Concept Paper Template

Provisional Paper Title: Relationship between schizophrenia polygenic risk (as expressed through placental biology) and general psychopathology

Proposing Author: Adrienne Romer

Author's Email: adrienne.romer@duke.edu

P.I. Sponsor: Ahmad Hariri and Avshalom Caspi

Today's Date: 2/28/18

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

ADDENDUM TO ORIGINAL CONCEPT PAPER APPEARS IN RED (July 2018)

The work proposed in this Concept Paper (Steps 1 and 2 below) has been carried out in Dunedin under an approved CP. We now seek approval to add an additional sample to the analysis: E-Risk.

Specifically, deidentified E-Risk SNP data will be scored for both the Placental and Non-Placental PRSs (at $p<5^{-08}$ and 1^{-06}) for Schizophrenia.

1. We will test the associations between these PRSs and the 'p' factor, and the three liabilities (Internalizing, Externalizing, and Psychotic Experiences), as described in Schaefer et al. 2008, Clin Psych Science).
2. We will test the above associations stratified by birthweight.
3. Power allowing, we will conduct within-twin comparisons to see if the PRS is more predictive of p in the smaller twin than the larger twin.

Analyses will be conducted by Avshalom Caspi

Objective of the study:

Increasing research has identified a general liability for psychopathology, often called the 'p factor' (Caspi et al., 2014; Lahey et al., 2017); however, the mechanisms underlying such a general factor are not yet clear. Our prior research sought to examine the neural underpinnings of this p factor in order to begin to identify common mechanisms underlying risk for developing multiple mental disorders (Romer et al., 2017). We identified deficits in cerebellar and occipital gray matter volume and poorer integrity of pontine white matter tracts as uniquely associated with higher p factor scores in a sample of 1236 university students aged 18-22 as part of the Duke Neurogenetics Study (DNS). The results of our analyses provide initial evidence that structural alterations in cortico-cerebellar circuitry supporting core functions

related to the basic integration, coordination, and monitoring of information may contribute to a general liability for common mental disorders.

In addition to examining the neural mechanisms underlying the p factor in DNS, we also began investigating genetic contributions to this general liability factor. Similar to findings from Caspi et al. (2014), we found that thought disorders, including mania, obsessive-compulsive disorder, and psychosis, were strongly correlated with the p factor in the DNS. As a result, we examined whether greater polygenic risk for schizophrenia, as one form of thought disorder, was associated with higher general psychopathology (p factor scores) in 524 non-Hispanic Caucasian DNS participants. We found that individuals with higher schizophrenia polygenic risk scores (PRS) had higher p factor scores; however, this positive association was relatively weak (r=.099, p=.024).

New research has examined the convergence of schizophrenia polygenic risk and placental biology (Ursini et al., in press, Nature Medicine). In particular, Ursini et al. (in press) identified a novel PRS based on genes that are dynamically modulated and highly expressed in placenta and that interact with obstetrical complications to increase risk for schizophrenia. Using this placental PRS (PlacPRS), we examined whether genes implicated in schizophrenia and specifically expressed in placenta might be more strongly related to p factor scores than genes implicated in schizophrenia that are not expressed in placenta in the 524 non-Hispanic Caucasian DNS participants. We found a slightly stronger positive relationship between PlacPRS (r=.125, p=.004) and p scores as opposed to the association between the full schizophrenia PRS and p (r=.099, p=.024). This is noteworthy because PlacPRS has much fewer loci underlying the PRS calculation than the full schizophrenia PRS. We also found that the PRS based on genes not expressed in placenta (i.e. non-PlacPRS) was unrelated to p factor scores (r=.020, p=.647), suggesting that genes specifically expressed in placenta related to schizophrenia risk are predictive of p factor scores in the DNS. Finally, we found a significant moderation of the relationship between placental PRS and p factor scores by pons white matter integrity. This moderation suggests that individuals with greater schizophrenia PlacPRS and who show poorer integrity of pontine white matter tracts have the greatest general liability for psychopathology.

In the current study, we propose to determine whether the associations between placental-based and non-placental-based schizophrenia PRS and p factor scores will replicate in the Dunedin cohort. We also propose to investigate potential moderators of this association including obstetrical complications and differences in brain structure.

Data analysis methods:

Analyses will be conducted in the following four steps:

1) Placental and Non-Placental PRS will be generated at $p<5^{-08}$ and 1^{-06} using summary statistics by the Weinberger group as performed in Ursini et al. (in press). An obstetrical complications index will be created by the Weinberger group using the McNeil-Sjöström scale (McNeil et al., 1994; McNeil, Cantor-Graae, & Sjostrom, 1994) as performed in Ursini et al.
2) The proposing author, Adrienne Romer, will examine associations between Placental and Non-Placental PRS (at $p<5^{-08}$ and 1^{-06}) and p factor scores using partial correlations

controlling for sex. This analysis answers the question of whether schizophrenia polygenic risk as expressed specifically through placental biology predicts a general liability for psychopathology. We hypothesize that p scores will be positively related to placental and unrelated to non-placental polygenic risk.

3) The proposing author will examine whether the association between PRS and p scores is moderated by obstetrical complications. This analysis examines the question of whether individuals with higher schizophrenia genetic risk as expressed through placental biology and greater history of obstetrical complications are at greatest risk for developing common mental disorders. We also will test whether individuals with serious obstetrical complications have higher PRS than individuals without complications, which was observed in the Ursini et al. study.
4) Finally, the proposing author will examine if the association between PRS and p scores is moderated by differences in gray matter volume of the cerebellum and occipital lobe and differences in fractional anisotropy (a metric of white matter integrity) of the pons. These analyses test whether individuals with higher schizophrenia genetic risk as expressed through placental biology and deficits in brain structure are at the greatest risk for developing multiple mental disorders.

Variables needed at which ages:

- Placental and Non-Placental PRS at $p<5^{-08}$ and 1^{-06} thresholds. The Weinberger group will calculate these scores.
- The Weinberger group will calculate an obstetric complications index using scoring from the McNeil-Sjöström scale. To calculate this index, we request obstetric complications data from Shalev et al. (2014) including:
    - maternal diabetes
    - glycosuria
    - epilepsy
    - hypertension
    - eclampsia
    - antepartum hemorrhage
    - accidental hemorrhage
    - placenta previa
    - having had a previous small baby
    - gestational age <37 weeks or >41 weeks
    - birth weight <2.5 kg
    - small size for gestational age
    - major or minor neurologic signs of the neonatal period (eg, jitteriness, tenseness, limpness, hypotonicity)
    - Rh incompatibility
    - ABO incompatibility
    - nonhemolytic hyperbilirubinemia
    - hypoxia at birth (idiopathic respiratory distress syndrome or apnea)
    - low Apgar score at birth
- p factor scores from the bifactor model (from Honalee)

- Extracted gray matter volume values for neocerebellum and occipital lobe region of interest (ROI; already have this from imaging data set per Annchen)
- Extracted fractional anisotropy values for pons ROI (already have this from imaging data set per Annchen)

Significance of the Study (for theory, research methods or clinical practice):

This research may begin to help us better understand the biological mechanisms underlying a general psychopathology factor. In particular, if our hypotheses are supported, this research would suggest that the biological mechanisms underlying schizophrenia may also underlie risk for developing a range of mental disorders including internalizing and externalizing disorders. One such mechanism or pathway underlying general liability for psychopathology may be conferred through placental abnormalities and early life complications in addition to deficits in cortico-cerebellar circuitry responsible for basic processing and monitoring of information. An association of PlacPRS with psychopathology ratings during adult life add strong evidence to the early developmental origins of a bias to the expression of psychopathology.

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Shalev, I., Caspi, A., Ambler, A., Belsky, D. W., Chapple, S., Cohen, H. J., ... & Sugden, K. (2014). Perinatal complications and aging indicators by midlife. *Pediatrics*, *134*(5), e1315-e1323.

Ursini, G., Punzi, G., Chen, Q., Marenco, S., Robinson, J., Porcelli, A., ... & Weinberger, D. (in press). Convergence of placental biology and genetic risk for schizophrenia. *Nature Medicine*.

Data Security Agreement

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Proposing Author	Adrienne Romer
Today's Date	2/19/18

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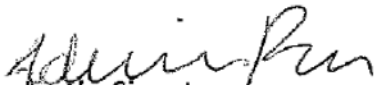
AR	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
AR	I will not "sync" the data to a mobile device.
AR	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)
AR	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
AR	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
AR	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: 

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Proposing Author	Adrienne Romer
Other Contributors	Danny Chen, Daniel Weinberger, Ahmad Hariri, Annchen Knodt, Terrie Moffitt, Avshalom Caspi, Karen Sugden, Renate Houts, Louise Arseneault Richie Poulton, David Ireland,
Potential Journals	
Today's Date	2/28/18
Intended Submission Date	7/1/18

B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature:

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