in 2nd trimester (RR = 1.62; CI: 1.19, 2.20)	Ecological study of famine exposure
Brown et al (2000)	224 Affective disorder; 84	Dutch population based study, registry based, births	Gestational exposure to extreme famine	Increased risk of BP for those exposed 2nd trimester (RR = 1.5; CI:	Confirmed and expanded 1995 study of effect of famine

	BP	1944-6		1.19, 1.9); those exposed 3rd trimester (RR = 1.45; CI: 1.7, 1.81)	exposure
Kleinhaus et al (2013)	120 BP	Jerusalem birth cohort, registry based	Gestational exposure to maternal stress: war	Increased risk of BP during first trimester war exposure (RR = 2.44; CI: 0.996, 5.99)	Women pregnant during war-time
Khashan et al (2011)	13,699 Affective disorder,16 BP	Danish population based study, registry based, births 1978-97	Gestational exposure to maternal stress: death of close relative during pregnancy	Increased risk of Affective disorder for male offspring following death of close relative during 2nd trimester (OR = 1.74; CI: 1.06, 2.84)	Effect only on male offspring; BP not analyzed, determined to be too rare
Class et al (2013)	8001 BP	Swedish population based study, registry based, births 1973-2008	Preconception, gestational, postnatal exposure to maternal stress: death of close relative	No effect on risk of BP	73 offspring affected by maternal loss of relative
Mortensen et al 2003)	2299 BP	Danish population based study, registry based	Loss of a parent during childhood	Increased risk of BP 13.6 times (CI: 11.81, 15.71) for first degree relative; maternal loss OR = 4.05 (CI: 1.68, 9.77)	
Tsuchiya et al (2005)	947 BP, 47,350 controls	Danish population based study, registry based, born 1960 or later	Loss of a parent during childhood	Increased risk of BP for parental suicide; paternal suicide OR = 1.83 (CI: 1.07, 3.12); maternal suicide OR = 3.44 (CI: 1.97, 6.0)	Maternal suicide remains significant through age 38; paternal suicide is not significant by age after controlling for covariates
Appel et al (2013)	555 BP	Danish population based study, registry based, births 1970-90	Loss of a parent during childhood	Increased risk of BP when loss is due to suicide: male offspring HR = 2.0 (CI: 1.18, 3.39); female offspring HR = 2.44 (CI: 1.56, 3.83)	Adjusted for age, cohort period, family psychiatric history
Clarke et al (2013)	165 BP	Helsinki births 1960-90	Loss of a parent during childhood	Increased risk of BP following loss father or sibling before age 5: OR = 1.6 (CI: 1.1, 2.5)	Adjusted for age, sex, family psychiatric history
Ogendahl et al (2006)	196 BP, controls matched 1:25 on time, age, sex	Danish population based study, births 1973-83, registry based	Low birth weight	Birthweight, birth length, parity, gestational age are not associated with BP	
Mortensen et al (2011)	127 BP, controls matched on sex, day of birth	Danish population based study, registry based	Maternal viral infection	HSV1, HSV2, T. gondii, CMV are not associated with BP	Neonatal dried blood spot
Zornberg et al (2000)	10 BP	19 year follow-up of community sample	Hypoxia-ischemia	Fetal hypoxic ischemia is not significantly associated with BP	
Haukvik et al (2013)	79 BP, 140 controls	Norway population, registry based	Hypoxia-ischemia	History of perinatal asphyxia is associated with smaller left amygdala in people with BP	Structural brain change
van Os et al (1997)	270 Affective disorder	British birth cohort, births March 3 to 9, 1946	Delayed motor milestones	Increased twitching and grimacing at age 15, speech defects, and cognitive impairment age 8, 11, and 15	
Frans et al (2008)	13,428 BP, controls matched 1:5 on sex and year of birth	Swiss population based nested case-control, registry based	Paternal age	ñ risk of BP for offspring of men 55 and older compared to men 20-24 (OR = 1.37; CI: 1.02, 1.84)	

Menezes et al (2010)	493 BP	Sweden population based study, births 1973-80, registry based	Parental age	Increased risk of BP for each 10 years increase in paternal age (HR = 1.28; CI: 1.11, 1.48); However, when controlling maternal age, finding is not significant. Maternal age was not associated with BP controlling for paternal age	Controlling for spouses age makes paternal and maternal age non-significantly associated with BP
Buizer-Voskamp et al (2011)	1121 BP, 4484 controls	Dutch population based study, registry based	Parental age	Paternal age is not significantly associated with BP	
Brown et al (2013)	94 BP, 746 controls	US Population based birth cohort, nested case-control	Parental age	Paternal age is not associated with BP (OR=1.03; CI: 0.98, 1.08) adjusted for maternal age. Maternal age is not associated with BP (OR = 0.96; CI: 0.90, 1.02) adjusting for paternal age	
Sacker et al (1995)	32 Affective disorder	British births during March 3-9, 1958, registry based	Parental age	Increased risk of Affective disorder for mothers older than 35 OR: 2.29 (CI 1.19, 4.39)	

finding that maternal influenza during the first half of pregnancy increased the risk of SZ by a factor of three (Brown, Begg et al. 2004).

Additionally, maternal smoking during pregnancy (Talati, Bao et al. 2013); delayed motor milestones (van Os, Jones et al. 1997); being born preterm or small for gestational age, with a likely dose-response effect such that early birth is associated with higher risk (Done, Johnstone et al. 1991, Laursen, Munk-Olsen et al. 2007, Nosarti, Reichenberg et al. 2012, D'Onofrio, Class et al. 2013); season of birth (Torrey, Miller et al. 1997, Tsuchiya, Byrne et al. 2003, Disanto, Morahan et al. 2012); in utero exposure to severe famine (Brown, Susser et al. 1995, Brown, van Os et al. 2000); in utero exposure to acute war-related maternal stress (Kleinhaus, Harlap et al. 2013); and the death of a parent between gestation and age 17, although possibly only when the death is by suicide (Agid, Shapira et al. 1999, Mortensen, Pedersen et al. 2003, Tsuchiya, Agerbo et al. 2005, Khashan, McNamee et al. 2011, Appel, Johansen et al. 2013, Clarke, Tanskanen et al. 2013); are each associated with a significantly increased risk of BP.

However, being small for gestational age or having lower birth weight at birth are not reported to be associated with increased risk of BP (Ogendahl, Agerbo et al. 2006, Laursen, Munk-Olsen et al. 2007). Regarding maternal viral exposures, Mortensen et al analyzed neonatal dried blood spots in a population based study of 127 adults diagnosed with BP and controls matched on date of birth and sex to assess

whether viral infection increased the risk of later BP. For herpes simplex, cytomegalovirus, and T. gondii, each of which have previously been associated with SZ, they found no association with later BP (Mortensen, Pedersen et al. 2011). Similarly, hypoxia-ischemia appears not to increase the risk for BP, although it does for SZ, but this negative finding may reflect the small sample size which included only 10 cases of BP (Zornberg, Buka et al. 2000), and another study found structural brain changes in adults with BP who had been exposed to prenatal and perinatal hypoxia (Haukvik, McNeil et al. 2013). A related issue is noted in a review of minor physical anomalies and risk for BP, in which the most commonly used measure of physical anomalies is said to poorly capture those conditions which are related to BP, resulting in a finding of no association (Tenyi, Trixler et al. 2009); but using a modified assessment, which re-categorized the shape of ear lobes and differentiated types of tongue furrow compared to the traditional scale, physical anomalies had a significant association with later BP (Akabaliev, Sivkov et al. 2011, Sivkov, Akabaliev et al. 2013). However, no population based, prospective studies have reported on minor physical anomalies and BP.

Evidence on parental age and BP is mixed, with some population based studies finding an increased risk (Frans, Sandin et al. 2008, Menezes, Lewis et al. 2010), but others finding no association (Buizer-Voskamp, Laan et al. 2011, Brown, Bao et al. 2013). The nested case-control study of BP in the CHDS birth cohort found no increased risk for BP associated with paternal age, controlling for maternal age (Brown, Bao et al. 2013). Treating paternal age as a continuous variable, no association was observed with BP (OR=1.00, 95% CI=0.97-1.04, p=0.83), and this did not meaningfully change when controlling for maternal age (OR=1.03, 95% CI=0.98-1.08, p=0.29). A prior study found maternal age associated with an increased risk of BP, although it became attenuated when controlling for paternal age (Menezes, Lewis et al. 2010). This was also tested in the nested case-control drawn from the CHDS. Again, no association was observed between maternal age and BP (OR=0.98, 95% CI=0.95-1.02, p=0.31), and controlling for paternal age did not alter this result (OR=0.96, 95% CI=0.90-1.02, p=0.16).

In summary, it does appear from the available research that a number of specific prenatal and perinatal exposures are associated with an increased risk of BP. It also appears that a number of exposures which have been associated with SZ are not also associated with BP. However, many of the putative risks have been tested with small samples and are underpowered to find significant association

with BP. Thus, for many prenatal and perinatal risks, insufficient evidence exists to determine whether or not specific prenatal and perinatal exposures increase the risk of BP (Tsuchiya, Byrne et al. 2003, Scott, McNeill et al. 2006, Sanches, Keshavan et al. 2008). In addition to small sample sizes, inferences are made more difficult by inclusion criteria for birth and pregnancy complications that differ from study to study. Finally, the varying diagnostic criteria which often aggregates a number of types of affective disorders and diagnoses as outcomes makes determining what condition is being caused by obstetric complication or physical anomaly more difficult to parse (Sanches, Keshavan et al. 2008).

Despite these problems and the need for further research, it does appear that some prenatal and perinatal exposures significantly increase the risk for later onset BP. These findings lend support to the neurodevelopmental hypothesis of BP.

Is there a BP prodrome?

Second, as in SZ, premorbid and prodromal symptoms have been identified in those who later developed BP. Evidence of identifiable, and preferably specific, symptom clusters during the premorbid and prodromal phases of BP would lend support to the neurodevelopmental hypothesis. In a prospective, population based study, Cannon et al reported a number of premorbid symptoms in people who later had a manic episode (Cannon, Caspi et al. 2002). This included social isolation, peer rejection, internalizing, and externalizing problems between the ages of 5 and 11, but no deficits in motor development or cognitive performance between the ages of 3 and 11. Some of these findings were not statistically significant, possibly due to the small sample size (n = 20), and a later study of this cohort reported only 8 subjects met criteria for BP (Koenen, Moffitt et al. 2009). This problem of small sample sizes is common in studies of premorbid and prodromal BP, especially population based or prospective studies (Sanches, Keshavan et al. 2008, Howes, Lim et al. 2011).

In a large prospective cohort study of patients recruited into a mood disorder study, and followed for an average of more than 17 years, approximately twenty percent of subjects originally enrolled converted from depression to BP. Those who converted to BP had a younger age of onset of mood symptoms, had a higher number of subthreshold hypomanic symptoms, and a family history of BP (Fiedorowicz, Endicott et al. 2011). This is similar to Akiskal et al's study patients with major depression,

Table 5: Prospective studies of BP Prodrome symptoms

Author/ year	Sample size (N)	Study type	Specific prodromal symptoms	Results	Significance
Akiskal et al (1995)	22 BP 1; 48 BP II	Prospective depression patient cohort, 11 years of follow-up	Risks for conversion from MDD to BP	Those who converted had significantly more episodes and more severe index episodes; worse GAF scores; and worse physician rated anxiety, concentration, and social withdrawal, as well as more delusional and hallucinations	Patients with depression who converted to BP over five years functioned worse and had greater numbers of symptoms
Cannon et al (2002)	20 BP	Prospective birth cohort, 26 year old follow-up	Motor Social isolation Peer rejection Language IQ	Early childhood (through age 11) significantly impaired in social isolation, peer rejection, some language impairment	Early childhood marked by social rejection and isolation
Koenen et al (2009)	8 BP	Prospective birth cohort, 32 year old follow-up	Childhood IQ	Significantly increased IQ at age 11 (OR = 3.1: CI: 1.18, 8.19)	All 8 subjects had average or higher IQ scores at age 11
Angst et al (2003)	86 BP, 261 controls	Prospective, representative community cohort study with 15 years of follow-up	Social characteristics, family history, mood	BP had frequent mood ups and downs (OR = 14.33; CI: 4.94, 41.59); family history of mania (OR = 6.81; CI: 1.95, 23.82); emotional lability or vegetative state (OR = 3.34; CI: 1.67, 6.66)	Mood lability and family history are significant prodromal factors; social characteristics had no predictive value
Meyer et al (2004)	9 BP	Prospective community study with 23 years of follow-up; participants are offspring of mother with unipolar depression, bipolar, or no history of psychiatric illness	Developmental and cognitive prodromal symptoms	GAF score lower in BP compared to no diagnosis group; IQ at ages 8-15 lower for BP; attentional, behavioral, and depressive symptoms more common for BP; impaired executive functioning	More symptoms during prodrome and worse cognitive performance and functioning
Beesdo et al (2009)	84 with manic episode; 115 with hypomanic episode	Prospective, representative community based cohort, 10 years follow-up	Incidence Risks at baseline which predict illness later in life	Although hypomanic, manic, and depression symptoms were common in the prodrome, conversion to BP was very low	Study is underpowered to predict BP
Tijssen et al (2010)	21 hypo (manic)	Prospective, community cohort, 10 years follow-up	Symptom persistence over time; number of symptoms	Increased persistence and number of symptoms was associated with BP	Many youth have some hypomanic symptoms which do not persist
Fiedorowicz et al (2011)	108 BP	Prospective, patients with mood disorders; mean follow-up of 17.5 years	550 mood disorder patients recruited and followed for conversion to BP	Hypomanic symptoms are associated with conversion to BP; family history of mania or hypomania increased risk; endorsing more symptoms at baseline increased risk (HR = 1.24; CI: 1.09, 1.41); psychosis at intake predicted conversion and time to conversion	Large observational study of patients with depression and risk of conversion to BP
Thompson et al (2003)	3 BP	Prospective case study of high risk for psychosis clinic patients, 1 year follow-up	Prodromal symptoms	Depression symptoms at presentation; anxiety, racing thoughts, and mood swings	Prospective observation of prodromal symptoms
Blechert et al (2005)	29 hypomanic	Community (school) based population study, 2 year	Prodromal personality	Hypomania high risk group significantly more likely to develop hypomania	Pre-onset hypomanic symptoms observed

		follow-up using SCID			
McCabe et al (2010)	280 BP	Swedish population based study, registry based	School performance, school grades at age 16	Low and high grades associated with BP; 2 standard deviation units below mean: HR = 1.96 (CI: 1.07, 3.56); 2 standard deviation units above mean: HR = 3.34 (CI: 1.82, 6.11)	U shaped increased risk based on school grades at age 16
Vonk et al (2012)	53 BP twin pairs; 42 healthy twin pairs	Dutch registry identification of case status and twin status	School performance, underperforming defined as: repeating a grade; special education; moved down to lower level of education	Affected twins completed fewer years of school and underperformed during schooling	School success is impaired during prodrome

which found that those who converted to BP had significantly more episodes and more severe index episodes; worse GAF scores; and worse physician rated anxiety, concentration, and social withdrawal, as well as more delusional and hallucinations (Akiskal, Maser et al. 1995).

A number of prospective, population based studies have explored what symptoms and characteristics might define the premorbid and prodromal periods of BP (Table 5). In summary, these studies find symptoms and behavioral markers, but few that are specific (Blechert and Meyer 2005, Beesdo, Hoefler et al. 2009, Olvet, Stearns et al. 2010, Tijssen, van Os et al. 2010, Schultze-Lutter, Schimmelmann et al. 2012, Ratheesh, Lin et al. 2013). The evidence that a prodrome exists is fairly strong, but whether it can be recognized prospectively remains in doubt. This is more true when the question is whether symptoms exist prior to onset, less so when the question is specificity and prediction of later onset BP. Hypomania, depression, mood lability, social isolation and withdrawal, and increased persistence of these symptoms have been found to define the premorbid and prodromal periods of later BP. Although non-specific, these symptoms and impairments denote the premorbid and prodromal periods, supporting the neurodevelopmental hypothesis.

This conclusion is consistent with other recent reviews which rely more on patient and retrospective studies (Conus, Ward et al. 2008, Skjelstad, Malt et al. 2010, Howes, Lim et al. 2011). Howes et al conclude that the fluctuating, cyclic nature of BP makes the identification of specific symptom clusters which might mark the prodrome, difficult. However, they suggest three stages of the prodrome based on their review: a cyclothymic, manic or hypomanic phase; followed by a worsening of symptoms phase possibly triggered by life events; and finally, a first manic episode (Howes, Lim et al. 2011). Two

studies are noted to have provided data to calculate specificity of symptoms in the prodromal phase, with many symptoms having high specificity, yet one of those two was a small sample of pediatric BP subjects with parental report of symptoms (Rucklidge 2008), the other reported only mood lability in a longitudinally followed community sample, with a specificity of 89 percent (Angst, Gamma et al. 2003). Skjelstad et al reviewed eight retrospective studies and concluded the prodromal period is marked by: irritability and aggressiveness, altered sleep patterns, mania, depression, anxiety, mood swings, and hyperactivity. However, all of the studies included in the review relied on patients or their parents to recall the onset of symptoms (Skjelstad, Malt et al. 2010). Conus et al reached similar conclusions, observing that in the months prior to the first manic episode, mood fluctuation, increased energy, sleep disturbance, irritability, and functional impairment may be apparent (Conus, Ward et al. 2008).

Evidence from patient studies provide some additional evidence. In a recent review of studies of children born to parents with BP, subjects thought to be at high risk to develop BP, reported disturbances in reality testing or thought disturbance among those offspring as a potential marker of prodrome (Narayan, Allen et al. 2013). However, only a few of the studies were longitudinal, and even those have not yet followed subjects through the primary window of risk for developing BP. Similar to the lack of specificity observed in the population studies, disturbance in reality testing is not specific to BP. The authors proposed further research on the developmental course of thought disturbances across a BP-SZ spectrum, rather thought disturbance being diagnostically specific.

A number of researchers have attempted to develop assessment instruments to improve the prediction of BP during prodrome. The symptoms identified for inclusion in these instruments have included: sleep and mood alterations, anxiety, fearfulness, and dissociative symptoms (Leopold, Ritter et al. 2012). Based on a literature review, Bechdolf et al created a "Bipolar At Risk" algorithm which includes a combination of mood fluctuations, symptom constellations related to mania or related to depression, and genetic risk (Bechdolf, Nelson et al. 2010, Bechdolf, Ratheesh et al. 2012). Specificity of the at risk criteria was reported to be 90 percent and sensitivity 83 percent. A third research group's review, seeking an approach to predicting BP, concluded that three key features could aid prediction: genetic high risk, environmental high risk (such as childhood abuse), and high risk biomarkers (Brietzke, Mansur et al. 2012). Of note, following a brief review of symptom clusters identified by others as marking the prodrome

of BP, Brietzke et al conclude that a lack of longitudinal and prospective data, and the non-specificity of identified symptoms, make utilization of the phenomenological features unlikely.

In summary, it appears that a prodrome in BP does occur, marked by broad symptom clusters. Yet, the symptoms are difficult to identify prospectively and have little specificity. This is similar to the problems in identifying people who will develop SZ as well, where high risk studies find conversion rates of about twenty-five percent of those identified (Simon, Velthorst et al. 2011). Certainly, further research may better identify specific symptom manifestations that denote the BP prodrome, but at this time, it is difficult to differentiate the BP prodrome from any number of other conditions and symptom clusters. Nevertheless, even though not specific, the research does clearly support the presence of premorbid and prodromal symptoms which in turn supports the neurodevelopmental hypothesis.

High risk and first episode

Third, high risk and first episode psychosis subjects manifest a number of identifiable symptomatic differences compared with both healthy controls and people with other psychiatric disorders. As noted in a recent review, because nearly all the high risk studies are conducted with those who seek help or have insight into some symptoms, this research is necessarily not representative of the population at risk for, or those who develop, BP; and because the conversion rates are low, some of the identified symptoms that qualify people as high risk, are not specific (Fusar-Poli, Yung et al. 2014). Regardless, some information about the course of those people with symptom clusters that may be predecessors to BP is observed in these studies which focus on the period prior to and including the onset. The existence and observation of symptoms which bring people into treatment and lead to diagnosis are a piece of evidence indicating that the illness course begins prior to first episode psychosis; and symptoms used to identify those people deemed to be at high risk may reflect neurodevelopmental processes more directly (Wood, Pantelis et al. 2008, Fusar-Poli, Deste et al. 2012). For instance, in a population based study of first episode psychosis, those with BP performed better, in general, than those with other psychotic disorders, but still performed worse than population controls, despite low power because the study included only 37 people with mania or BP (Zanelli, Reichenberg et al. 2010). Similarly, as noted above, high risk studies have identified some clinical and behavioral symptoms which appear to mark the BP

prodrome and first onset, including mood lability, family history of psychosis, racing thoughts, anxiety, and irritability (Skjelstad, Malt et al. 2010, Howes and Falkenberg 2011).

Table 6: Population based high risk and first episode studies

Author/year	Sample size (N)	Study type	Specific high risk or first episode symptoms	Results	Significance
Kravariti et al (2009)	35 BP, 274 community controls, 105 IQ matched controls	First episode BP with psychotic features	Cognition at first episode	BP had statistically significantly lower current IQ (approximately 6 points lower); semantic verbal fluency was significantly impaired (OR = 5.49; CI: 1.87, 9.11 compared to all controls)	Specific deficit in verbal fluency
Zanelli et al (2010)	37 BP	Population based first episode case-control	Cognition at first episode	BP have equivalent current IQ as controls; significantly impaired delayed verbal memory and category fluency compared to controls, non-significantly impaired on processing speed and executive functioning	BP have impaired performance but out-perform those with other psychotic disorders
Owoeye et al (2013)	73 BP	Population based, 13 year prospective first episode	Symptom severity	BP had lower premorbid adjustment scores and performed better on an executive functioning interview compared to those with major depression with psychotic features	Comparison to other people at first episode
Bechdolf et al (2010)	5 BP	High risk community mental health clinic followed prospectively; retrospective file review	BP at risk criteria development	Those who converted to BP had depressive symptoms prior to onset, and either cyclothymic symptoms or first degree relative with BP	Community sample testing prodromal symptom scale for prediction of BP
Olvet et al (2010)	8 BP	Clinical high risk	Attenuated psychotic symptoms and cognition	Compared to non-converters, BP had 10 point lower IQ score and lower global cognition score (non-significant); significantly more severe positive symptoms	Prodromal BP lower scores on cognitive testing and more positive symptoms
Schultz-Lutter et al (2012)	10 BP	Clinical high risk group of people seeking help, prospectively followed for 53 months	Positive and negative symptoms	BP group less symptomatic than the SZ group; Psychotic features of Affective disorder and SZ are more similar than those without pre-psychosis	Group comparisons between prodromal Affective disorder with psychotic features and without, and SZ
Ratheesh et al (2013)	16 BP; 46 high risk non-converters; 66 controls	High risk clinic group; mean follow-up over 8 years	Cognition Symptoms	GAF at baseline significantly lower for BP; BP performed significantly worse than controls on IQ, abstract visual reasoning, processing speed and attention	No differences between BP and non-converters

Prospective studies of those at high risk for BP report a number of symptoms and deficits which are associated with onset (Table 6). It remains difficult to distinguish between those who will develop BP and those who will develop SZ or major depression as a result of symptom non-specificity (Olvet, Stearns et al. 2010, Scott, Hermens et al. 2013). One recent first episode psychosis study, however, differentiates major depressive disorder with psychosis onset from that of SZ and BP, finding that first episode major

depression was evenly distributed across life-span, whereas first episode BP and SZ are primarily disorders of late adolescence and young adulthood (Owoeye, Kingston et al. 2013).

In summary, studies of those considered to be at high risk for BP have not identified specific symptoms that predict BP. Because of the low conversion rates in most of these high risk studies, the evidence of what constitutes high risk for BP is not condition specific. Moreover, even studies aimed at specificity, such as the clinical high risk study for SZ by Olvet et al in which eight subjects unexpectedly converted to BP, the outcome diagnosis is very difficult to predict (Olvet, Stearns et al. 2010). In summary, the high risk for BP studies offer limited support for the neurodevelopmental hypothesis because the small numbers who have been enrolled and go on to develop BP, and because of the lack of specificity of symptoms. In this way, however, the at-risk for BP research overlaps with the at-risk for SZ research in that both conditions exhibit similar symptom patterns and risk patterns, and neither set of those patterns predict disease onset well.

Neurocognition

A final critical pillar of support for the neurodevelopmental hypothesis of SZ is the evidence of cognitive impairment during the premorbid and prodromal periods (Keshavan, Kennedy et al. 2004, Reichenberg and Harvey 2007, Woodberry, Giuliano et al. 2008, Mesholam-Gately, Giuliano et al. 2009, Consortium 2013, Olvet, Burdick et al. 2013). For instance, a nested case-control study of SZ drawn from the same CHDS birth cohort as in the present research, compared childhood cognitive performance as measured by the Peabody Picture Vocabulary Test (PPVT) given at ages 5 and 9-11, and re-administered in adulthood, to examine the course of cognitive functioning over 33 years. This study found a ten point difference in the early childhood PPVT, with those who would later develop SZ performing more poorly than the matched controls. In adulthood, the gap in performance was wider, with those who had developed SZ scoring 15 points below the controls (Kremen, Vinogradov et al. 2010). The ten point difference observed in childhood scores is consistent with the neurodevelopmental hypothesis of SZ.

Evidence of cognitive impairment at each of the illness stages of BP also tend to support the neurodevelopmental hypothesis, but the effect sizes of impairment tend not to be as large as those observed with SZ, and the impairments tend to be domain specific as opposed to the broad, global

deficits seen with SZ. On average, people who are later diagnosed with BP are observed to have cognitive impairment during all phases of illness, including during the premorbid period of development (Reichenberg, Weiser et al. 2002, Martinez-Aran, Vieta et al. 2004, Daban, Martinez-Aran et al. 2006, Goodwin, Martinez-Aran et al. 2008, Kurtz and Gerraty 2009, Reichenberg, Harvey et al. 2009, Bearden, Woogen et al. 2010, Harvey, Wingo et al. 2010, Pol, van Baal et al. 2012, Hill, Reilly et al. 2013).

A number of meta-analyses and reviews have reported domain specific significant cognitive impairment in people with BP (Bearden, Hoffman et al. 2001, Quraishi and Frangou 2002, Savitz, Solms et al. 2005, Daban, Martinez-Aran et al. 2006, Goodwin, Martinez-Aran et al. 2008, Stefanopoulou, Manoharan et al. 2009, Bearden, Woogen et al. 2010, Harvey, Wingo et al. 2010, Lim, Baldessarini et al. 2013). Meta-analyses of euthymic patients with BP have also found cognitive deficits in a number of domains, reporting moderate to large effect sizes even after controlling for a number of potential confounders (Robinson, Thompson et al. 2006, Torres, Boudreau et al. 2007, Arts, Jabben et al. 2008, Bora, Yucel et al. 2009, Kurtz and Gerraty 2009, Latalova, Prasko et al. 2011, Mann-Wrobel, Carreno et al. 2011, Bourne, Aydemir et al. 2013). The cognitive domains in which deficits are observed are executive functioning, verbal learning, verbal memory, sustained attention, and psychomotor speed. The effect sizes are moderate and large in these domains. These studies are often used to support the notion that cognitive impairment is a trait of those who develop or have BP. Similarly, few differences are observed when comparing cognitive deficits between BP 1 and BP 2, with some slightly better performance on verbal memory for those with BP 2, but generally similar domains of impairment (Bora, Yucel et al. 2011, Sole, Martinez-Aran et al. 2011, Sole, Bonnin et al. 2012); small differences are observed when comparing BP with psychosis and without on specific domains (Bora, Yucel et al. 2010); and impairment is observed across all phases of illness, with executive function performance decline during mania (Martinez-Aran, Vieta et al. 2004, Ryan, Vederman et al. 2012). The evidence of cognitive impairment across mood phases and in remitted states supports the hypothesis that cognitive deficits are components of the illness (a trait) rather than reflecting a disease state which varies according to mood. These findings also suggest that investigating at what stage of illness (premorbid, prodromal, at first onset) cognitive impairment becomes observable.

Population based studies of premorbid functioning have found differences between those who develop BP and the general population (see Table 7). A review of population based studies concluded that the evidence of premorbid cognitive impairment does not yet support a conclusion that such impairments define a trait of later BP (Kravariti, Kane et al. 2009). Although draft board neuropsychological batteries lack the specificity and breadth of a complete functional assessment, they do provide useful population based information on a testing battery that mimics IQ assessments. One large Danish draft board study reported small IQ difference for both BP and unipolar depression compared with the general population but no significant differences between illnesses (Sorensen, Saebye et al. 2012), and a second Danish draft board study observed small deficits in IQ for people who developed affective disorders (as well as schizophrenia; non-schizophrenic, non-affective psychotic disorder; neurotic or stress disorder; and personality disorders) compared to population controls (Urfer-Parnas, Mortensen et al. 2010). A third Danish draft board study of all men born in 1953, compared testing at ages 12 and 18 for those who later developed BP, also reporting impaired cognition compared to those without BP, but the sample size (N=16) is reported to be too small to offer stable results (Osler, Lawlor et al. 2007). A more recent analysis of four Swedish birth cohorts which compared trend data for testing at ages 13 and military induction testing at age 18 reported that the 18 subjects with BP performed better than the population at both time points on verbal, spatial, and inductive reasoning (MacCabe, Wicks et al. 2013). However, a Finnish population based cohort study, analyzing conscript testing at ages 18-19, reported that worse premorbid performance on a test of visuospatial ability predicted later onset BP (Tiihonen, Haukka et al. 2005).

Table 7: Population based studies of premorbid and prodromal cognition

Author/year	Sample size (N)	Study type	Specific cognitive domains	Results	Significance
Cannon et al (2002)	20 mania	Prospective, representative cohort	Motor, language, IQ	Only motor development was significantly impaired; language was impaired or above average at different ages	Receptive language is low at ages 3 and 9, high at 5 and 7, study is underpowered
Reichenberg et al (2002)	68 BP (non-psychotic)	Israeli prospective conscript cohort 1985-95, registry based	Conscript battery, language, IQ, visuospatial, arithmetic	No association between premorbid tests and BP	No impairment observed
Zammit et al (2004)	108 BP	Swedish population based study, conscripts in 1969-70	Conscript battery, verbal, visuospatial, general knowledge, mechanical	No association between premorbid IQ and later BP	IQ is coded on a 9 point scale
Meyer et al (2004)	9 BP	Prospective community study with 23 years of follow-up; participants are offspring of mother with unipolar depression, bipolar, or no history of psychiatric illness	Developmental and cognitive prodromal symptoms	IQ at ages 8-15 lower for BP; attentional, behavioral, and depressive symptoms more common for BP; impaired executive functioning	worse cognitive performance and functioning
Reichenberg et al (2005)	801 BP (non-psychotic)	Israeli population based cohort, registry based	Conscript battery, language, IQ, visuospatial, arithmetic	No association between premorbid IQ and later BP	Analyses focused on SZ, limited detail on BP
Tiihonen et al (2005)	100 BP	Finnish population based cohort, births 1962-7, registry based	Conscript battery, visuospatial, arithmetic, verbal	Premorbid impairment on visuospatial reasoning performance and higher than average performance on arithmetic	Visuospatial reasoning impairment
Osler et al (2007)	16 BP	Danish prospective birth cohort, 1953 births, registry based	Cognitive testing at ages 12 and 18, visuospatial, arithmetic, verbal	Impairment observed at both 12 and 18 in all areas, but non-significant	Impairment prior to onset is similar to those who develop SZ, but the study is underpowered for BP
Koenen et al (2009)	8 BP	Prospective birth cohort, 32 year old follow-up	Childhood IQ	Significantly increased IQ at age 11 (OR = 3.1: CI: 1.18, 8.19)	All 8 subjects had average or higher IQ scores at age 11
MacCabe et al (2010)	280 BP	Swedish population based study, school grades1988-97	School grades from ages 15-6	Both high and low grades had higher risk for BP: 2 or more standard deviations above mean had a 3.34 increased risk (adjusted) and 2 or more below had a 1.96 increased risk (adjusted)	U shaped increased risk for BP
Urfer-Parnas et al (2010)	1845 Affective disorder	Danish prospective birth cohort, births 1950-61, registry based	Conscript testing, IQ test: letter matrices, verbal analogies, number series, geometric figures	Compared to controls, significantly lower IQ scores	All psychiatric groups performed worse than controls, those with affective disorder performed better than other groups
Sorensen et al (2012)	294 BP	Danish prospective birth cohort, births 1950-61, registry based	Conscript testing, IQ test: letter matrices, verbal analogies, number series, geometric figures	Although IQ was lower compared to controls, it was less than 2 points lower; mean educational level was equal to controls	No significant premorbid IQ difference observed
Vonk et al	53 BP twin	Dutch registry	School	Affected twins completed fewer	Underperformed at

(2012)	pairs; 42 healthy twin pairs	identification of case status and twin status	performance, underperforming defined as: repeating a grade; special education; moved down to lower level of education	years of school and underperformed during schooling	school and fewer years completed
MacCabe et al (2013)	18 BP	Swedish representative sample cohort, registry based	Cognitive testing at ages 13 and 18, verbal, spatial, inductive	Performance is better than controls on all measures at both ages periods	Although verbal and spatial decline between 13 and 18, BP perform better than control on all tests at both times
Ratheesh et al (2013)	16 BP; 46 high risk non-converters; 66 controls	High risk clinic group; mean follow-up over 8 years	Cognition	BP performed significantly worse than controls on IQ, abstract visual reasoning, processing speed and attention	No differences between BP and non-converters

Olvet et al recently reviewed longitudinal, family, and first episode neuropsychological studies to assess whether cognitive impairment could serve as a predictor of later onset BP (Olvet, Burdick et al. 2013). They concluded that some domain specific functions (executive and memory) might serve as predictors, and have been shown to be consistently impaired in those who later develop BP.

In a prospective study which followed children into adulthood, children tested between ages 3 and 11 who later developed bipolar mania, had receptive and expressive language skills that varied between testing periods compared with controls (expressive language was higher at age 3, lower at ages 5 and 7, and higher at age 11; receptive language was lower at age 3, higher at 5 and 7, and lower at age 11; IQ was slightly higher at age 7 and lower at age 11), and more behavioral difficulties (Cannon, Caspi et al. 2002). This study included only 20 people who developed mania in adulthood through age 26, and none of the scoring differences reached statistical significance. Another prospective study, this one of children at high risk for BP followed for 23 years, reported that the 9 people who developed BP had lower IQ scores than those who developed unipolar (n = 22) and those without mood disorder (n = 64), although all the scores are within the normal range (Meyer, Carlson et al. 2004). In addition, they found that those who developed BP performed significantly worse on executive functioning measures prior to onset.

An exploratory high risk for psychosis study prospectively followed and compared 16 people who converted to BP to 46 who did not convert to psychosis matched on age and sex, and 66 healthy comparison subjects (Ratheesh, Lin et al. 2013). At baseline, the clinical characteristics of all those at high risk were similar; subjects who later developed BP had lower full scale IQ scores compared to controls (approximately twelve points lower than healthy controls and four points lower then other high

risk subjects), and performed significantly worse on a measure of executive functioning. Another comparison of high risk subjects, this one comparing pre-conversion functioning for 8 subjects who later converted to BP, 24 who later converted to SZ, and 115 non-converters, found that at baseline the BP subjects had IQ scores approximately 10 points lower than non-converters, although this was non-significant likely due to low power (Olvet, Stearns et al. 2010). Although reporting that the BP group performed worse than non-converters on other neuropsychological tests, and that they also demonstrated more variance in scoring, the authors note that the study was underpowered.

A twin study of school success observed that those who later developed BP had fewer years of education and worse performance compared with matched, control twins (Vonk, van der Schot et al. 2012), and this finding is also reported in case-control studies (Glahn, Bearden et al. 2006). Cannon et al demonstrated worse premorbid sociability, adjustment, and schooling for those who later developed BP (Cannon, Jones et al. 1997). However, others have reported that both low and high premorbid school performance is a risk factor for BP based on a longitudinally followed, nationally representative cohort (MacCabe, Lambe et al. 2010).

In summary, cognitive functioning prior to the onset of illness, one key pillar of the neurodevelopmental hypothesis, remains to be more fully explored in BP. It appears from the available research, that domain specific impairments are documented at least during the prodromal period, but that during the premorbid period, it is less clear, with conflicting evidence. Further investigation of the mixed evidence of premorbid cognitive functioning in those who later develop BP may further our understanding of whether BP should be considered a neurodevelopmental illness.

On average, people who are later diagnosed with BP are observed to have cognitive impairment during all phases of illness, including during the premorbid period of development (Martinez-Aran, Vieta et al. 2004, Goodwin, Martinez-Aran et al. 2008, Kurtz and Gerraty 2009, Bearden, Woogen et al. 2010, Hill, Reilly et al. 2013), but the impairments are in specific cognitive domains, unlike the broad impairment across many domains observed in SZ, and are typically not as severe as those seen in premorbid and prodromal SZ (Reichenberg, Weiser et al. 2002, Daban, Martinez-Aran et al. 2006, Reichenberg, Harvey et al. 2009, Harvey, Wingo et al. 2010).

Neurocognitive deficits are consistently observed in premorbid and prodromal BP. Some large studies have also reported high IQ as a risk for BP (Table 7). This U shaped cognitive risk differs from what is observed in SZ, where impaired cognition is much more common. Those studies which report impairment in cognitive functioning in BP also identify specific domains of deficit, in contrast to SZ in which the deficits are reported to be more global. Sufficient evidence supports the presence of these cognitive deficits throughout the course of the various mood and remission states after onset of BP as well. The presence of cognitive impairment in specific domains and superior performance on global and school measures, provides support for the neurodevelopmental hypothesis BP.

Discussion

The neurodevelopmental basis for BP is not clear cut, but the majority of accumulating studies, especially from population based research with sufficient power, supports that the illness is one characterized by an altered, pathological, or delayed maturation of the developing brain, that progresses through stages, shifting the neurodevelopmental trajectory prior to onset. Nevertheless, further research is needed to derive better specificity of the stages of pre-onset illness, the causes which precipitate changes, and the mechanisms by which they occur.

Paper 2: Prenatal and perinatal environmental risks for bipolar

The causes of Bipolar disorder (BP) are not currently known, and the early life risks for later onset illness have been examined in only a limited number of studies to date. Historically, BP has been thought to be related closely to SZ, and as the neurodevelopmental hypothesis of SZ has become increasingly accepted, a similar hypothesis has been applied to BP. The neurodevelopmental hypothesis posits that altered, pathological, or delayed maturation of the developing brain, long before the manifestation of disease, shifts the neurodevelopmental trajectory, followed by later life onset of psychiatric illness (Oneal and Robins 1958, Fish, Shapiro et al. 1965, Nasrallah and Weinberger 1986, Murray and Lewis 1987, Meyer and Feldon 2010, Millan 2013). The evidence supporting the neurodevelopmental hypothesis of BP is less robust than the evidence supporting the hypothesis of SZ, both because of less research attention and because the evidence that does exist has been less clear cut for BP, especially concerning prenatal and perinatal risks.

The neurodevelopmental approach to the origin and course of SZ and BP holds promise for better outcomes because it searches for the causes and mechanisms which result in illness later in life, opening the potential for earlier and more effective intervention and prevention. As suggested by Insel, the neurodevelopmental approach identifies stages of disease progression, each of which may offer specific types of intervention and prevention (Insel 2010). Another way to ask this question is: during which periods do the divergences from typical developmental course occur, and why have they occurred? The neurodevelopmental hypothesis suggests that the divergences may begin before conception and that the risk for them continues through illness onset, at least. For each symptom cluster that constitutes the diagnostic criteria for illness, the timing and mechanism of divergence offers the potential for prevention or remediation. In order to identify the interventions and preventive steps that might work, further research on the antecedent risks, mechanisms, and causes are needed.

In order to test some specific components of the neurodevelopmental hypothesis of BP and compare them to what is known about SZ, both prenatal and perinatal exposures should be considered. Here, one of each type of environmental exposure is investigated for possible associations with later onset BP: the prenatal infectious exposure to toxoplasmosis and the administration of oxytocin to induce labor. Examining these two risks will allow for determination of specificity of exposures and testing of

potential mechanisms. A finding that prenatal exposures such as these are risks for later illness would support the idea that BP is a neurodevelopmental disease, and whether either exposure has an effect on cognition during the developmental period may elucidate the role of cognitive impairment in later illness.

Prenatal exposure: Toxoplasma gondii

Toxoplasma gondii (T. gondii), a ubiquitous intracellular parasite (Scheld, Whitley et al. 2004, Remington 2011), is able to cross the placental barrier to cause congenital malformations (Sullivan and Jeffers 2012); it infects neurons, enabling its own spread throughout the central nervous system, causing negative neuropsychiatric outcomes, including psychiatric illnesses (Carruthers and Suzuki 2007, Fekadu, Shibre et al. 2010). A number of studies of adults have found elevated seroprevalence for T. gondii among those with SZ and BP (Torrey, Bartko et al. 2007, Tedla, Shibre et al. 2011, Arias, Sorlozano et al. 2012, Torrey, Bartko et al. 2012).

The association between serologically documented maternal T. gondii and offspring BP has not previously been assessed. However, research in the CHDS birth cohort found an association between serologically documented maternal T. gondii IgG antibody during pregnancy and an increased risk of offspring schizophrenia spectrum disorder (Brown, Schaefer et al. 2005). Analyzing maternal sera obtained during pregnancy and comparing moderate (1:16 to 1:64) and high (>1:128) IgG antibody titers to a negative referent group (<1:16), Brown et al found a 2.61 times increased risk for SZ among those with high titer compared with the referent. That finding has been replicated (Mortensen, Norgaard-Pedersen et al. 2007, Blomstrom, Karlsson et al. 2012) and confirmed in a meta-analysis (Torrey, Bartko et al. 2012). Further, at least one prospective, population based study found T. gondii associated with risk of SZ when measured prior to onset of symptoms (Pedersen, Stevens et al. 2011). However, no association was observed between maternal T. gondii and offspring BP (Mortensen, Pedersen et al. 2011), although that study analyzed dried blood spots on filter paper obtained from the infant and not maternal sera obtained during pregnancy. This difference could be important if placental transfer of IgG diluted the measurable effect or the aging and preservation of the blood spot on filter paper made detection more difficult.

Additionally, in SZ an association has been observed between maternal T. gondii and offspring cognition. Only a limited number of studies have examined cognition in offspring of exposed mothers. Brown et al reported an association of maternal infections, including T. gondii, with impaired executive functioning in SZ (Brown, Vinogradov et al. 2009). For adult exposure to the virus, limited evidence suggests no association (Yolken, Torrey et al. 2011, Guenter, Bielinski et al. 2012), but exposure during neurodevelopment, when maternal inflammation and immuno-response affects fetal processes, remains to be tested more comprehensively.

This association of T. gondii with cognition is not fully developed, but both animal models and observational studies support an association (Kannan and Pletnikov 2012). One prior study found children exposed prenatally to T. gondii and treated had significant neurologic and cognitive impairment through childhood (Roizen, Swisher et al. 1995), and evidence indicates that T. gondii continues to spread and cause damage in the fetal brain once the maternal immune system responds to the infection (Ferguson, Bowker et al. 2013). A recent international meta-analysis found an association between T. gondii and learning difficulties, developmental delays, impaired cognition, and vision loss or deficit in children with congenital exposure (Mwaniki, Atieno et al. 2012).

Prenatal exposure to T. gondii's possible association with impaired cognition, and its association with SZ, makes it an important antecedent to test as a possible neurodevelopmental risk for BP. Much of the prior evidence is either ecological or based on adult exposure rather than prenatal exposure which would affect development, making determinations about mechanism untestable. The mechanism by which the parasite proliferates, specifically affecting the central nervous system, suggests that prenatal exposure is likely an important period of risk for neuronal maldevelopment. Thus, the purported mechanism by which T. gondii could affect neurodevelopment, both impairing cognition and increasing risk for psychiatric illness, in which cognitive impairment may mediate the association between T. gondii and later psychosis, can be analyzed in this case-control study directly to assess the neurodevelopmental effects of exposure.

Perinatal exposure: Oxytocin to induce labor

The evidence that obstetric complications increase the risk for BP is mixed, with methodological concerns hampering the understanding of the associations or absence of associations. For instance, grouping obstetric complications into scales treats all the complications the same, without determining the risk associated with a specific complication (Lewis and Murray 1987, Verdoux and Bourgeois 1993, Kinney, Yurgelun-Todd et al. 1998, Buka and Fan 1999, Buka, Goldstein et al. 2004, Scott, McNeill et al. 2006, Singh, DelBello et al. 2007).

This study used a single perinatal complication, induced labor by administration of oxytocin, identified prospectively and documented in medical charts contemporaneously, to assess one specific and common procedure. Inducing labor may be undertaken because of labor difficulties or for other reasons, but the procedure is relatively common and understudied. The rate of induction has increased in recent decades, with oxytocin now being the most used means for inducing (Mealing, Roberts et al. 2009, Moleti 2009). However, oxytocin to induce labor has been shown to have risks for the mother and neonate (Buchanan, Patterson et al. 2012). These risks include a greater need for neonatal intensive care and lower Apgar scores (Oscarsson, Amer-Wahlin et al. 2006, Selo-Ojeme, Rogers et al. 2011); an increased risk for ADHD (Kurth and Haussmann 2011); and an increased risk for autism (Gregory, Anthopolos et al. 2013).

Excess oxytocin, as measured in adults and in animal models, has been associated with impairments in learning, attention, and memory, and oxytocin is reported to reduce cognitive ability in experimental models (Demitrack and Gold 1988). During the peripartum period, neurons in the limbic regions of the brain have an increased density of oxytocin receptors, suggesting a developmental window of importance for the social and bonding behaviors associated with endogenous oxytocin (Zingg, Bourque et al. 1998). The hypothesized mechanism by which maternal oxytocin exposure may affect offspring proposes that oxytocin causes fetal hypoxia, restricts neural blood flow, and increases fetal bilirubin and the risk of jaundice (Drew and Kitchen 1976, Connor and Seaton 1982).

The finding that SZ is associated with obstetric complications has been frequently reported. Yet no research to date has examined the association with oxytocin in either SZ or BP, despite its relationship to other psychiatric illnesses and a mechanism of action which is hypothesized to increase the risk for SZ

in other obstetric complications. Similarly, although some obstetric complications have been associated with childhood cognitive deficits (Seidman, Buka et al. 2000, Leitner, Fattal-Valevski et al. 2007), no studies of oxytocin's potential association with cognitive performance have been conducted.

Maternal oxytocin to induce labor, therefore, merits further investigation for its association with BP and cognitive impairment, given the possible mechanisms by which it alters neurophysiology and its use during birth when the developing brain is at increased risk. The primary hypotheses tested here are: 1) whether the offspring of mothers who received oxytocin to induce labor are at greater risk for later life BP; 2) whether the offspring of mothers who received oxytocin perform worse on childhood cognitive testing; and 3) if oxytocin is associated with both BP and cognition, whether cognitive performance mediates the association between oxytocin and BP.

Secondary analyses are also conducted to attempt to differentiate the possible effect of oxytocin as an agent and oxytocin as a proxy marker (confounding). Three sets of analyses were conducted: 1) examining prolonged labor: it is possible that prolonged labor is an antecedent of oxytocin, where oxytocin is given to induce if labor was extended, or that oxytocin and labor length share a common cause and labor length is associated with BP. Length of labor could be a confounder or an antecedent or not associated with BP, and each of these suggests different potential points of prevention or intervention; 2) analgesics: it is possible that analgesics given during labor have a direct effect on BP and share a common cause with oxytocin, or that they interact with oxytocin to increase the risk of BP. This analysis addresses whether any drug intervention increases the risk of BP, or if the possible effect is specific to one medication, and also tests an interaction effect which has been hypothesized (Oscarsson, Amer-Wahlin et al. 2006); and 3) delivery type: it is possible that delivery type, dichotomized between cesarean and vaginal, is associated with BP and shares a common cause with oxytocin to induce labor. For instance, a common condition during labor may have led doctors to recommend cesarean rather than oxytocin, and it is the common cause of both delivery type and oxytocin which explains a possible relationship with BP. If an unmeasured confounder causes both oxytocin use and any of the three testable covariates, both oxytocin and that covariate would be associated with BP. If, on the other hand, oxytocin is associated with BP, but one or more of the other covariates is not, then the association

between oxytocin and BP would be considered more robust because the effect is less likely caused by an unmeasured confounder.

Methods

The Child Health and Development Study (CHDS) is a large, representative birth cohort, containing 19,044 live births. This cohort has been followed prospectively, with prenatal serologic samples obtained during pregnancies, perinatal measures obtained during routine medical care, childhood cognitive assessment performed at ages 5, 9-11, and 15-17 on subsets of the birth cohort, and psychiatric diagnoses confirmed in adulthood. Using a nested case-control design to obtain all BP cases and matched controls from the CHDS, this research investigates the relationship between serologically obtained prenatal exposure (T. gondii) and BP, and a perinatal exposure (oxytocin) and BP, as well as testing whether these effects are mediated by cognition.

Cases and controls for the Prenatal Factors and Bipolar Disorder Study were drawn from the CHDS birth cohort (van den Berg, Christianson et al. 1988). The CHDS recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (Kaiser) in Alameda County, California between 1959 and 1966. Contemporaneously completed medical records, maternal interviews, child assessments, and other sources were generated prospectively during the course of prenatal and perinatal medical care provided by Kaiser. Kaiser reflects the population of the Bay Area of California at the time, providing care to approximately 30% of the population of Alameda county, with some underrepresentation at both the extremes of income. This birth cohort has been extensively studied for prenatal and other early developmental risk factors for SZ (Susser, Schaefer et al. 2000).

Case Identification

People with potential DSM-IV BP, which included BP I, BP II, BP NOS, and BP with psychotic features, were ascertained by screening procedures which used data from three sources: Kaiser's electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailing to the entire living CHDS birth cohort (mothers and children). This approach

sought to maximize ascertainment of individuals with BP. CHDS cohort members who belonged to Kaiser when first treated would have been ascertained from this source. Subjects who left Kaiser prior to the first treatment of BP and who did not have other health insurance, but who still lived in Alameda County, would likely have been treated by ABHCS and therefore ascertained. Subjects who were not ascertained by these two approaches were ascertained by a mailed survey to the entire cohort.

The ascertainment process identified 448 subjects who potentially met the criteria for BP and psychotic disorder.

Ascertainment of Kaiser subjects

Subjects with potential BP (and other psychotic disorders) were identified by screening Kaiser's inpatient and outpatient databases. Computerized record linkages between CHDS and Kaiser identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of Kaiser members regardless of the hospital at which treatment is received. This covered the period from 1981-2010. Those with discharge diagnoses of ICD-9 295-298 from the Kaiser inpatient database were considered as potential BP subjects. A database of outpatient treatment was introduced in 1981, but did not contain searchable codes for diagnoses until 1995. Potential BP cases from the outpatient database were considered to screen positive if they received ICD-9 diagnoses of 295-298 excluding unipolar major depressive disorder. Case ascertainment also used the Kaiser outpatient pharmacy database, which commenced in 1992. Cases screened positive based on prescriptions for mood stabilizing medications used in the treatment of BP (lithium, carbamazepine, valproic acid). Before contacting subjects who were currently enrolled in Kaiser, the subject’s treating psychiatrist was contacted, informed about the study, and asked to approve contact with the subject to seek his/her consent to participate.

Any subjects identified by these methods were invited to participate in the study, receiving a letter to the most recent address, and those who did not refuse contact by returning a postcard, were contacted to arrange an appointment for a diagnostic interview. Up to several repeat appointments were scheduled for subjects who failed to attend the interview. Extensive efforts were made to locate individuals who were no longer living at the most recent listed address, including Department of Motor Vehicles records,

telephone directories, and contacting the subjects' parents or siblings from CHDS or Kaiser files. Mortality records, reverse directories, jail searches, and visits to previous addresses were also used as necessary.

Ascertainment by Alameda County Behavioral Health Care Services (ABHCS)

Outpatients with potential BP were also ascertained by electronic record linkage between the CHDS and ABHCS identifiers. The ABHCS database included treatment from 1993-2009. These subjects screened positive based on ICD-9 outpatient diagnoses of 295-298, excluding unipolar major depressive disorder. Procedures for finding and recruiting these potential subjects were similar to those described above for ascertainment by Kaiser.

Ascertainment of CHDS birth cohort by mailed questionnaire and follow-up

The third method of ascertainment was initiated by letters mailed to all living mothers (N=6,971) and cohort members (N=13,009) with known addresses in the entire CHDS cohort (excluding families in which potential cases had already been identified in the Kaiser and/or ABHCS) along with a questionnaire on mental and physical health. This was conducted from 2009-11. Questionnaire respondents who reported "mental health problems" in an eligible cohort member (including the respondent him or herself) were contacted by a trained Kaiser study interviewer who administered the Family Interview for Genetic Studies (FIGS) to screen for possible BP or psychotic illness in the cohort member. If the FIGS indicated at least one bipolar and/or psychotic symptom (delusions/hallucinations), then the cohort member was considered to have screened positive, and was invited to participate in the diagnostic interview. If the respondent (mother or sibling) described symptoms in a birth cohort member, the respondent was asked if he or she would be willing to have the study contact the affected family member about participation in the study. If the respondent agreed, the affected cohort member was contacted by letter and invited to participate.

Diagnostic protocol

Accurate diagnosis of BP is critical to understanding its causes. A number of prior studies, as noted above, have suffered from poor diagnostic specificity of BP, grouping a number of illnesses into

catch-all categories such as “affective disorders.” The current research benefits from the careful diagnostic assessment and inclusion of confirmed cases of BP.

A total of 214 subjects (48% of those ascertained) were interviewed using the Structured Clinical Interview for DSM-IV TR (SCID). The reasons that some subjects were not interviewed were: 100 could not be contacted, 80 refused or failed to keep the appointment, and 54 who could not be interviewed because he or she had died, were incarcerated, permission from the physician could not be obtained, or because the person was too psychotic or mentally disabled.

Study interviewers had a minimum of a master’s degree in a mental health field and were trained to reliability on the SCID. DSM-IV-TR diagnoses including diagnostic qualifiers representing subtypes of BP were systematically assigned by consensus of three experienced clinicians (psychiatrists/Ph.D. psychologist), based on review of the SCID and medical records. This yielded 72 total BP cases. Among those interviewed, consensus diagnoses of non-BP disorders were also assigned: there were 61 cases of SZ and other schizophrenia spectrum disorders, 62 cases of major depressive disorders, and 19 cases with other diagnoses. These non-BP categories were not included in the present study. Although unipolar major depressive disorder was not included in the screening procedure, the diagnostic protocol enabled us to exclude subjects with database diagnoses of BP and/or psychotic disorders who were found instead to have unipolar depressive disorder in accord with structured research criteria.

Ascertainment from PDS I study

Additional cases of BP had been ascertained through Kaiser records by an earlier study (Prenatal Determinants of Schizophrenia I, PDS I) were included in the present study (Susser, Schaefer et al. 2000). Although the purpose of PDS I was to identify SZ and other schizophrenia spectrum disorder cases, BP cases were also diagnosed by interview in that study. The protocol for the PDS I included the same electronic linkages with the Kaiser inpatient, outpatient, and pharmacy databases, and utilized the same ICD-9 diagnostic codes (295-298). Ascertainment covered the period from 1981-1998. The only other differences in the screening methods are that the PDS I did not include review of pharmacy records for treatment with mood stabilizers, and the PDS I included a second screening step, which involved psychiatrist review of abstracted data from inpatient/outpatient records for symptoms of psychosis. The

Diagnostic Interview for Genetic Studies (DIGS), rather than the SCID, was used for interviewing potential subjects in the PDS I. There were 23 BP cases diagnosed in the PDS I study.

In total, then, 95 people with BP were diagnosed following ascertainment from all sources and clinical interview.

After complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Kaiser.

Control Selection

In order to ensure that controls would have been equally likely (as their matched cases) to be ascertained if they had been treated for BP in Kaiser or ABHCS, controls were matched to cases on membership in Kaiser (for cases ascertained through Kaiser records) or residence in Alameda County (for cases ascertained through ABHCS or by CHDS mailing survey) in the year the case was first treated as reported in the SCID. For Kaiser, membership in the plan at that time was used for control matching, since cohort members would have been documented in Kaiser databases if they sought care for BP. The DMV was used to ensure place of residence at the time of diagnosis for cases treated by ABHCS and those identified from the mailed survey, since these subjects would have been the population at risk for treatment at same time. The vast majority of the subjects who received the mailing were Alameda County residents.

Control matching criteria included: date of birth (+/- 30 days), sex, and availability of maternal archived sera (for serologic studies). A maximum of an 8:1 ratio of controls to cases was achieved, as it represented the maximum number of controls that could be successfully matched to cases on all criteria and to maximize statistical power.

Exclusion criteria (prior to matching) were: all of the CHDS cohort members who screened positive for potential bipolar or psychotic disorders (N=376) and siblings of those cases; potential controls who belonged to Kaiser at the time of case ascertainment were excluded from the control pool for cases identified from ABHCS or the cohort mailing; and siblings of selected controls were excluded from further

control selection, so that all controls were independent observations, each representing a single family or pregnant woman.

This protocol yielded 754 matched controls.

Measurement

Method for T. gondii

The CHDS aimed to obtain maternal serum for each pregnancy during each trimester. At each blood draw, 30 cc were collected and spun, dividing the sera into four aliquots of approximately 2 cc each. The samples were transferred to glass vials and stored frozen at -20 degrees since being obtained. One-two cc of maternal sera were provided for each time point during pregnancy for each case and control. These serum samples have been successfully analyzed now for a number of biomarkers, including for T. gondii. Biomarker evidence, obtained prospectively, is the gold standard for assessing the exposure and ensuring pre-birth maternal exposure.

The T. gondii assays were performed in the Toxoplasma Serology Laboratory at the Palo Alto Medical Foundation Research Institute, which is the T. gondii reference laboratory for the US (Montoya 2002). Three assays were used. The first two concern the assessment of T. gondii IgG antibody titer. Samples were screened for the presence of IgG antibody titer and then the Sabin-Feldman dye test (Sabin and Feldman 1948) was performed in the samples that screened positive. T. gondii IgM antibody was also assayed, which is indicative of recent infection, using the double sandwich enzyme-linked immunosorbent test (IgM-ELISA). The seroprevalence of IgG antibody was 22/123 (17.9%) in controls. This value is similar to the 17.5% seroprevalence found in a large previous study of T. gondii in reproductive-aged women (Jones, Kruszon-Moran et al. 2001). None of the control serum samples tested by ELISA were positive for T. gondii IgM antibody. This was not unexpected, as T. gondii IgM antibody is indicative of active infection within 2 months of the blood draw, which is unlikely given the low incidence of toxoplasmosis during this time frame (Remington 2011).

For the primary analysis, T. gondii IgG for the last serum sample drawn for each pregnancy (late third trimester/perinatal) was analyzed. This replicates the methods used in the PDS study of T. gondii and SZ (Brown, Schaefer et al. 2005). The third trimester/perinatal period of gestation provides the

greatest opportunity to detect T. gondii infection if it occurred at any time during pregnancy because even an infection that occurred early in pregnancy will result in elevated IgG antibodies for many months or years following infection (Remington 2011).

The dye test IgG titers was classified into three groups: negative (<1:16) (reference), moderate titer (1:16-1:64), and high titer (≥1:128). We hypothesize that the high IgG titer group will have an increased risk of BP.

The T. gondii analyses include 85 cases, matched 1:2 with controls, for whom the serological assay for T. gondii was available. T. gondii exposure is categorical (high, medium, and unexposed). This study has sufficient power to detect a moderate association (OR = 2.7, power of .8 and p = .05), similar to the effect size previously observed in the SZ study for T. gondii in this cohort (Brown, Schaefer et al. 2005), and thus, a reasonable a priori hypothesis.

T. gondii has been assayed from the maternal sera which were obtained for each gravida in the cohort. The association between T. gondii and BP, using the IgG results was estimated using conditional logistic regression. Results are reported as hazard ratios because of the incidence density sampling for the nested case-control. Maternal age (<35 [reference], ≥35), maternal ethnicity (Caucasian [reference], African American, other), maternal educational achievement (defined as maternal education: <high school, high school only [reference], some college/college graduate), parity, and gestational age of the serum sample (in days after last menstrual period) will be considered as potential confounding variables. Fetal hypoxia was considered as a potential confounder but no reliable measure of it was available in these data. Any of these potential confounders which is associated with exposure and outcome at a probability greater than 0.1 will be controlled in the analyses. A previous study examining the association between T. gondii and SZ tested similar potential confounders, finding only maternal age to be associated with T. gondii titer level (Brown, Schaefer et al. 2005). Yet, others have hypothesized a host of potential confounders related to T. gondii (Mortensen, Pedersen et al. 2011), and epidemiological surveys have reported differences by job type, SES, education level, and ethnicity (Jones, Kruszon-Moran et al. 2001), suggesting that these potential confounders be considered. Each of the above specified covariates will be tested for their possible association with both the exposure (T. gondii) and the outcome (BP).

Method for oxytocin

Oxytocin administration to induce labor was contemporaneously documented in medical charts in the CHDS and systematically abstracted from the medical records by the CHDS. The CHDS noted oxytocin in four separate fields which have been combined to construct a dichotomized variable: oxytocin versus no oxytocin. The analyses will consider whether oxytocin exposure during maternal labor is associated with BP.

Conditional logistic regression models will be used for the matched case-control analyses as described above. The oxytocin analyses include all 93 cases, matched 1:8 with controls, with 9 controls missing. This gives sufficient power to observe a moderate effect (OR = 2.4, power of .8 and p = .05). Gestational age and maternal psychiatric history will be tested as a potential confounders since both could be related to oxytocin use and BP. Potential confounders, as described above, will also be controlled when associated with exposure and outcome at a probability greater than 0.1.

Method for prolonged labor

The CHDS documented length of labor contemporaneously to each birth by noting time from onset of labor to delivery as well as second stage to delivery. Using the current definitions of prolonged labor, equal to or greater than six hours for first stage, and equal to or greater than two hours for second stage for first births and equal to or greater than one hour for additional births (ACOG 2003, Zhang, Landy et al. 2010, Spong, Berghella et al. 2012), this variable was dichotomized to prolonged versus not prolonged. In addition, labor time was examined as a continuous variable using the time noted in the medical charts in the CHDS. Each of the stages and the continuous length of labor was tested for an association with BP using conditional logistic regression.

Prolonged labor could be an antecedent to oxytocin in that women with longer labors might be more likely to be induced with oxytocin, which in turn increases the risk for BP. Alternatively, it could confound the relationship between oxytocin and BP in that longer labor shares a common cause with oxytocin to induce. Therefore, the association between prolonged labor and BP are tested, as are the association between prolonged labor and oxytocin. These analyses are a method for testing the whether the potential oxytocin relationship to BP is confounded by or the result of labor length.

Method for analgesics

Analgesics were coded by drug given in the CHDS and here, a dichotomous variable for any analgesic versus none was constructed for analyses. Testing a potential role of analgesics, as a confounder or for possible interaction with oxytocin, could provide support for the specificity of oxytocin. It is possible that women who receive oxytocin are more likely to also be given an analgesic. It is also possible that being given any drug intervention at a late stage of pregnancy could increase the risk for BP. To test for this, analgesics will be treated first as a potential confounder and then tested for possible multiplicative or additive interaction with oxytocin and risk of BP. Conditional logistic regression is used for these analyses.

Method for delivery type

Delivery type was documented by the CHDS as well. It is possible that labor complications lead to caesarean as a medical intervention. This may also be a reason that oxytocin to induce labor was used. In this way, labor complications may be an unmeasured common cause of both delivery type and oxytocin. Delivery type is analyzed as a potential confounder, similar to the demographic covariates which are tested for potential confounding. Delivery type is presented as a separate comparison because of its temporal association with the use of oxytocin in the birth process. A dichotomous comparison between caesarean and vaginal delivery and BP disorder was analyzed. Again, conditional logistic regression was used to model the associations.

Results

First, for the BP case-control, potential confounders were assessed by comparing differences between cases and controls. As can be seen in Table 8, none of the potential demographic confounders is associated with case status with the exception of maternal race. However, maternal race was not associated with oxytocin (for African-Americans, $p = 0.90$; for “other,” $p = 0.94$) nor with BP (for African-Americans, $p = 0.70$; for “other,” $p = 0.2$), and maternal psychiatric history was not associated with

oxytocin (p = 0.46) nor with BP (p = 0.43). Therefore, none of the demographic covariates were treated as confounders.

Table 8: Demographic comparison of cases and controls

	Bipolar Cases (N = 94)	Controls (N = 746)	P value
Maternal age at child's birth, Mean (SD)	27.3 (6)	28.0 (6)	0.32
Maternal education, N (%)			0.85
< High school	18 (21)	128 (19)	
High school graduate	32 (37)	271 (39)	
Some college or college graduate	36 (42)	293 (42)	
Maternal race, N (%)			0.07
white	64 (69)	425 (58)	
African-American	24 (26)	215 (29)	
other	5 (5)	92 (13)	
Paternal education N (%)			0.51
< High school	12 (14)	134 (20)	
High school graduate	26 (32)	192 (28)	
Some college or college graduate	44 (54)	350 (52)	
Paternal race, N (%)			0.14
white	55 (70)	387 (59)	
African-American	19 (24)	189 (29)	
other	5 (6)	79 (12)	
Maternal psychiatric history (any), N (%)	24 (25)	132 (18)	0.07
Birthweight in grams, Mean (SD)	3374 (21)	3289 (17)	0.17
Gestational age in days, Mean (SD)	281 (16)	280 (14)	0.33

Results for T. gondii

For the 255 samples tested, 35 were high IgG titer and 20 were moderate IgG titer. Table 9 displays the comparison between low titer (the referent) and moderate and high titers for risk of BP. Neither high nor moderate titers were associated with BP. None of the potential confounders were found to differ significantly between cases and controls.

Table 9: Maternal T. gondii titer levels and risk of offspring BP

	Hazard Ratio	CI
Low Titer	Referent	--
Moderate Titer	1.43	(0.491, 4.171)
High Titer	1.6	(0.738, 3.478)

Discussion of T. gondii

This finding is consistent with that reported by Mortensen et al (Mortensen, Pedersen et al. 2011), and confirms their result in an independent birth cohort. That study, as noted, analyzed dried blood spots

on filter paper obtained from the infant and not maternal sera obtained during pregnancy. This study used maternal sera drawn at birth but reaches the same result.

Therefore, distinct from the risk that T. gondii poses for later life SZ (Brown, Schaefer et al. 2005), it does not appear that prenatal exposure to T. gondii increases the risk of offspring BP. As the mechanisms by which T. gondii increases the risk of SZ become better elucidated, it may be possible to further differentiate this risk as a potential cause for SZ but not BP. However, this non-significant result may reflect a lack of power. The effect size does increase as the titer increases, and the confidence interval is smaller for the high titer, suggesting a dose-response effect. Further testing of T. gondii in larger samples is warranted.

Results for Oxytocin

Of 831 subjects, 34 received oxytocin to induce labor: 8 cases and 26 controls. As shown in Table 10, oxytocin is associated with a 2.45 times increased risk of BP in adulthood (HR = 2.45, CI: 1.08, 5.58). Controlling for gestational age has almost no effect on the finding and controlling for maternal psychiatric history may slightly enlarge the effect of oxytocin.

Table 10: Oxytocin and risk for later BP

	Hazard Ratio	CI
Oxytocin	2.45	(1.08, 5.58)
Oxytocin controlling for gestational age	2.44	(1.07, 5.55)
Oxytocin controlling for maternal psychiatric history	2.99	(1.08, 8.3)

Results on the falsification of the oxytocin finding

In order to further parse the oxytocin finding, the three potential alternative explanations were tested: prolonged labor, analgesics, and delivery type. First, prolonged length of labor as a continuous time, from time of active onset to birth, was not associated with BP ($p = 0.41$) in an unadjusted model. Prolonged first stage of labor was not associated with BP ($p = 0.1$) in an unadjusted model. Prolonged second stage of labor was not associated with BP ($p = 0.064$) in an unadjusted model. However, no people who had prolonged second stage labor also received oxytocin. Continuous labor length was

associated with 1.7 times increased use of oxytocin (parameter estimate = 0.32, chi square = 7.85, p =0.005), but the increase is for mothers with shorter labor.

Second, for 840 births, 748 mothers received an analgesic. Analgesics were not associated with BP (chi-square = 0.21, p = 0.65). To test the hypothesis that analgesics could interact with oxytocin, a model was tested which included a cross-product of those two exposures. The interaction term was not associated with BP (p = 0.988). However, only a single person who received oxytocin did not also receive an analgesic. This means that off support data makes the analysis of interaction in this case-control study not feasible. Third, for delivery type, 795 had vaginal births and 42 had cesarean births. Neither cesarean nor vaginal births were associated with BP (for both variables, p = 0.99).

Discussion of oxytocin

Oxytocin to induce labor is associated with a 2.45 times increased rate of later life BP. Controlling for gestational age, which could be related to oxytocin because longer gestation might lead to an increased use of oxytocin, made no difference in the effect size of oxytocin on BP. Controlling for maternal psychiatric history may increase the observed effect slightly.

The observed effect appears to be directly related to oxytocin as a drug, not as a proxy for other complications. In an effort to more clearly test the specificity by which oxytocin is associated with BP, and to rule out some potential avenues of confounding, delivery type, analgesics, and duration of labor were each tested. Delivery type, which might have reflected a similar type of labor complication resulting in medical intervention (e.g., where labor complications are a common cause), was not associated with BP or with oxytocin. This supports the conclusion that oxytocin's effect is not a generic proxy for labor complications. Analgesics, which might reflect a non-specific effect of drug interventions during labor or share a common cause with oxytocin, was also not associated with BP. Although it is not possible to test for interaction in this study, Oscarsson et al had similarly tested whether analgesics played a role in poor outcomes associated with induced labor and also found that they did not (Oscarsson, Amer-Wahlin et al. 2006). Again, this supports the conclusion that the effect of oxytocin is specific.

Third, prolonged labor, which conceptually could be associated with an increased use of oxytocin to induce labor, did not act as hypothesized. It is associated with a 1.7 times increased use of oxytocin,

but for mothers with shorter rather than longer duration of labor. Moreover, no subjects with prolonged second stage of labor received oxytocin to induce labor, which runs counter to the hypothesis that the longer second stage would lead physicians to induce more often.

These findings suggest a specific effect of oxytocin on the risk for BP. As noted above, oxytocin has been reported to increase the risk of neonatal intensive care and lower Apgar scores (Oscarsson, Amer-Wahlin et al. 2006, Selo-Ojeme, Rogers et al. 2011), is associated with an increased risk of ADHD (Kurth and Haussmann 2011), and an increased risk for autism in a large cohort from North Carolina (Gregory, Anthopolos et al. 2013). Kurth and Haussmann suggested that future research should consider whether the combination of oxytocin and an analgesic best explained the increased risk of psychiatric illness because those who received oxytocin were more likely to be given an epidural anesthesia in their sample (Kurth and Haussmann 2011). The current study does not support the hypothesis that analgesics and oxytocin interact to increase the risk for BP, but instead indicate that oxytocin, and not analgesics, act to increase risk.

It is usually hypothesized that the mechanism by which maternal oxytocin exposure may affect offspring is fetal hypoxia, restricted neural blood flow, and increased fetal bilirubin (Drew and Kitchen 1976, Connor and Seaton 1982). This study does not rule that hypothesis out, but it does suggest that the mechanism may be more specific to oxytocin itself.

Uterine contractions during parturition are prompted by endogenous maternal oxytocin, released from the hypothalamus and pituitary (Maggi, Baldi et al. 1994, Brunton, Russell et al. 2013). Endogenous oxytocin also plays a critical role in the maternal stress response, a response which is suppressed during pregnancy and birth to avoid premature labor from emotional and physical stressor exposures, such as immune challenges from viral exposure or social stress (Brunton and Russell 2008, Brunton and Russell 2011). Disruption of the maternal stress response system, which exogenous oxytocin to induce labor could plausibly prompt, has been shown to affect fetal neuronal development, neural plasticity, and myelination (Brunton and Russell 2011, Duthie and Reynolds 2013). Further, endogenous maternal oxytocin signals a temporary GABA switch in the fetus, from excitatory to inhibitory, in preparation for labor (Tyzio, Cossart et al. 2006, Khazipov, Tyzio et al. 2008, Ceanga, Spataru et al. 2010); this switch is thought to protect the fetal brain, but may become excessive with the addition of exogenous oxytocin

because the neuroprotective effect occurs only within a narrow range of oxytocin expression (Ceanga, Spataru et al. 2010). During brain development, GABA, and its precursor glutamate, affect neuronal migration, differentiation, and survival; GABA maturation continues through adolescence in normal development (Catts, Fung et al. 2013); and, alterations of the GABA neurotransmitter system have been found in people with BP (Benes, Lim et al. 2007, Gigante, Bond et al. 2012). In addition, high concentrations of maternal oxytocin just prior to labor increase the risk for fetal hypoxia-ischemia (Ceanga, Spataru et al. 2010).

Although plausible, these findings require confirmation and further testing before the mechanism can be meaningfully tested. That research suggests a plausible biologic mechanism for the observed effect of oxytocin, and because the effects observed appear to be specific to oxytocin as a chemical agent rather than as a proxy or place-holder, replication is warranted. Finally, the increased use of oxytocin has been associated with neonatal morbidity generally (Oscarsson, Amer-Wahlin et al. 2006, Buchanan, Patterson et al. 2012), but whether the increased use is associated with an increased incidence of BP is not known and should also be considered.

Conclusion

In summary, the results of this study of the prenatal and perinatal risks for BP are that T. gondii was not associated with later BP. This differs from the findings for SZ, in which an association is observed. As a result, this may suggest potential causal differences between BP and SZ, but the small sample size may mean that this study is underpowered to have observed the hypothesized effect.

In contrast, oxytocin to induce labor is associated with BP, and the association appears to be specific to the chemical agent itself. Oxytocin has not been studied as a risk factor for SZ and further research is needed as a result, but this finding corresponds with other recent research which indicates that oxytocin is a risk for autism and ADHD.

In conclusion, this research supports the neurodevelopmental hypothesis in the sense that a specific early life exposure has been found to alter the course of neurodevelopment. It lends some specificity to the search for putative causes and mechanisms of BP.

Paper 3: Premorbid cognition, environmental exposures, and Bipolar disorder (BP)

One key pillar of support for the neurodevelopmental hypothesis of schizophrenia (SZ) is the evidence of cognitive impairment during the premorbid and prodromal periods (Keshavan, Kennedy et al. 2004, Reichenberg and Harvey 2007, Woodberry, Giuliano et al. 2008, Mesholam-Gately, Giuliano et al. 2009, Consortium 2013, Olvet, Burdick et al. 2013). For instance, a nested case-control study of SZ drawn from the Child Health and Development Study (CHDS) birth cohort, compared childhood cognitive performance as measured by the Peabody Picture Vocabulary Test (PPVT) given at ages 5 and 9-11, and re-administered in adulthood, to examine the course of cognitive functioning over 33 years. This study found a ten point difference in the early childhood PPVT, with those who would later develop SZ performing more poorly than the matched controls. In adulthood, the gap in performance was wider, with those who had developed SZ scoring 15 points below the controls (Kremen, Vinogradov et al. 2010). The ten point difference observed in childhood scores is consistent with the neurodevelopmental hypothesis of SZ.

Evidence of premorbid and prodromal cognitive impairment in BP would similarly support the neurodevelopmental hypothesis for BP. Numerous studies and meta-analyses have reported cognitive impairments in all phases of illness, including the premorbid and prodromal periods of developments, for the high risk, at first onset, in euthymic states, and for each type of BP: BP I, BP II, BP NOS, BP with and without psychotic features (Bearden, Hoffman et al. 2001, Quraishi and Frangou 2002, Reichenberg, Weiser et al. 2002, Martinez-Aran, Vieta et al. 2004, Savitz, Solms et al. 2005, Daban, Martinez-Aran et al. 2006, Daban, Martinez-Aran et al. 2006, Robinson, Thompson et al. 2006, Torres, Boudreau et al. 2007, Arts, Jabben et al. 2008, Goodwin, Martinez-Aran et al. 2008, Bora, Yucel et al. 2009, Kurtz and Gerraty 2009, Reichenberg, Harvey et al. 2009, Stefanopoulou, Manoharan et al. 2009, Bearden, Woogen et al. 2010, Harvey, Wingo et al. 2010, Latalova, Prasko et al. 2011, Mann-Wrobel, Carreno et al. 2011, Pol, van Baal et al. 2012, Bourne, Aydemir et al. 2013, Hill, Reilly et al. 2013, Lim, Baldessarini et al. 2013). Cognitive deficits are observed in the domains of executive functioning, verbal learning, verbal memory, sustained attention, and psychomotor speed. The effect sizes are moderate and large in these domains. These studies are often used to support the notion that cognitive impairment is a trait of those who develop or have BP.

Some, but not all, population based studies, many of them using conscript testing, have reported premorbid cognitive impairment. These draft board neuropsychological batteries lack the specificity and breadth of a complete functional assessment, although they do provide useful population based information on a testing battery that mimics IQ assessments. One large Danish draft board study reported small IQ difference for both BP and unipolar depression compared with the general population, with no significant differences between illnesses (Sorensen, Saebye et al. 2012). A second Danish draft board study observed small deficits in IQ for people who developed affective disorders (as well as schizophrenia; non-schizophrenic, non-affective psychotic disorder; neurotic or stress disorder; and personality disorders) compared with population controls (Urfer-Parnas, Mortensen et al. 2010). And, a third Danish draft board study of all men born in 1953, compared testing at ages 12 and 18 for those who later developed BP, also reporting impaired cognition compared to those without BP, but the sample size (N=16) is reported to be too small to offer stable results (Osler, Lawlor et al. 2007). A more recent analysis of four Swedish birth cohorts compared trend data for testing at ages 13 and military induction testing at age 18. They reported that the 18 subjects with BP performed better than the population at both time points on verbal, spatial, and inductive reasoning (MacCabe, Wicks et al. 2013). In contrast, a Finnish population based cohort study, analyzing conscript testing at ages 18-19, reported that worse premorbid performance on a test of visuospatial ability predicted later onset BP (Tiihonen, Haukka et al. 2005).

Population based studies that assess cohorts on other types of cognitive testing than the conscript studies tend to indicate deficits in specific domains. In a prospective study which followed children into adulthood, children tested between ages 3 and 11 who later developed bipolar mania, had receptive and expressive language skills that varied between testing periods compared with controls (expressive language was higher at age 3, lower at ages 5 and 7, and higher at age 11; receptive language was lower at age 3, higher at 5 and 7, and lower at age 11; IQ was slightly higher at age 7 and lower at age 11), and they had more behavioral difficulties (Cannon, Caspi et al. 2002). This study included only 20 people who developed mania in adulthood through age 26, and none of the scoring differences reached statistical significance. Another prospective study, this one of children at high risk for BP followed for 23 years, reported that the 9 people who developed BP had lower IQ scores than those

who developed unipolar (n = 22) and those without mood disorder (n = 64), although all the scores were within the normal range (Meyer, Carlson et al. 2004). In addition, they found that those who developed BP performed significantly worse on executive functioning measures prior to onset.

High risk studies have tended to find differences between those who develop BP and those who do not. An exploratory high risk for psychosis study prospectively followed and compared 16 people who converted to BP with 46 who did not convert to psychosis, and to 66 healthy comparison subjects, matched on age and sex (Ratheesh, Lin et al. 2013). At baseline, the clinical characteristics of all those at high risk were similar; subjects who later developed BP had lower full scale IQ scores compared with controls (approximately twelve points lower than healthy controls and four points lower then other high risk subjects), and performed significantly worse on a measure of executive functioning. Another comparison of high risk subjects, this one comparing pre-conversion functioning for 8 subjects who later converted to BP, 24 who later converted to SZ, and 115 non-converters, found that at baseline the BP subjects had IQ scores approximately 10 points lower than non-converters, although this was non-significant (Olvet, Stearns et al. 2010). Although reporting that the BP group performed worse than non-converters on other neuropsychological tests, and that they also demonstrated more variance in scoring, the authors note that the study was underpowered.

School performance reflects another arena in which to consider premorbid functioning. A twin study of school success observed that those who later developed BP had fewer years of education and worse performance compared with matched, control twins (Vonk, van der Schot et al. 2012), and this finding is also reported in case-control studies (Glahn, Bearden et al. 2006). Cannon et al demonstrated worse premorbid sociability, adjustment, and schooling for those who later developed BP (Cannon, Jones et al. 1997). However, others have reported that both low and high premorbid school performance is a risk factor for BP based on a longitudinally followed, nationally representative cohort (MacCabe, Lambe et al. 2010).

In summary, cognitive functioning prior to the onset of illness, one key pillar of the neurodevelopmental hypothesis, tends to demonstrate domain specific impairments on average, with some worse and some superior performance on global measures such as IQ. The effect sizes are larger for people during the prodromal period then during the premorbid period, but none of the effect sizes are

as large as those observed in people who later develop SZ. A review of population based studies concluded that the evidence of premorbid cognitive impairment does not yet support a conclusion that such impairments define a trait of later BP (Kravariti, Kane et al. 2009). One limitation of the premorbid studies has been the small sample sizes and the narrow test batteries used prospectively for assessment. Further investigation of the mixed evidence of premorbid cognitive functioning in those who later develop BP may improve our understanding of whether BP should be considered a neurodevelopmental illness.

The BP nested case-control study drawn from the CHDS birth cohort provides an opportunity to further test the premorbid cognitive functioning of those who later develop BP. Prospectively administered cognitive testing in this well defined birth cohort, and the availability of large numbers of children tested, permits analyses of premorbid functioning without retrospective biases. These data also allow for testing of the relationship among prenatal and perinatal exposures and cognition, and the relationships between those early life exposures, cognitive performance in childhood, and later life BP.

Childhood diagnostic measures included the Peabody Picture Vocabulary Test (PPVT) and the Raven Matrices (Raven). The PPVT is a well-known, commonly used test which estimates receptive verbal ability. Alternate form reliability of the PPVT is estimated to be r = .77 (Dunn 1965). The examinee is shown a plate with four pictures, the examiner speaks a word describing one of the four, and the examinee selects the correct picture either by speaking or pointing. The test manual indicates that it can be used with children as young as two and a half years old, and the instrument does not require reading, writing, or verbal ability. The PPVT was originally normed on 4012 children between the ages of 2 and 18, with a total of 133 aged 5 and 962 between ages 9-11 (Dunn 1965). In the CHDS, the PPVT was given to 3,413 children at age 5 and 3,737 at ages 9-11. The size of the birth cohort allows for cohort specific norming of the PPVT, rather than relying on the much smaller age specific standardization sample conducted for the original publication of the instrument.

The Raven instruments are cognitive tests of visual-spatial processing, inductive reasoning, relational reasoning, and problem solving. Test-retest reliability of the Raven for children under age 13 is estimated to be r = .88 (Raven 1958). Each question displays a pattern with a block missing, and four choices to choose from, one of which accurately completes the pattern. It is commonly described as well correlated with standard IQ test measures, primarily because of its correlation with measures of fluid

intelligence. The Raven, or tests which mimic the design of the Raven, have been used in numerous tests batteries of premorbid and post onset cognition in those who later developed psychotic disorders, with impaired performance on the Raven consistently being associated with psychosis (Berman and Weinberger 1990, Welham, Scott et al. 2010, Zanelli, Reichenberg et al. 2010). Worse performance on the Raven has been reported for those who later developed SZ compared with controls (Caspi, Reichenberg et al. 2003, Cannon, Moffitt et al. 2006). Zanelli et al (2010) used the Raven as a measure of executive functioning in a study of first episode psychosis and found that, although all first episode psychosis groups were impaired compared with healthy controls, those with SZ, depressive psychosis, and other psychosis performed substantially worse than those with BP (Zanelli, Reichenberg et al. 2010).

The CHDS prospectively documented a number of prenatal and perinatal exposures, including gestational influenza and oxytocin, and obtained maternal sera for each pregnancy which was tested for T. gondii. Each of these exposures may have a negative effect on cognition. First, maternal infections during pregnancy, including influenza, are associated with cognitive impairment in offspring who develop SZ when they reach adulthood (Brown, Vinogradov et al. 2009). Exposure to maternal influenza has been reported to affect childhood cognition in some specific domains in those who develop SZ, although not in controls (Ellman, Yolken et al. 2009). It has also been suggested that men potentially exposed in utero to the main outbreak of pandemic flu in the winter of 1968-9 in Norway, performed significantly more poorly on military conscript testing compared to those born in non-flu years (Eriksen, Sundet et al. 2009). They found that scores for men born 6 to 9 months after the epidemic were lower than scores for the men born in the same months, but in the years before and after the epidemic. The study did not have confirmation of exposure to influenza in individual pregnancies, however. A similar result, although using less standardized testing measures at ages 7 and 11, has also been reported from the National Child Development Study in the UK (Kelly 2011). Controlled administration of maternal influenza to pregnant rhesus monkeys did affect offspring neurodevelopment, specifically reducing gray matter in the cortex and white matter in the parietal cortex (Short, Lubach et al. 2010), providing animal model support for influenza as a causal agent which impairs cognition. Similarly, maternal viral infection in a number of animal species has been associated with behavioral and cognitive impairments in offspring (Meyer and Feldon 2010). The CHDS prospectively documented exposure to influenza during pregnancy.

Second, prenatal exposure to T. gondii's and the possible association with impaired cognition, and its association with SZ, makes it an important antecedent to test as part of considering whether BP is neurodevelopmental as well as for better understanding the potential mechanisms of BP. Much of the prior evidence is either ecological or based on measures of adult exposure. Prenatal exposure, however, would affect development, thereby offering evidence of a developmental cognitive effect. The Collaborative Perinatal Project, a multisite, prospective study of more than 22,000 births, reported on childhood cognitive outcomes at age 7, finding that the highest maternal T. gondii titer was associated with a thirty percent increased risk of offspring IQ below 70 and with neurological soft signs (Sever, Ellenberg et al. 1988). The mechanism by which the parasite proliferates, specifically affecting the central nervous system, suggests that prenatal exposure is likely an important period of risk for neuronal maldevelopment. Thus, the purported mechanism by which T. gondii could affect neurodevelopment, both impairing cognition and increasing risk for psychiatric illness, can be analyzed in this case-control study directly to assess the neurodevelopmental effects of exposure.

Third, induction with oxytocin has been associated with an increased risk BP (above), ADHD (Kurth and Haussmann 2011), and autism (Gregory, Anthopolos et al. 2013). Oxytocin, as measured in adults and in animal models, has been associated with impairments in learning, attention, and memory, and oxytocin is reported to reduce cognitive ability in experimental models (Demitrack and Gold 1988). Although some obstetric complications have been associated with childhood cognitive deficits (Seidman, Buka et al. 2000, Leitner, Fattal-Valevski et al. 2007), no prospective population based studies of oxytocin have been identified.

Methods:

The Child Health and Development Study (CHDS) is a large, representative birth cohort, containing 19,044 live births. This cohort has been followed prospectively, with prenatal serologic samples obtained during pregnancies, perinatal measures obtained during routine medical care, childhood cognitive assessment performed at ages 5, 9-11, and 15-17 on subsets of the birth cohort, and psychiatric diagnoses confirmed in adulthood. Using a nested case-control design to obtain all BP cases

and matched controls from the CHDS, this research investigates the relationship between serologically obtained prenatal exposures and birth complications, early childhood cognition, and onset of BP.

Cases and controls for the Prenatal Factors and Bipolar Disorder Study were drawn from the CHDS birth cohort (van den Berg, Christianson et al. 1988). The CHDS recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (Kaiser) in Alameda County, California between 1959 and 1966. Contemporaneously completed medical records, maternal interviews, child assessments, and other sources were generated prospectively during the course of pre and perinatal medical care provided by Kaiser. Kaiser reflects the population of the Bay Area of California at the time, providing care to approximately 30% of the population of Alameda county, with some underrepresentation at both the extremes of income. This birth cohort has been extensively studied for prenatal and other early developmental risk factors for SZ (Susser, Schaefer et al. 2000).

Two analyses are reported here. The first examines premorbid cognition and the risk of BP in the nested case control birth cohort. The second investigates the associations among gestational exposure to maternal influenza, prenatal exposure to T. gondii, and oxytocin to induce labor, and childhood cognitive performance.

Case Identification

People with potential DSM-IV BP, which included BP I, BP II, BP NOS, and BP with psychotic features, were ascertained by screening procedures which used data from three sources: Kaiser's electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailing to the entire living CHDS birth cohort (mothers and children). This approach sought to maximize ascertainment of individuals with BP. CHDS cohort members who belonged to Kaiser when first treated would have been ascertained from this source. Subjects who left Kaiser prior to the first treatment of BP and who did not have other health insurance, but who still lived in Alameda County, would likely have been treated by ABHCS and therefore ascertained. Subjects who were not ascertained by these two approaches were ascertained by a mailed survey to the entire cohort.

The ascertainment process identified 448 subjects who potentially met the criteria for BP and psychotic disorder.

Ascertainment of Kaiser subjects

Subjects with potential BP (and other psychotic disorders) were identified by screening Kaiser's inpatient and outpatient databases. Computerized record linkages between CHDS and Kaiser identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of Kaiser members regardless of the hospital at which treatment is received. This covered the period from 1981-2010. Those with discharge diagnoses of ICD-9 295-298 from the Kaiser inpatient database were considered as potential BP subjects. A database of outpatient treatment was introduced in 1981, but did not contain searchable codes for diagnoses until 1995. Potential BP cases from the outpatient database were considered to screen positive if they received ICD-9 diagnoses of 295-298 excluding unipolar major depressive disorder. Case ascertainment also used the Kaiser outpatient pharmacy database, which commenced in 1992. Cases screened positive based on prescriptions for mood stabilizing medications used in the treatment of BP (lithium, carbamazepine, valproic acid). Before contacting subjects who were currently enrolled in Kaiser, the subject's treating psychiatrist was contacted, informed about the study, and asked to approve contact with the subject to seek his/her consent to participate.

Any subjects identified by these methods were invited to participate in the study, receiving a letter to the most recent address, and those who did not refuse contact by returning a postcard, were contacted to arrange an appointment for a diagnostic interview. Up to several repeat appointments were scheduled for subjects who failed to attend the interview. Extensive efforts were made to locate individuals who were no longer living at the most recent listed address, including Department of Motor Vehicles records, telephone directories, and contacting the subjects' parents or siblings from CHDS or Kaiser files. Mortality records, reverse directories, jail searches, and visits to previous addresses were also used as necessary.

Ascertainment by Alameda County Behavioral Health Care Services (ABHCS)

Outpatients with potential BP were also ascertained by electronic record linkage between the CHDS and ABHCS identifiers. The ABHCS database included treatment from 1993-2009. These subjects

screened positive based on ICD-9 outpatient diagnoses of 295-298, excluding unipolar major depressive disorder. Procedures for finding and recruiting these potential subjects were similar to those described above for ascertainment by Kaiser.

Ascertainment of CHDS birth cohort by mailed questionnaire and follow-up

The third method of ascertainment was initiated by letters mailed to all living mothers (N=6,971) and cohort members (N=13,009) with known addresses in the entire CHDS cohort (excluding families in which potential cases had already been identified in the Kaiser and/or ABHCS) along with a questionnaire on mental and physical health. This was conducted from 2009-11. Questionnaire respondents who reported “mental health problems” in an eligible cohort member (including the respondent him or herself) were contacted by a trained Kaiser study interviewer who administered the Family Interview for Genetic Studies (FIGS) to screen for possible BP or psychotic illness in the cohort member. If the FIGS indicated at least one bipolar and/or psychotic symptom (delusions/hallucinations), then the cohort member was considered to have screened positive, and was invited to participate in the diagnostic interview. If the respondent (mother or sibling) described symptoms in a birth cohort member, the respondent was asked if he or she would be willing to have the study contact the affected family member about participation in the study. If the respondent agreed, the affected cohort member was contacted by letter and invited to participate.

Diagnostic protocol

Accurate diagnosis of BP is critical to understanding its causes. A number of prior studies, as noted above, have suffered from poor diagnostic specificity of BP, grouping a number of illnesses into catch-all categories such as “affective disorders”. The current research benefits from the careful diagnostic assessment and inclusion of confirmed cases of BP.

A total of 214 subjects (48% of those ascertained) were interviewed using the Structured Clinical Interview for DSM-IV TR (SCID). The reasons that some subjects were not interviewed were: 100 could not be contacted, 80 refused or failed to keep the appointment, and 54 who could not be interviewed

because he or she had died, were incarcerated, permission from the physician could not be obtained, or because the person was too psychotic or mentally disabled.

Study interviewers had a minimum of a master's degree in a mental health field and were trained to reliability on the SCID. DSM-IV-TR diagnoses including diagnostic qualifiers representing subtypes of BP were systematically assigned by consensus of three experienced clinicians (psychiatrists/Ph.D. psychologist), based on review of the SCID and medical records. This yielded 72 total BP cases. Among those interviewed, consensus diagnoses of non-BP disorders were also assigned: there were 61 cases of SZ and other schizophrenia spectrum disorders, 62 cases of major depressive disorders, and 19 cases with other diagnoses. These non-BP categories were not included in the present study. Although unipolar major depressive disorder was not included in the screening procedure, the diagnostic protocol enabled us to exclude subjects with database diagnoses of BP and/or psychotic disorders who were found instead to have unipolar depressive disorder in accord with structured research criteria.

Ascertainment from PDS I study

Additional cases of BP had been ascertained through Kaiser records by an earlier study (Prenatal Determinants of Schizophrenia I, PDS I) were included in the present study (Susser, Schaefer et al. 2000). Although the purpose of PDS I was to identify SZ and other schizophrenia spectrum disorder cases, BP cases were also diagnosed by interview in that study. The protocol for the PDS I included the same electronic linkages with the Kaiser inpatient, outpatient, and pharmacy databases, and utilized the same ICD-9 diagnostic codes (295-298). Ascertainment covered the period from 1981-1998. The only other differences in the screening methods are that the PDS I did not include review of pharmacy records for treatment with mood stabilizers, and the PDS I included a second screening step, which involved psychiatrist review of abstracted data from inpatient/outpatient records for symptoms of psychosis. The Diagnostic Interview for Genetic Studies (DIGS), rather than the SCID, was used for interviewing potential subjects in the PDS I. There were 23 BP cases diagnosed in the PDS I study.

In total, then, 95 people with BP were diagnosed following ascertainment from all sources and clinical interview.

After complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Kaiser.

Control Selection

In order to ensure that controls would have been equally likely (as their matched cases) to be ascertained if they had been treated for BP in Kaiser or ABHCS, controls were matched to cases on membership in Kaiser (for cases ascertained through Kaiser records) or residence in Alameda County (for cases ascertained through ABHCS or by CHDS mailing survey) in the year the case was first treated as reported in the SCID. For Kaiser, membership in the plan at that time was used for control matching, since cohort members would have been documented in Kaiser databases if they sought care for BP. The DMV was used to ensure place of residence at the time of diagnosis for cases treated by ABHCS and those identified from the mailed survey, since these subjects would have been the population at risk for treatment at same time. The vast majority of the subjects who received the mailing were Alameda County residents.

Control matching criteria included: date of birth (+/- 30 days), sex, and availability of maternal archived sera (for serologic studies). A maximum of an 8:1 ratio of controls to cases was achieved, as it represented the maximum number of controls that could be successfully matched to cases on all criteria and to maximize statistical power.

Exclusion criteria (prior to matching) were: all of the CHDS cohort members who screened positive for potential bipolar or psychotic disorders (N=376) and siblings of those cases; potential controls who belonged to Kaiser at the time of case ascertainment were excluded from the control pool for cases identified from ABHCS or the cohort mailing; and siblings of selected controls were excluded from further control selection, so that all controls were independent observations, each representing a single family or pregnant woman.

This protocol yielded 754 matched controls.

Measurement

Cognitive measures in childhood: The Peabody Picture Vocabulary Test (PPVT)

Standardization of the PPVT for this sample was performed by converting raw scores to standard scores (z scores) by using the mean and standard deviation observed in each tested sample by age group. For the PPVT, the mean was set at 100, standard deviation of 15, as is the common practice for measures which estimate IQ. Once standardized, testing for ages 5 and 9-11 were combined. Standardized scores for the entire birth cohort tested have been calculated and normed for the cohort, including all cases and controls. Although standardization was done by the CHDS researchers previously, they normed the standardization for age, race, and gender. Because of the nature of the tests, use of age, race, and sex norms is unwarranted. Age variation is minimal, in fact a smaller range than is commonly used for norming test instruments, and race and sex can be controlled in the modeling and analyses if they prove to be potential confounders. Controlling for these variables in the norming makes it more difficult to assess whether or not they act as confounders.

Cognitive measures in childhood: Raven Progressive and Colour Matrices (Raven)

In the CHDS, a randomly selected subset of children in the birth cohort were tested at age 5 with the Raven Coloured Matrices, which consists of 21 plates. Twenty-one plates were shown to each child, and they were asked to choose among the four options to complete the pattern in the picture. At age 9-11, another randomly selected subset was tested, this time with the age appropriate Raven Progressive Matrices, which consists of 60 plates. Children are shown 60 plates and asked, for each, to select the pattern that completes the image from among four options. Researchers from the CHDS constructed standardized z-scores for each test, with a mean of 50 and standard deviation of 10. However, they used age, race, and sex to norm the standardization. As with the PPVT, if race or sex is found to be a potential confounder, it can be controlled in the analyses rather than assuming the potential effect and constructing norms with those variables. The original standardization sample for Coloured Matrices included 608 children between the ages of five and 11 ½ (Raven 1956). The Progressive Matrices was normed on a representative British sample (Raven 1960) and no sample size is provided in the manual. The CHDS contains many more age cohort subjects for norming, drawn from the same Northern California region,

and captures the population at risk most appropriately. Moreover, the number of children administered the tests is substantially larger than typically obtained for norming. A total of 3,412 five year olds were assessed with the Raven, and 3,737 children at ages 9-11.

For these analyses, cohort norms for the Raven have been calculated using a mean set at 0 and a standard deviation of 1. After converting into standard units based on the proportion correct, the results have been combined for age 5 and ages 9-11 such that the entire cohort can be analyzed at once.

Analytic method for testing the association between childhood cognitive performance and BP

Fifty cases and 215 matched controls were tested in childhood. None of those tested at age 5 were also tested at ages 9-11 in this subset of the birth cohort. These subjects were randomly selected for testing in childhood from the full birth cohort. As a result of standardizing the scoring on the different instruments used for assessment, differences between groups will be observed by standard deviation units. This study has sufficient power to detect a large association (OR = 2.8, power of .8 and p = .05),

The relationship between cognition and BP was assessed using conditional logistic regression. It was hypothesized that cognition may be directly related to risk of BP. If it is, mediational analyses will be undertaken to assess whether cognition mediates the relationship between T. gondii, oxytocin and BP. The central role of cognition in SZ, and potentially in BP, suggests that it may be one of the mechanisms that leads to later onset of psychotic illnesses. Mediation was analyzed by testing the associations of each exposure with BP directly, then testing the association with cognition as a potential mediator in the model. Analyses will compare changes in the beta estimate of the models, assuming no unmeasured confounding or effect modification (Baron and Kenny 1986). It is not expected that cognition would fully mediate the relationship, but a priori, a ten percent change in beta estimate was considered meaningful.

Maternal age (<35 [reference], ≥35), maternal ethnicity (Caucasian [reference], African American, other), maternal educational achievement (defined as maternal education: <high school, high school only [reference], some college/college graduate), parity, gestational age (number of days after last menstrual period), and maternal psychiatric history are considered as potential confounding variables. Each covariate's association with BP and with cognition was tested for significance of a possible association.

Fetal hypoxia was considered as a potential confounder but no reliable measure of it was available in these data.

Analytic method for testing the association between prenatal/perinatal exposures and childhood cognition

Next, each of the prenatal and perinatal exposures (gestational influenza, T. gondii, and oxytocin to induce labor during pregnancy), as documented in the CHDS contemporaneous to birth, was analyzed for a potential effect on childhood cognition. Influenza and oxytocin to induce labor are documented in medical charts of the CHDS for each birth. These analyses investigate whether induced labor or gestational influenza are associated with cognitive performance on the childhood measures. In total, at ages 5 or 9-11, 7096 children were given the Raven and 7039 were given the PPVT. Gestational influenza and oxytocin are tested in the full birth cohort because those conditions were noted in the medical records. Thus, whether those conditions have an effect on cognition in childhood can be ascertained. The association between influenza and BP has been demonstrated in previous studies in this birth cohort (Parboosing, Bao et al. 2013, Canetta, Bao et al. 2014), as noted above, but the association or role of cognition in that association has not yet been tested.

Analytic method for testing the association between gestational influenza and childhood cognition

Maternal influenza during pregnancy was coded in the CHDS for nearly every birth, permitting assessment of cognition as an outcome for all those children tested in childhood. The literature review did not uncover a prior study of the relationship between maternal influenza and childhood cognition in a birth cohort. Moreover, documentation of influenza was obtained at birth, not retrospectively from maternal interview, as part of the medical care provided to all the women in the cohort. This significantly improves on previous research by eliminating recall biases.

GEE models were used because of siblings in the birth cohort. The exchangeable correlation structure, which produced the smallest QIC (quasi Akaike Information Criterion), is reported (Pan 2001).

Analytic method for testing the association between Toxoplasmosis (T. gondii) and childhood cognition

The CHDS aimed to obtain maternal serum for each pregnancy during each trimester. At each blood draw, 30 cc were collected and spun, dividing the sera into four aliquots of approximately 2 cc each. The samples were transferred to glass vials and stored frozen at -20 degrees since being obtained. One-two cc of maternal sera were provided for each time point during pregnancy for each case and control. These serum samples have been successfully analyzed now for a number of biomarkers, including for T. gondii. Biomarker evidence, obtained prospectively, is the gold standard for assessing the exposure and ensuring pre-birth maternal exposure.

The T. gondii assays were performed in the Toxoplasma Serology Laboratory at the Palo Alto Medical Foundation Research Institute, which is the T. gondii reference laboratory for the US (Montoya 2002). Three assays were used. The first two concern the assessment of T. gondii IgG antibody titer. Samples were screened for the presence of IgG antibody titer and then the Sabin-Feldman dye test (Sabin and Feldman 1948) was performed in the samples that screened positive. T. gondii IgM antibody was also assayed, which is indicative of recent infection, using the double sandwich enzyme-linked immunosorbent test (IgM-ELISA). The seroprevalence of IgG antibody was 22/123 (17.9%) in controls. This value is similar to the 17.5% seroprevalence found in a large previous study of T. gondii in reproductive-aged women (Jones, Kruszon-Moran et al. 2001). None of the control serum samples tested by ELISA were positive for T. gondii IgM antibody. This was not unexpected, as T. gondii IgM antibody is indicative of active infection within 2 months of the blood draw, which is unlikely given the low incidence of toxoplasmosis during this time frame (Remington 2011).

For the primary analysis, T. gondii IgG for the last serum sample drawn for each pregnancy (late third trimester/perinatal) was analyzed. This replicates the methods used in the PDS study of T. gondii and SZ (Brown, Schaefer et al. 2005). The third trimester/perinatal period of gestation provides the greatest opportunity to detect T. gondii infection if it occurred at any time during pregnancy because even an infection that occurred early in pregnancy will result in elevated IgG antibodies for many months or years following infection (Remington 2011).

The dye test IgG titers will be classified into three groups: negative (<1:16) (reference), moderate titer (1:16-1:64), and high titer (≥1:128). We hypothesized that the high IgG titer group would have worse

performance on cognitive testing in childhood. The hypothesis is tested by conditional logistic regression in the nested case control sample.

Analytic method for testing the association between in utero exposure to oxytocin and childhood cognition

Oxytocin administration to induce labor was contemporaneously documented in medical charts in the CHDS. The CHDS noted oxytocin in four separate fields which have been combined to construct a dichotomized variable: oxytocin versus no oxytocin. The analyses will consider whether oxytocin exposure during maternal labor is associated with performance on the Raven and the PPVT.

GEE models were used because of siblings in the birth cohort. The exchangeable correlation structure, which produced the smallest QIC (quasi Akaike Information Criterion) value, is reported.

Results

Results for childhood cognition and BP

Fifty people who later developed BP and 215 matched controls underwent cognitive assessments during childhood. Table 11 presents the summary data on the childhood testing. On average, those who later develop BP had a higher PPVT score than those who did not, but also a lower Raven score. The range of scores for cases on the PPVT was much wider than for cases, with a longer right tail, indicating some very high scores compared to controls. The range of scores of the Raven, in contrast, is narrower for those who later develop BP, with a truncated right tail.

Table 11: Summary data for childhood cognitive testing

		Mean	Standard Deviation	Minimum	Maximum
PPVT	Case (N = 50)	103.1	14.69	53.93	145.47
	Control (N = 213)	100.1	12.45	73.78	127.8
Raven	Case (N = 50)	0.0237	0.85	-2.327	1.62
	Control (N = 214)	0.0254	0.996	-2.327	2.33

Using conditional logistic regression for the matched case-controls sets, childhood cognition is not associated with later life BP (Table 12). Neither test was significantly associated with BP and the effect size is negligible.

Table 12: Childhood cognition and rate for BP

Parameter	Hazard Ratio	Confidence Interval
PPVT	1.016	(0.992, 1.041)
Raven	1.015	(0.732, 1.408)

In secondary analyses, the association of childhood cognition and BP with and without psychotic features was tested (Table 13). Dividing BP into these two types did not change the lack of association between childhood cognition and later BP.

Table 13: Childhood cognition and BP with and without psychosis

	Hazard Ratio	Confidence Interval
Raven, psychotic features	1.047	(0.629, 1.742)
Raven, without psychotic features	0.994	(0.649, 1.522)
PPVT, psychotic features	1.012	(0.978, 1.048)
PPVT, without psychotic features	1.019	(0.986, 1.053)

Post hoc tests for possible negative confounding by gestational age, maternal race, and maternal education confirmed that these covariates are not confounders, and did not alter the lack of association observed for childhood cognition and BP.

Discussion of childhood cognition and BP

These results of the relationship between premorbid cognition and later onset BP are consistent with previously published studies, but those studies have shown both better and worse performance during the premorbid period (Meyer, Carlson et al. 2004, Osler, Lawlor et al. 2007, Koenen, Moffitt et al. 2009, Sorensen, Saebye et al. 2012, MacCabe, Wicks et al. 2013). Those who later develop BP perform slightly better than controls on the PPVT and also have a wider spread of scores, with both the high and low scores beyond those obtained by controls. On the Raven, where those who later develop BP have a slightly lower mean, the minimum scores are equivalent for cases and controls but the maximum scores obtained are truncated for cases. Thus, people who later develop BP perform on average better on the global measure of cognition (PPVT) and the same or slightly weaker on visuospatial reasoning. The

consistency with other research serves as a validity check despite the sample being underpowered to reach conclusions.

It is also possible that the lack of association between childhood cognition and later BP may be explained by a number of factors specific to this birth cohort and these test instruments, or it may be a reflection of the true lack of association in BP, which would distinguish BP from SZ. The expected size of premorbid cognitive deficit has recently been reported for a number of cognitive domains to range between none and an effect size of approximately .8 for verbal learning and delayed visual and verbal memory (Kurtz and Gerraty 2009). Relevant for comparison to this study, the visual spatial domain was less impaired (Cohen's d = .55) in that meta-analysis (Kurtz and Gerraty 2009). Neither of the two test instruments in the CHDS are likely to assess the areas of impairment most observed in BP. Kremen et al observed a difference on the PPVT with fewer cases (n = 10) in this same cohort for those who later developed SZ (Kremen, Vinogradov et al. 2010), supporting the hypothesis that a more generalized, global impairment is observed in premorbid SZ compared to premorbid BP. The finding may reflect a true lack of association between premorbid cognition and BP as well. The evidence to date is mixed, with support for deficits in some specific cognitive domains, and strengths in others. The variability of cognitive performance in premorbid BP may make cognition a less useful early marker of disease as compared to that observed in SZ.

Overall, this finding does not support the neurodevelopmental hypothesis of BP.

Results for gestational influenza and childhood cognition

Exposure to maternal influenza during gestation is not associated with childhood cognition (Table 14). Using GEE models and reporting the exchangeable correlation, neither the PPVT nor the Raven is significantly associated with gestational influenza. The direction of the result is towards worse performance on childhood testing for those exposed, but it is a small and non-significant effect.

Table 14: Gestational influenza and childhood cognition

	Parameter Estimate	Confidence interval
PPVT (N = 6609)	-0.54	(-2.18, 1.78)
Raven (N = 6667)	-0.0495	(-0.18, 0.083)

Discussion of gestational influenza

Gestational influenza is not associated with cognitive impairment in childhood. The sample size is large, meaning there is sufficient power to observe an effect if one exists. This study offers a direct test of the findings from observational studies. Those observational studies suggested worse performance in those who were exposed. However, the lack of direct measures of the exposure (with estimates of exposure based on time of birth and high point of circulation of the virus) make the association difficult to determine and requires parsing from a number of other exposures that might confound the association. Here, the medical record notation of maternal influenza during pregnancy provides a very good, prospectively documented record of exposure, and with this clear measure, no association is observed.

It remains possible that direct testing of the maternal sera would provide a better and more precise measure of maternal influenza, as it remains possible that medical staff noted any viral infection as influenza when it may have been another virus.

Results for T. gondii and childhood cognition

In this birth cohort, T. gondii is not associated with childhood cognitive performance (Table 15). None of the titer levels of maternal sera are associated with offspring cognition. Post-hoc analyses of a possible association between T. gondii titer and BP with psychotic features was also not significant.

Table 15: Gestational T. gondii titers and childhood cognition

	Compared to Reference Titer (<1:16)	Chi-square	Confidence Interval	P-value
PPVT (N = 250)	Moderate (1:16-1:64)	0.07	(0.52, 2.35)	0.8
	High (1:128-1:512)	0.2	(0.49, 1.56)	0.66
Raven (N = 146)	Moderate (1:16-1:64	0.24	(0.32, 6.60)	0.63
	High (1:128-1:512)	0.06	(0.39, 2.08)	0.81

Discussion

The prospectively obtained, frozen serum based measurement of T. gondii in this cohort makes these data unique. T. gondii is not associated with BP or childhood cognition, unlike SZ, where it is

associated with both (Brown, Schaefer et al. 2005, Brown, Vinogradov et al. 2009). This is consistent with a previous finding (Mortensen, Pedersen et al. 2011). This finding suggests that T. gondii, observed in patient samples, is not associated with BP, and does not provide support for the neurodevelopmental hypothesis for BP. It also suggests that at least some prenatal exposures could be specific to SZ and BP, rather than the two conditions having similar causes but differing phenotypes.

Results for oxytocin to induce labor and childhood cognition

In bivariate analyses to test for potential confounders (Table 16), gestational age, maternal education, and maternal race were each significantly associated with oxytocin and cognition.

Table 16: Bivariate analyses of covariates and oxytocin

	Parameter Estimate	95% CI	Pr > |Z|
Maternal race: African-American	-0.67	(-0.72, -0.61)	<.0001
Maternal race: other	-0.04	(-0.13, 0.05)	0.395
Maternal education: HS graduate	-0.287	(-0.35, -0.22)	<.0001
Maternal education: some college or more	0.396	(0.34, 0.45)	<.0001
Gestational age	0.004	(0.003, 0.006)	<.0001
Maternal psychiatric history, any	-0.046	(-0.122, 0.29)	0.23

Notes: White is the reference group for maternal race; Less than high school is the reference group for maternal education. Gestational age, maternal race, and maternal education were tested in bivariate models with only oxytocin.

First, an unadjusted model (Table 17) to test the association between oxytocin and childhood cognitive performance found that oxytocin given to induce labor is significantly associated with a reduced score of .14 (CI: -0.26, -0.03, p = .02) standard deviation units on the Raven (N = 7017). It is non-significantly associated with a reduced score of .45 (CI: -2.12, 1.23, p = 0.6) standard deviation units on the PPVT (N = 6959).

Table 17: Unadjusted association between oxytocin and childhood cognitive tests

	Parameter Estimate	95% CI	Pr > |Z|
Raven (N = 7017)	- 0.14	(-0.26, -0.03)	0.02
PPVT (N = 6959)	- 0.45	(-2.12, -1.23)	0.6

In the fully adjusted model, oxytocin remains significantly related to worse Raven performance. This model (Table 18) controls for the covariates which may confound the relationship. The effect size for the reduced score on the Raven is relatively the same as the unadjusted model.

Table 18: Fully adjusted association between oxytocin and childhood Raven

	Parameter Estimate	95% CI	Pr > |Z|
Intercept	-0.55	(-0.96, -0.14)	0.0088
Oxytocin	-0.14	(-0.26, -0.03)	0.0141
Gestational age	0.002	(0.001, 0.004)	0.004
Maternal psychiatric history	-0.019	(-0.09, 0.06)	0.618
Maternal education: HS graduate	-0.20	(-0.27, -0.14)	<.0001
Maternal education: some college or more	0.38	(0.33, 0.43)	<.0001
Maternal race: African-American	-0.61	(-0.66, -0.55)	<.0001
Maternal race: other	0.02	(-0.06, 0.11)	0.6477

Discussion

This is the first time that oxytocin to induce labor has been evaluated for a possible effect on childhood cognition in a longitudinally followed, prospective birth cohort. The finding that the performance on the Raven is significantly worse for those who are induced, but that the PPVT is not, may suggest a specific mechanism or neural region which is affected, but further testing would be needed to assess that hypothesis. It is worth noting that oxytocin has a negative effect on cognitive performance but gestational age has a positive effect (longer gestation is associated with better performance). This suggests some specificity related to oxytocin, and that oxytocin is not simply a marker for longer gestational age.

Conclusion

Childhood cognition was not associated with BP, although the small but better performance on the PPVT, and the slightly worse performance on the Raven, is generally consistent with other research. The finding that oxytocin to induce labor is associated with worse cognitive performance on the Raven suggests a need for further research on the effects of oxytocin. None of the other prenatal and perinatal exposures were associated with childhood cognition.

As noted, the neuropsychological battery used by the CHDS focused on global functional ability and school readiness. As such, it is not surprising that no association with BP is observed on these premorbid test instruments. In considering whether these data support the neurodevelopmental hypothesis of BP, they do not particularly. Yet, the comparison of mean scores and the distribution of scores is suggestive of a possible premorbid cognitive pattern observed in other studies: slightly higher scores on global measures, with both very high and very low scores; as well as slightly lower scores on more specific domain measures, as reflected here by the range on the Raven. Larger samples may have enough power to determine whether these small differences are premorbid to BP or normal population variation. The two tests in the CHDS battery do not assess some of the areas of impaired performance during the premorbid period such as executive functioning and verbal memory. Future studies would ideally have additional measures which specifically assess the domains hypothesized to differ during the premorbid period of BP.

Conclusions, Strengths, and Limitations

The clearest strength of this research lies in the quality of the prospective birth cohort; the prospectively obtained data, including serologically obtained biomarkers and medical record maintenance; and the research diagnosis for all potential case subjects. The long follow-up period (1981-2009) means that cases have been identified at the point of first treatment, allowing for comparison of incident cases. This allows for time at risk between the exposed and unexposed to be directly comparable. Second, the prospective nature of this study and the continuous follow-up means that data are not dependent on maternal recall or other retrospective techniques, increasing accuracy. Third, although loss to follow-up and the moderate response rate could induce bias, it is expected to be non-differential. Although this cannot be directly tested, every effort to assess the consequences of the loss to follow up was undertaken using sensitivity analyses. Fourth, case identification, as described above, used research criteria applied by direct assessment with structured, standardized research instruments (the Structured Clinical Interview for DSM-IV (SCID) for BP and the Diagnostic Interview for Genetic Studies for Schizophrenia), thereby reducing misclassification. The DIGS was developed from the SCID, and is also based on DSM-IV criteria, and thus the two interviewers are highly comparable with one another.

There are also limitations to this study: first, despite being substantially larger than most studies of BP, a number of potential cases could not be enrolled because they could not be located or refused or failed to participate. Thus, as with all longitudinal studies, loss to follow-up potentially biases this study. The ascertainment process was conducted to capture as many potential cases as possible and every effort was made to locate and interview each. While few meaningful demographic differences are observed, it is not possible to calculate the extent to which bias from loss to follow-up might be having an effect or the direction of that hypothetical effect. The sensitivity analyses suggest that the effect of this loss to follow-up was negligible. Those calculations are based on information about the exposed in the full cohort, allowing for a direct assessment of potential bias in ascertainment. Further, the prevalence of BP cases identified in this study comports with the national and international rates (Merikangas, Akiskal et al. 2007, Merikangas, Jin et al. 2011), providing some confidence that few cases have been missed.

Second, because of concern that inclusion of potential case siblings would mean correlation between cases and/or between cases and controls, potential case subject siblings were excluded from being controls. This may have introduced bias in making the controls healthier than they should have been. Third, for the cognitive testing, a random sample of the cohort was tested at ages 5 and 9-11, meaning that some of the current study subjects were not tested in childhood. The random selection of subjects for testing makes this unlikely to bias results, but it does reduce the number of subjects in the study, limiting power. Further, the limited testing battery which focused on global strengths and weaknesses is likely to underestimate the more specific cognitive deficits that have been reported in BP, possibly explaining the lack of association observed.

Taken as a whole, the findings suggest support for the neurodevelopmental hypothesis of BP being both similar to and different from the course observed in SZ. In the largest view, these data lend support to some specificity in the risks for BP, and provide further evidence for risks which are observed in SZ not being similarly associated with BP. In the narrowest view, one specific potential risk is observed to affect both cognition and BP, although it is not a mechanism that acts to mediate the disease course itself.

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