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The Origins of Obsessive-Compulsive Disorder: Prenatal and Perinatal Risk Factors and the Promise of Birth Cohort Studies

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Obsessive-compulsive disorder (OCD) is a developmental neuropsychiatric illness with onset typically during adolescence or young adulthood. It can cause substantial lifelong disability due to the severe and chronic course of the illness. As with most complex neuropsychiatric disorders, the causes and pathophysiological mechanisms underlying OCD are not well understood. This limits our ability to discover new treatments and interventions that will alleviate suffering for the millions of people worldwide with this disorder. It is clear that there is a genetic contribution to OCD risk, with modern estimates of heritability in the range of 40–50%.[1] While less often studied, environmental risk factors (e.g. infection, trauma) have also been suggested in OCD, although causal associations are less certain. There is great hope that continued study of genetic, epigenetic, and environmental susceptibility in OCD will provide needed insights into disease mechanisms and risk factors that can be leveraged for prevention and intervention.

In this issue of *JAMA Psychiatry*, Brander et al.[2] present data from Swedish national registers to investigate, prospectively, a number of perinatal risk factors that might be associated with the subsequent development of OCD. A tremendous strength of this study, aside from the power afforded by such a sizable cohort, is the use of within-family controls (full siblings, raised in the same family, who had a different exposure to the potential risk factor) to mitigate the effect of unmeasured environmental and genetic confounders, which would presumably be shared by siblings. This study represents a significant advancement in the field of OCD research by identifying several factors that are associated with increased disease risk after correcting for unmeasured confounders and measured covariates. These risk factors include: maternal smoking of at least 10 cigarettes per day during pregnancy,

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caesarian section delivery, preterm birth, low birth weight, large for gestational age, breech presentation at labor, and low Apgar scores at 5 minutes after delivery. Furthermore, preterm and low birth weight associations showed dose-response relationships, supporting OCD causality. As might be expected, OCD risk also increases as the number of these perinatal events increase. Indeed, they found that fully 40% of all identified OCD cases had at least one of these risk factors! This is a finding of clear public health significance.

Judging by the effect sizes reported in the current study (hazard ratios of ~1.1–1.5), the effects reported for common genetic variants in OCD,[3] and previous estimates of the effects of genetics and environment,[4] it appears that environmental risk factors carry at least as much of an impact on OCD risk as some common genetic variants. While the mechanisms underlying the association between OCD and these identified perinatal risk factors have yet to be precisely identified, the present findings lend support to the long hypothesized critical importance of the fetal environment that may hold relevance for the etiology of OCD and other developmental neuropsychiatric disorders.[5,6] The authors of the current study cite the relevant literature that speculate on several mechanisms that could lead from perinatal insult to aberrant brain development and subsequent neuropsychiatric illness.

There is a tendency in psychiatry to speak about “nature versus nurture”, implying that biological risk and environmental risk are mutually exclusive or that there should be an effort to determine which set of risk factors exerts the greater influence on disease. However, if the overarching goal is to clarify the underlying biology of a disorder in order to focus new research and treatment targets, a more productive approach might be to look for points of convergence among studies that focus on biological *and* environmental risk. In this regard, one might ask what the genetic data tells us about OCD etiology and whether there are points of convergence with the present study that would strengthen the case for the importance of the perinatal time period. In fact, we were fascinated to find that these environmental and genetic data may be highlighting a similar story.

In the first published whole-exome sequencing study in OCD parent-child trios, Cappi et al.[7] identified 20 genes harboring rare de novo, protein altering mutations. Next, the authors generated a protein-protein interaction (PPI) network and demonstrated its relatedness to the most promising findings from earlier OCD GWAS studies.[8,9] Using Ingenuity Pathway Analysis (IPA, QIAGEN Redwood City, www.qiagen.com/ingenuity) to look for enrichment of the 37 most densely connected PPI genes in known biological networks, they found the greatest enrichment within a network associated with embryonic development. Examination of these genes using data from the BrainSpan Atlas of the Developing Human Brain (www.brainspan.org)[10], a rich dataset that allows one to map gene expression trajectories across multiple brain regions over the full course of human development, shows that these 37 genes identified by Cappi et al. reach their peak expression in the orbital prefrontal cortex and striatum, brain areas suspected to play key roles in OCD pathophysiology,[11,12] during perinatal time periods.

These findings also point to the importance of epigenetic modifications that alter how our DNA is read and transcribed very early in human brain development. It is clear that the regulatory regions of the human genome are unique to our species and that they directly

impact the complex and dynamic regulation of gene expression during the course of development.[10] Given that heavy maternal smoking may set the stage for OCD and related neurodevelopmental disorders such as Tourette syndrome,[13] it will be important to explore the epigenetic modifications that associated maternal smoking during gestation and their overlap with genetic variants in OCD.[14]

In our estimation, the findings presented by Brander et al.[2] provide one more important step in efforts to elucidate OCD biology and risk. They also raise more questions than answers at this stage. For example, are there different risk factors or biological mechanisms that might lead to more severe or earlier-onset illness? The authors of the current study point out that their cohort is overly representative of more severe cases, so it is not poised to address this question in relation to perinatal risk factors. There is also a need for genetic studies that are well-powered to address potential genetic contributions to OCD severity and age of onset.

Based on the work of Cappi et al.[7] and Lennington et al.,[15] another question of great interest, in our opinion, is whether there is any evidence from pre- and perinatal factors in this cohort to strengthen some of the first genetic evidence for immune mechanisms underlying some cases of OCD and related conditions.

The findings presented in this issue of *JAMA Psychiatry* are certainly intriguing and have great public health significance. Additionally, they bring us one step further in our understanding of OCD risk and underlying biology and are likely to influence the design of future genetic, epigenetic, and environmental investigations. Further studies are required to replicate these findings, and much more work will need to be done, for example in animal and cell models, to dissect the mechanisms underlying the reported associations. Ultimately, this work will continue to increase our understanding of OCD etiology and inform novel interventions to alleviate and potentially prevent suffering from this common and debilitating disorder.

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References

1. Monzani B, Rijsdijk F, Harris J, Mataix-Cols D. The structure of genetic and environmental risk factors for dimensional representations of DSM-5 obsessive-compulsive spectrum disorders. JAMA psychiatry. 2014; 71(2):182–189. [PubMed: 24369376]
2. Brander G, Rydell M, Kuja-Halkola R, et al. Perinatal Risk Factors in Obsessive-Compulsive Disorder: A population-based sibling comparison study. JAMA psychiatry. 2016; XXX(XXX):XXX–XXX.
3. Taylor S. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol Psychiatry. 2013; 18(7):799–805. [PubMed: 22665263]

4. Mataix-Cols D, Boman M, Monzani B, et al. Population-based, multigenerational family clustering study of obsessive-compulsive disorder. JAMA psychiatry. 2013; 70(7):709–717. [PubMed: 23699935]
5. Vasconcelos MS, Sampaio AS, Hounie AG, et al. Prenatal, perinatal, and postnatal risk factors in obsessive-compulsive disorder. Biol Psychiatry. 2007; 61(3):301–307. [PubMed: 17123475]
6. Newman L, Judd F, Olsson CA, et al. Early origins of mental disorder - risk factors in the perinatal and infant period. BMC psychiatry. 2016; 16(1):270. [PubMed: 27473074]
7. Cappi C, Brentani H, Lima L, et al. Whole-exome sequencing in obsessive-compulsive disorder identifies rare mutations in immunological and neurodevelopmental pathways. Transl Psychiatry. 2016; 6:e764. [PubMed: 27023170]
8. Mattheisen M, Samuels JF, Wang Y, et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry. 2014
9. Stewart SE, Yu D, Scharf JM, et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry. 2013; 18(7):788–798. [PubMed: 22889921]
10. Kang HJ, Kawasawa YI, Cheng F, et al. Spatio-temporal transcriptome of the human brain. Nature. 2011; 478(7370):483–489. [PubMed: 22031440]
11. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neuroscience and biobehavioral reviews. 2008; 32(3):525–549. [PubMed: 18061263]
12. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. The Psychiatric clinics of North America. 2000; 23(3):563–586. [PubMed: 10986728]
13. Browne HA, Modabbernia A, Buxbaum JD, et al. Prenatal Maternal Smoking and Increased Risk for Tourette Syndrome and Chronic Tic Disorders. Journal of the American Academy of Child & Adolescent Psychiatry.
14. Joubert BR, Felix JF, Yousefi P, et al. DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. Am J Hum Genet. 2016; 98(4):680–696. [PubMed: 27040690]
15. Lennington JB, Coppola G, Kataoka-Sasaki Y, et al. Transcriptome Analysis of the Human Striatum in Tourette Syndrome. Biol Psychiatry. 2016; 79(5):372–382. [PubMed: 25199956]