**Concept Paper Template**

**Provisional Paper Title:** Replication and extension of brain structural and genetic correlates of the p factor in a representative birth cohort

**Proposing Author:** Adrienne Romer

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

**P.I. Sponsor:** Ahmad Hariri and Terrie Moffitt

**Today's Date:** 5/17/18

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**Objective of the study:**

Accumulating mental health research encourages a shift in focus towards transdiagnostic dimensional features that are shared across categorical psychiatric disorders. In support of this shift, recent studies have identified a general liability factor for psychopathology – called the 'p factor' – that underlies shared risk for a wide range of mental disorders. Identifying the neural and genetic correlates of this general liability would substantiate its importance in characterizing the shared origins of mental disorders and help us begin to understand the mechanisms.

We previously published a study of the structural neural correlates of the p factor in 1,246 university students as part of the Duke Neurogenetics Study (DNS; see Romer et al., 2018). 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 terms of genetic correlates, we also found that polygenic risk for schizophrenia is correlated with higher p factor scores in 475 Non-Hispanic Caucasian DNS participants. Collectively, these findings provide initial evidence that genetic liability for schizophrenia may increase individual risk for multiple common forms of mental illness in part through compromised structural integrity of cortico-cerebellar circuits supporting information processing and behavioral monitoring.

In the current study, we propose to determine whether the neural and genetic correlates of the p, internalizing, externalizing, and thought disorder factors identified in the DNS will replicate in the Dunedin cohort. We also propose to examine whether there are any additional structural alterations associated with these disorder-liability factor scores present in the Dunedin cohort that were not identified in the DNS sample.

**Data analysis methods:**

Analyses of brain structure will be conducted using diffusion tensor imaging (DTI) as a measure of the structural integrity of white matter pathways, voxel-based morphometry (VBM) as a measure of regional GMV, and the spatially unbiased infratentorial template (SUIT) as a measure of cerebellar GMV. All structural neural analyses will control for sex and average whole-brain FA values for the DTI and total intracranial volume for the VBM analyses. All structural neural analyses also will be conducted using Monte Carlo simulation-derived whole-brain corrected thresholds with an overall family-wise error rate of $\alpha < .05$. Genetic analyses will be conducted using summary statistics from the Psychiatric Genomic Consortium's genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Analyses will be conducted in the following five steps (all conducted by proposing author).

1) Conduct region-of-interest (ROI) analyses (i.e., linear regressions) of differences in FA of the pons and GMV of the cerebellum and occipital cortex associated with p factor scores based on findings from the DNS sample. To do this analysis, I will create masks of the significant clusters within the pons, cerebellum, and occipital cortex to restrict analyses of FA and GMV to the regions I found to be associated with p factor scores in the DNS.
2) Conduct exploratory whole-brain analyses of FA and GMV using linear regressions with p factor scores predicting differences in FA and GMV. Analyses of cerebellar GMV will be conducted using linear regressions with p factor scores predicting differences in GMV using SUIT to improve the anatomical localization of gray matter correlates of p factor scores.
3) Based on the results from the Dunedin ROI analyses in Step 1, I will examine whether internalizing, externalizing, and thought disorder factor scores from the correlated factors model are associated with differences in pons FA and cerebellar and occipital GMV. To do this analysis, I will extract pons FA and occipital and cerebellar GMV from significant clusters identified in Step 1 to examine associations with internalizing, externalizing, and thought disorder factor scores using partial correlations.
4) Similar to Step 2, I will conduct exploratory whole-brain analyses of FA and GMV using linear regressions with internalizing, externalizing, and thought disorder factor scores predicting differences in FA and GMV.
5) I will examine the relationship between p, internalizing, externalizing, and thought disorder factor scores and schizophrenia polygenic risk scores (PRS) including the 108 top associated loci from the Psychiatric Genomics Consortium's genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics, 2014). I will use partial correlations to assess the associations between schizophrenia PRS and disorder-liability factor scores controlling for sex in the Dunedin cohort.

**Variables needed at which ages:**

- Schizophrenia PolygenicRS including the top associated loci (108 SNPs)
- p factor scores from the bifactor model
- sex
- DTI, VBM, and SUIT data

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

If the neural and genetic correlates are consistent across these very different samples, Duke students and the Dunedin Study members we have greater evidence that the neurobiological mechanisms underlying the p factor generalize to a wide range of adults. If these correlates do not replicate across samples, we can begin to understand how the p factor might confer risk for multiple mental disorders in these different groups of people and at different ages.

**References cited:**

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., ... & Moffitt, T. E. (2014). The p factor: one general psychopathology factor in the structure of psychiatric disorders?. *Clinical Psychological Science*, *2*(2), 119-137.

Romer, A. L., Knodt, A. R., Houts, R., Brigidi, B. D., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2018). Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Molecular psychiatry 23*(4), 1084–1090.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427.

**Data Security Agreement**

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| | |
|---|---|
| AR | I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent) |
| AR | My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution. |
| AR | I will treat all data as "restricted" and store in a secure fashion.<br>My computer or laptop is:<br>a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines)<br>b) password-protected<br>c) configured to lock-out after 15 minutes of inactivity AND<br>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.<br><br>*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.<br><br>The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses. |

**Signature:** Adrienne Romer

**CONCEPT PAPER RESPONSE FORM**

**A**

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| Provisional Paper Title | Replication and extension of brain structural and genetic correlates of the p factor in a representative birth cohort |
| Proposing Author | Adrienne Romer |
| Other Contributors | Annchen Knodt, Renate Houts, HonaLee Harrington, Dan Belsky, Terrie Moffitt, Avshalom Caspi, Ahmad Hariri, Richie Poulton, Sandhya Ramrakha, Tracy Melzer, Ross Keenan, David Ireland |
| Potential Journals | |
| Today's Date | 5/17/18 |
| Intended Submission Date | 5/17/19 |

***Please keep one copy for your records and return one to the proposing author***

**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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