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**Citation**

Bas-Hoogendam, J. M., Bernstein, R., Benson, B. E., Salum, G. A., Pan, P. M., Jackowski, A. P., ... Pine, D. S. (2021). P.0035 Structural brain correlates of childhood inhibited temperament: rationale and methodology for an ENIGMA-Anxiety mega-analysis. *European Neuropsychopharmacology*, 53(S1), S26-S27. doi:10.1016/j.euroneuro.2021.10.041

Version: Accepted Manuscript

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**Note:** To cite this publication please use the final published version (if applicable).

## References

- [1] BOE.es - BOE-A-2020-3692 Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19. [Internet]. [cited 2021 Mar 10]. Available from: <https://www.boe.es/eli/es/rd/2020/03/14/463/con>
- [2] Anderberg, P, Barnestein-Fonseca, P, Guzman-Parra, J, Garolera, M, Quintana, M, Mayoral-Cleries, F, et al., 2019 Jun 21. The Effects of the Digital Platform Support Monitoring and Reminder Technology for Mild Dementia (SMART4MD) for People With Mild Cognitive Impairment and Their Informal Carers: Protocol for a Pilot Randomized Controlled Trial. *JMIR Research Protocols* 8 (6), e13711.
- [3] Goodman-Casanova, JM, Guzmán-Parra, J, Guerrero, G, Vera, E, Barnestein-Fonseca, P, Cortellessa, G, et al., 2019 Sep 6. TV-based assistive integrated service to support European adults living with mild dementia or mild cognitive impairment (TV-AssistDem): study protocol for a multicentre randomized controlled trial. *BMC Geriatrics* 19 (1), 247.
- [4] Bédard, M, Molloy, DW, Squire, L, Dubois, S, Lever, JA, O'Donnell, M, 2001 Oct 1. The Zarit Burden Interview: A New Short Version and Screening Version. *The Gerontologist* 41 (5), 652-657.
- [5] Gómez-Gallego, M, Gómez-Amor, J, Gómez-García, J., 2012 Jan 1. Validación de la versión española de la escala QoL-AD en pacientes con enfermedad de Alzheimer, cuidadores y profesionales sanitarios. *Neurología* 27 (1), 4-10.

doi: [10.1016/j.euroneuro.2021.10.040](https://doi.org/10.1016/j.euroneuro.2021.10.040)

## P.0035

### Structural brain correlates of childhood inhibited temperament: rationale and methodology for an ENIGMA-Anxiety mega-analysis

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**Introduction:** Social anxiety disorder (SAD) is one of the most prevalent, chronic and impairing mental disorders in adolescents. As SAD is difficult to treat effectively, the personal and societal costs of SAD are substantial. Understanding the susceptibility to SAD can guide early identification of high-risk youth to advance targeted preventive interventions.

Family and twin studies have demonstrated that social anxiety has moderate heritability, indicating that genetic vulnerability is important in the pathogenesis of SAD [1]. Inhibited temperament (IT) - a stable, heritable and observable trait associated with an elevated risk for developing SAD and other anxiety disorders - may mediate the genetic risk for SAD [2]. Specifically, brain characteristics (i.e. brain structure, function, and connectivity) may provide the foundation for IT and the associated anxiety vulnerability [2,3]. Understanding of this 'neural risk signature' is still limited, as studies of the neurobiological characteristics associated with the temperamental vulnerability to SAD are scarce and

often focus on particular regions of interest. Moreover, most findings are derived from a single sample, and have not been replicated across studies [3].

**Aim and hypotheses:** This project aims to extend prior work by examining the neurobiological characteristics associated with childhood IT, as an early marker of risk for (social) anxiety later in life. We will use a mega-analytic approach and investigate changes in brain structure over the whole brain. Based on previous work, we expect to find IT-related alterations in brain circuits involved in processing fear, reward and emotion regulation, with small-to-medium effect sizes. **Methods:** Within the framework of the ENIGMA (Enhancing Neuro/imaging Genetics through Meta-Analysis)-Anxiety Working Group [4,5], we will assemble T1-weighted structural MRI-images (MRIs) of the brain, previously acquired at multiple institutes. Subsequently, we will perform mega-analyses on the largest sample related to childhood temperament available to date (data we currently have:  $n = 660$ ; expected total sample size: 2300 MRI-datasets from 11 sites).

Data will be obtained from studies where subjects underwent MRI-scanning at various ages (up to age 25 years). Regardless of the age at scan, all participants will have undergone an (retrospective) assessment of childhood temperament (i.e., up to and including age 12). MRI-images will be processed using FreeSurfer software, resulting in individual estimates of regional cortical thickness, cortical surface area, and subcortical volumes. Analyses will compare participants with and without childhood IT.

Information on variables of interest (demographic variables, clinical information, questionnaire data) is also obtained to enrich the dataset and facilitate analyses of clinical outcomes and environmental influences. The study will be preregistered and analyses will start in autumn 2021.

**Innovative character:** This initiative is the first mega-analysis of the neurobiological characteristics associated with the innate risk for developing SAD, with the potential to detect novel IT-related brain alterations and to shed light on the mixed findings of prior work [3]. Thereby, we expect this project to increase our understanding of the pathways leading to (social) anxiety, providing new avenues to prevent the development of psychopathology in youth at risk.

#### Conflict of interest

**Disclosure statement:** JMBH is funded by a Rubicon grant from the Dutch Research Council NWO (019.2015G.022) KAD: grant support from NIMH (U01MH093349) NAF: grant support from NIMH (U01MH093349), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Science Foundation (NSF), the National Institutes of Health Environmental influences on Child Health Outcomes (NIH ECHO) consortium, the Russell Sage Foundation, and the Lumos Foundation. NAF has received royalties from Guilford Press and Harvard University Press. NAF has received honoraria for lectures to professional audiences HAH: grant support from NIMH (U01MH093349) and the Social Sciences and Humanities Research Council of Canada AJS: NIMH R01 MH107444 and NIMH R01 MH121409 KEG: NSF GRFP DGE1255832 KPE: NIMH R01 MH094633 SYH: current (AA021746) and past grant support (AA05909 and AA08082) MB (past grants): National Alliance for Research in Schizophrenia and Depres-

sion 2006 Independent Investigator Award Italian Ministry of Health Strategic Research 2008-2010 Grant Italian Ministry of University and Research, Rome (Co-Fin grant 11/2001-113555\_004) CARIPO Foundation 'Human Talents' Grant for Academic Centres of Excellence in Post-Graduate Teaching DNK: NIMH R01 MH 069942 JUB: NIMH K01-MH083052 and F30-MH097344 JAC: NIMH F30-MH097344 EPH: Brain-SCAN initiative at Western University funded by the Canada First Research Excellence Fund (CFREF) MRJV: CIHR Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Award PMT: received partial research support from Biogen, Inc., unrelated to this work DJS: received research grants and/or consultancy honoraria from Johnson & Johnson, Lundbeck, Servier and Takeda. The ENIGMA-Anxiety working group gratefully acknowledges support from the NIH Big Data to Knowledge (BD2K) award (U54 EB020403) to PMT.

#### References

- [1] Bas-Hoogendam, JM, Blackford, JU, Brühl, AB, Blair, KS, van der Wee, NJA, Westenberg, PM., 2016. Neurobiological candidate endophenotypes of social anxiety disorder. *Neurosci Biobehav Rev* 71, 362-378.
- [2] Clauss, JA, Blackford, JU., 2012. Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. *J Am Acad Child Adolesc Psychiatry* 51, 1066-1075.
- [3] Blackford, JU, Clauss, JA, Benningfield, MM., 2018. The Neurobiology of Behavioral Inhibition as a Developmental Mechanism BT - Behavioral Inhibition: Integrating Theory, Research, and Clinical Perspectives. Pérez-Edgar K, Fox NA, editors. *Behav. Inhib.* 113-134. doi:10.1007/978-3-319-98077-5\_6, Cham: Springer International Publishing.
- [4] Bas-Hoogendam, JM, Groenewold, NA, Aghajani, M, Freitag, GF, Harrewijn, A, Hilbert, K, et al., 2020. ENIGMA-anxiety working group: Rationale for and organization of large-scale neuroimaging studies of anxiety disorders. *Hum Brain Mapp* 1-30. doi:10.1002/hbm.25100.
- [5] Zugman, A, Harrewijn, A, Cardinale, EM, Zwiebel, H, Freitag, GF, Werwath, KE, et al., 2020. Mega-analysis methods in ENIGMA: The experience of the generalized anxiety disorder working group. *Hum Brain Mapp* 1-23. doi:10.1002/hbm.25096.

doi: 10.1016/j.euroneuro.2021.10.041

#### P.0036

#### The neural correlates of trait-anxiety in humans: a systematic review

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**Background** Trait-anxiety is widely conceptualized as the predisposition to appraise stimuli as threatening and respond with anxiety. Individuals with trait-anxiety are a het-