1. Voorblad

Understanding pre-adolescent psychotic experiences

Grant type: PhD project

Projectleaders:

1. Prof. Dr. Henning Tiemeier
Department of Epidemiology
Tel: 010-7043489
Email address: h.tiemeier@erasmusmc.nl
Room number: NA: 28-14
Head of Department: Prof. Dr. M.A. Ikram

2. Prof. Dr. Steven Kushner
Department of Psychiatry
Tel: 010-7033227
Email address: s.kushner@erasmusmc.nl
Room number: EE-1442
Head of Department: Prof. Dr. W. Hoogendijk

3. Prof. Dr. Manon Hillegers
Department of Child and Adolescent Psychiatry
Tel: n/a (assumes office May 2017 in the EMC)
Email: m.h.j.hillegers@umcutrecht.nl
Room number: KP-2
Head of Department: Prof. Dr. Manon Hilligers

Collaborators in the project team

Department	Investigators	Expertise
Epidemiology	Prof. Dr. Henning Tiemeier	Study Design, Modeling, Generation R
	Prof. Dr. M. Arfan Ikram	Population Imaging
Child Psychiatry	Prof. Dr. Manon Hillegers	Adolescent Psychosis
	Dr. Laura Blanken, Koen Bolhuis	Childhood traits
	Dr. Tonya White	Pediatric Imaging, Generation R
Psychiatry	Prof. Dr. Steven Kushner	Schizophrenia Genetics
Radiology	Prof. Dr. Aad van der Lugt	Neuroradiology

2.1. Understanding pre-adolescent psychotic experiences

2.2. Summary

Visual and auditory perceptive phenomena and thought disorder occur in adults as symptoms of primary psychotic disorders, neurological diseases or drug abuse. However, it is increasingly recognized that in late childhood such symptoms frequently occur sub-clinically. Remarkably, an estimated 15% of 11 to 13 year olds report hallucinations, paranoid symptoms or thought problems, a finding that has been consistently reported across multiple countries. These psychotic experiences are predictive of schizophrenia, borderline personality disorder, and suicidal behavior. However, which youths develop these symptoms, i.e. the etiology, is poorly understood; longitudinal studies are lacking. In this proposal we describe our approach to study these risk factors. Using a genetically sensitive design we wish to identify groups of children that might be specifically vulnerable for developing psychotic experiences. In particular, we aim to study the association of childhood trauma and bullying with the emergence of psychotic experiences. Additionally, we will examine which neurobiological factors are associated with psychotic experiences through neuroimaging, in order to identify brain regions that might index vulnerability to psychosis at an early age. Taken together, we hope to shed more light on the etiology of childhood psychotic experiences in order to identify modifiable risk factors.

2.3. Lekensamenvatting

Psychotische ervaringen, zoals hallucinaties, komen voor bij kinderen, tot 15% van de 11 tot 13-jarigen rapporteren deze symptomen. Het is bekend dat deze symptomen ernstige psychiatrische stoornissen, zoals schizofrenie, voorspellen. Met dit onderzoek hopen wij risico-factoren, zoals sociale isolatie, genen en veranderde hersenontwikkeling, te identificeren waardoor we deze problemen beter kunnen begrepen en eventueel kunnen voorkomen.

2.4. Samenwerking tussen twee of meer afdelingen.

Investigators from four departments will jointly conduct this research, which is embedded in Generation R. This project will bring together epidemiological expertise with the clinical and clinical research expertise of the new head of Child and Adolescent Psychiatry, and more fundamental psychiatric research expertise of Adult Psychiatry.

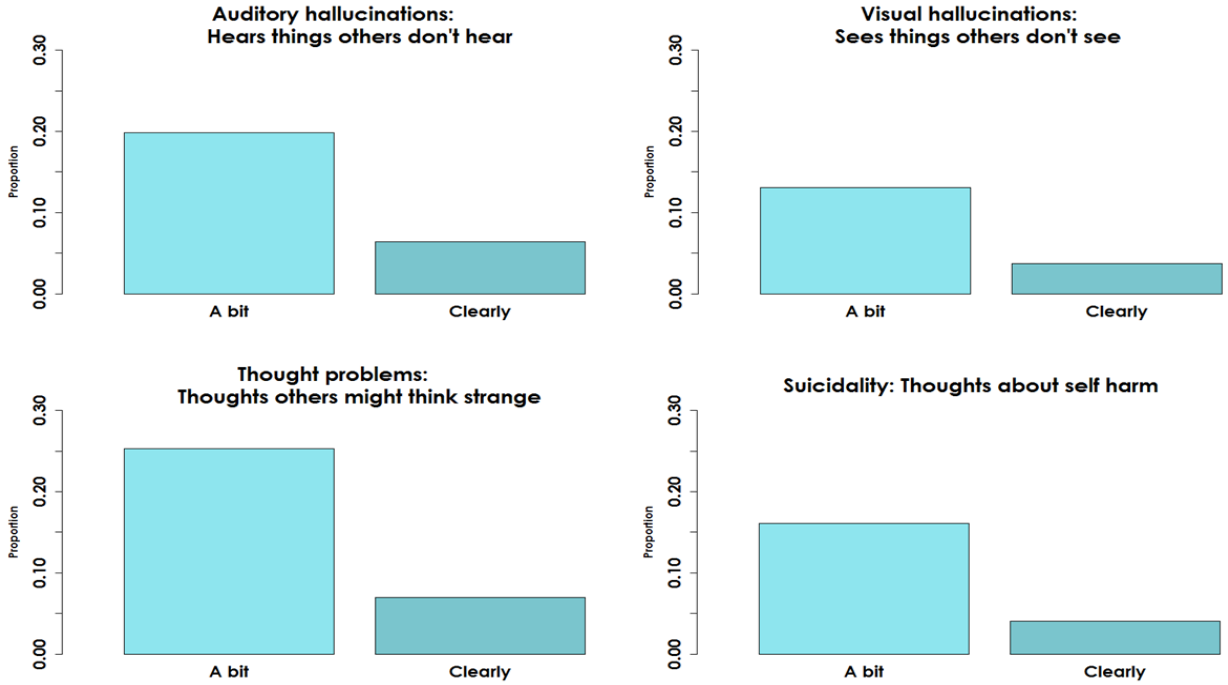
2.5. Objective

The overall objective of this project proposal is to understand the etiology of common psychotic experiences in pre-adolescence.

A. What is the prevalence of pre-adolescent psychotic experiences?

In this project, we will first map the emergence of psychotic experiences in childhood in the Generation R Study. These experiences comprise thought problems and hallucinations. In Generation R, psychotic experiences have been measured long before the age of onset of any clinical psychotic disorder (which typically occur in late adolescence or young adulthood). However, pre-adolescence is the time when they these symptoms are most common and occur in up to 20 percent of persons in population-based cohorts (1). As expected, throughout adolescence much lower levels are reported in population-based studies (around 7%). Early auditory and visual hallucinations are highly predictive of later disorders such as schizophrenia, borderline personality disorder, severe anxiety disorders, and suicidality (2). We will study prevalence and childhood symptoms predicting adolescent psychiatric symptoms.

Figure 1: Pilot data child self-reported auditory and visual hallucinations at age 10 years (*n* = 4353) in Generation R.



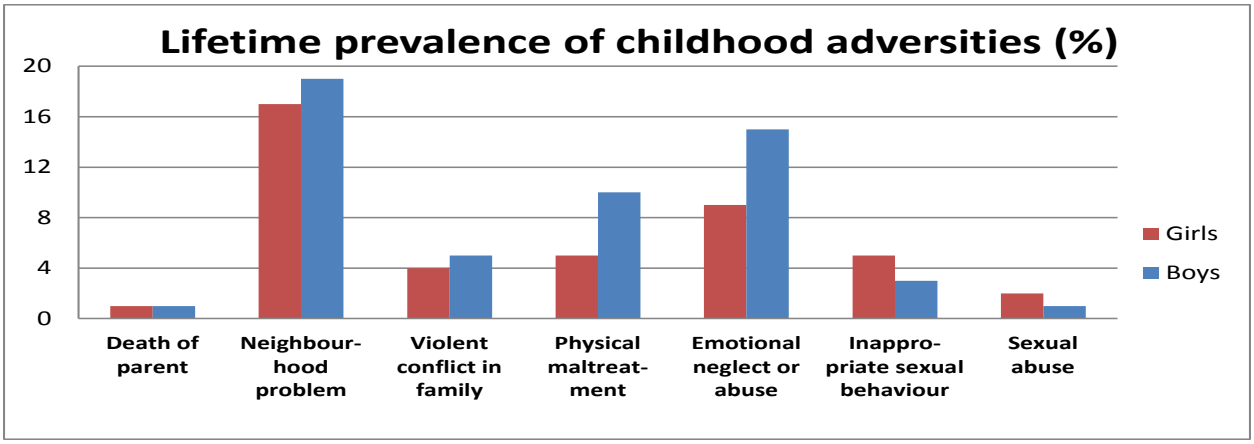
The figure clearly illustrates that the prevalence of psychotic experiences in the Generation R population is well in line with earlier reports. We now plan to study which developmental symptoms, such as autistic traits or anxiety, predict these symptoms. Note that the above is quantified using child self-report, while parental reporting yields much lower prevalence estimates of approximately 5% or less.

B. Can we identify a genetic vulnerability to early psychotic experience?

There is an important contribution of common genetic variances to the canonical psychotic disorder, schizophrenia (3,4). However, whether these same genetic factors underlie psychotic experiences in young people is unknown but can be tested with polygenic risk scores derived from genome wide association studies. Importantly, here we will use risk scores from the published genome wide association studies (GWAS) of schizophrenia, neuroticism and bipolar disorder, whereas a GWAS study will be conducted in the EAGLE consortium

C. Are trauma and social exclusion risk factor for early psychotic experience?

Schizophrenia is a very heritable disorder, but some environmental risk factors such as trauma and social exclusion have been clearly established (5). In Generation R, childhood trauma was assessed as well as social exclusion and bullying. We will also study how these environmental actors interact with genetic vulnerability.



D. Do early psychotic experiences correspond to brain structural and functional changes?
Using structural and functional neuroimaging modalities, we aim to identify how brain development is shaped by the above mentioned risk factors (e.g. childhood psychotrauma or social exclusion) and underlies the risk of psychotic experiences. There is little work in this field but there have been promising findings. For example, psychotic-like experiences are associated with the integrity of certain white matter tracts in the brain such as the uncinate fasciculus
and those in the left parietal lobe (6). This implies that these brain regions might index vulnerability to psychosis at an early age before the onset of the clinical disorder but need to be further tested (7). We aim to extend these preliminary findings by providing multimodal MRI population-based neuroscience studies at different stages of childhood development.

2.6. Study Design
This study is part of the large population-based Generation R Study in Rotterdam, for which more than 6,000 children are still actively participating in this birth cohort. Detailed information on family background will allow us to control for confounders. Importantly, detailed and repeated assessments of child emotional and behavioral problems with the Child Behavior Checklist have been conducted at ages 1.5, 3, 6, and 10 years to assess other dimensions and DSM-scales such as ADHD, depression and aggression.

Primary outcome: psychotic experiences
Psychotic experiences were measured using child self-report at age 10 and age 13 years (on-going data collection). Parental report is also available but previous studies have shown that parents are largely unaware of these symptoms in their preadolescent children. Questions are based on the Adolescent Psychotic Symptom Screener and include the question “Have you ever heard voices or sounds that no one else can hear?”, which demonstrate excellent positive and negative predictive value for phenomena that, on subsequent interview, are clinically verifiable as psychotic in nature (2).

Genetics
Genotyping was performed on cord blood collected at birth or on venous blood from venipuncture at the research center during the second assessment wave on Illumina 610K and 660K genotyping platforms. Genome wide association studies (GWAS) in adults have now identified several genetic risk loci for most common psychiatric disorders. Genetic susceptibility can be indexed by polygenic risk scores of the

group of genome-wide significant loci, which together explain up to 12% of the variance for schizophrenia (3). Importantly, unpublished work from our group shows that these polygenic risk scores explain differences in behaviour and emotional problems in childhood (8). Previous studies with the schizophrenia risk score suggest the potential utility in predicting vulnerability to adversity (9,10). Also, polygenetic risk scores for bipolar disorder and neuroticism are available. Finally, the first applicant leads the EAGLE consortium (EArly Genetics and Lifecourse Epidemiology) workgroup for behavior and has led and published several GWAS of behavioral traits and problems with his group (11). The group is very experienced in such genetic modeling (12)

Social exclusion: class network centrality, bullying and perceived social exclusion
It is challenging to study peer victimization, at any age. In children, social exclusion is often studied in the context of classroom bullying and peer-relations. In the Generation R Study, several observational measures of social exclusion are available: peer-reported bullying, closeness centrality in peer networks, and reciprocity of friendships. On average, 21 classmates rated each of the participating children from the Generation R Study. With this novel approach using a peer-nomination method, it is possible to study bullying and social exclusion in middle childhood (13).
Another measure available in the Generation R Study is reaction towards social exclusion or ostracism. This was measured in the Cyberball task, which is a computerized game in which participants were told that they would toss a ball with two other children and asked to imagine how it would be to play the game in real life. The other two children however, are virtual players programmed to exclude the participant after the first six ball tosses. During the game, participants were recorded with a webcam. These videos are being coded for the facial expression of negative emotions.
Using these aforementioned paradigms, we will have the opportunity to investigate to what extent *perceived* and *actual* social exclusion are related to the development of psychotic experiences.

Traumatic life experiences
Traumatic life experiences were measured using a standardized interview (maternal report) at age 10. The validity of this interview is high and preferred above a questionnaire, as trained interviewers can ask in a standardized way how much impact a traumatic life event had on the child.

Neuroimaging
There have been two waves of neuroimaging data collection to date in Generation R. The first wave involved 1070 children aged 6-8 years-old and the second included nearly 4100 children aged 9-11 years-old (14). To complete the assessment of brain development from pre-puberty through adolescence, a new wave of MRI neuroimaging data is now being collected at ages 13-14 in 5000 adolescents. The neuroimaging session includes structural MRI, diffusion tensor imaging, and resting-state functional MRI (rs-fMRI). The brain MRI assessments are performed in a dedicated Generation R scanner: a 3-Tesla General Electric MR750W System. No changes are made to the MRI system or sequences to assure consistency over time for longitudinal analyses. A series of publications document the skills of our group to perform large scale imaging studies (15-17)

Clinical relevance, novelty and long term perspective
Psychotic disorders are among the 10 leading causes of disability, yet little is known about the prodromal window before overt clinical onset. Contrary to the historical understanding, psychotic experiences are

now recognized as relatively common symptoms observed in child- and adolescent psychiatry. Notably, it is considered as the single best predictor of severe psychopathology in young adulthood (2). This proposal combines novel genetic insights with environmental and neurobiological risk factors to study the onset of such psychotic experiences. From a clinical perspective, environmental factors represent potentially modifiable risk factors that have the potential to be implemented towards prevention of psychotic symptoms, and ultimately severe mental illness, in vulnerable pre-adolescents.

2.7. Statistical techniques and power calculation.

Different statistical modelling techniques will be employed for the different aims. For the first aim, simple descriptive test and general mixed linear models will be used. For other aims, mostly regression analyses or standard polygenic risk score and GWAS techniques are sufficient. Here we will detail only one more advanced technique that we plan to employ to perform hypothesis free analyses of imaging data (next to a standard approach to test the hypothesis based on prior publications, (5)). In Generation R, different structural and functional imaging techniques are used to assess brain morphology, structural connectivity and functional connectivity. Our data driven approach will involve the use of parallel independent component analyses (pICA), which is an innovative and mature data-driven approach to evaluate networks. pICA identities component scores among variables in two or more multivariate sets of variables to quantify associations between components across domains. The components underlying multiple adversity exposures will be tested for associations with components underlying multivariate neuroimaging data. pICA simultaneously performs two or more ICA decompositions on two linked datasets, while also identifying patterns in both modalities which are correlated. Following these analyses, each subject's genetic risk scores and environmental exposure and MRI data are reduced to a linear combination of linked components and pairwise correlations that are tested using multiple comparison correction.

The power to detect an exposure-outcome association for continuous thought problem measures in 4000 children (assuming 15% loss to follow-up) at an unadjusted $\alpha = .05$ is 80% for a very small effect at $R^2 = .0018$. Even when tested at Bonferroni adjusted $\alpha = .0005$, we have 80% power to detect very small effects sizes of $R^2 = .0042$. For categorical analyses, given a period-prevalence of thought problems in adolescence between 9-11 years of age exceeding 15%, we expect at least 500 cases. This gives us sufficient power (80%) to detect a small difference (RR=1.2) per standard deviation of a continuous measure.

4. Selected References Applicants.
References underscored and in bold are from the project group.

1. Kelleher, I., Keeley, H., Corcoran, P. […] & Cannon, M. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *Br J Psychiatry*, 201:26-32, 2012.
2. Kelleher, I., Harley, M., Murtagh, A., & Cannon, M. Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophr. Bull.*, 37:362-369, 2011.
3. Schizophrenia Working Group of the Psychiatric Genetics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511: 421-427, 2014.
4. Neumann, A., Pappa, I., Lahey, B.B., […] & **Tiemeier, H.** Single nucleotide polymorphism heritability of a general psychopathology factor in children. *J Am Acad Child Adolesc Psychiatry*, 55: 1038-1045, 2016.
5. **Hillegers, M. H**., Burger, H., Wals, M., Reichart, C. G., Verhulst, F. C., Nolen, W. A., & Ormel, J. (2004). Impact of stressful life events, familial loading and their interaction on the onset of mood disorders. *The British Journal of Psychiatry*, *185*(2), 97-101.
6. O'Hanlon, E., Leemans, A., Kelleher, I. […] & Cannon, M. White matter differences among adolescents reporting psychotic experiences: a population-based diffusion magnetic resonance imaging study. *JAMA Psychiatry*, 72: 668-677, 2015.
7. Stedehouder J, **Kushner SA.** Myelination of parvalbumin interneurons: a parsimonious locus of pathophysiological convergence in schizophrenia. Mol Psychiatry. 2016 Sep 20. doi: 10.1038/mp.2016.147 (Epub)
8. Jansen, P.R., Polderman, T, **White T.** […] & **Tiemeier, H**. (in preparation). Psychiatric polygenic risk scores and their association with childhood behavior problems.
9. Derks, E.M., Vorstman, A., Ripke, S. […] & Ophoff, R.A.. Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. *PLoS One*, 7(6):e37852, 2012.
10. Jones, H.J., Stergiakouli, E., Tansey, K.E. et al. Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population. *JAMA Psychiatry*, 73: 221-228, 2016.
11. Pappa I, St Pourcain B, Benke K […] Boomsma DI, **Tiemeier H**.A genome-wide approach to children's aggressive behavior: The EAGLE consortium. *Am J Med Genet.* 2016 Jul;171(5):562-72.
12. Pappa I, Fedko IO, Mileva-Seitz VR, […] **Tiemeier H,** Verhulst FC, van IJzendoorn MH, Boomsma DI. Single Nucleotide Polymorphism Heritability of Behavior Problems in Childhood: Genome-Wide Complex Trait Analysis. *J Am Acad Child Adolesc Psychiatry*. 2015 Sep;54(9):737-44.
13. Verlinden, M., Veenstra, R., Ringoot, A.P.[…] & **Tiemeier, H.** Detecting bullying in early elementary school with a computerized peer-nomination instrument. *Psychol. Assess.*, 26: 626-641, 2014.
14. **White, T.**, El Marroun, H., Nijs, I., […], **Tiemeier, H.** & Verhulst, F.C**.** Pediatric population-based neuroimaging and the Generation R Study: the intersection of developmental neuroscience and epidemiology. *Eur J Epidemiol*, 28: 99-111, 2013.
15. Kocevska D, Muetzel R, Luik AI, Luijk MP, Jaddoe VW, Verhulst FC, **White T, Tiemeier H**. The developmental course of sleep disturbances across childhood relates to brain morphology at age seven. The Generation R Study.Sleep. 2016 Sep 26. [Epub ahead of print]

16 Mous SE, **White T**, Muetzel RL, El Marroun H, Rijlaarsdam J, Polderman TJ, Jaddoe VW, Verhulst FC, Posthuma D, **Tiemeier H**. Cortical morphology as a shared neurobiological substrate of attention-deficit/hyperactivity symptoms and executive functioning: a population-based pediatric neuroimaging study. J Psychiatry Neurosci. 2016 Sep 23;41(6):150371
17 Blanken LM, Mous SE, Ghassabian A, […] Hofman A, Verhulst FC, **Tiemeier H, White T.** Cortical morphology in 6- to 10-year old children with autistic traits: a population-based neuroimaging study. Am J Psychiatry. 2015 May;172(5):479-86.