An Array of Studies Addressing Cognition and Cognitively Defined Neuropsychiatric Conditions: Many More Connections Than You Might Think

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Six articles in the June 2020 issue of the *American Journal of Psychiatry* address the overall construct of cognition. These articles have a broad connection to cognition, which is itself a broad concept. From the experimental psychology perspective, cognition is the set of processes associated with attending, learning, knowing, and remembering. From the clinical perspective, a number of neuropsychiatric conditions are defined by the presence of cognitive impairment, with onset ranging from childhood, such as attention deficit hyperactivity disorder and intellectual disability, to later life, such as dementia. Other conditions have notable cognitive impairments even if specific cognitive impairments are not an explicit part of their formal diagnostic criteria, including autism spectrum disorder and schizophrenia. Thus, the array of articles in this issue are related to each other and also may make important points about the role of cognition in everyday functioning and the connections between cognitive impairments in neuropsychiatric conditions and in the human population in general. Further, these articles address the neurobiological substrates that have an impact on cognition, with important implications in other domains, such as genomics. Finally, through sophisticated research methods, they clarify the results of previous studies that were affected by a variety of methodological challenges.

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One important issue for all neuropsychiatric conditions that do not arise from focal brain damage or dysfunction is whether the cognitive impairments in these conditions are generalized or specific. This discussion parallels research and conceptual thinking on the nature of cognitive functions in humans in general. For years, the conceptualization of a general ability factor, referred to as "g" (1, 2), has been a point of debate. The broad acceptance of the importance of generalized cognitive abilities is reflected in society's wide use of global indices of cognitive abilities, such as IQ, SAT, GRE, LSAT, and MCAT scores. In fact, despite concerns about the potential bias in using these indices to make decisions with lifelong consequences (3), these global ability scores centrally define conditions addressed in the articles in this issue, such as dementia, intellectual disability, and autism spectrum disorder (ASD).

Increasing evidence suggests that global intellectual ability not only is psychometrically plausible but also is likely genomically determined. Twin study evidence from over a half a century has suggested this (4), but recent advances in genomic research have expanded these findings into the general population. For instance, three recent publications with partially overlapping samples have identified genomic correlates of global cognitive performance (5) (N=300,486), intelligence (6) (N=269,867), and educational attainment (7) (N=1.1 million). Further, my colleagues and I recently reported on the substantial overlap between the genomics of cognition in schizophrenia and bipolar illness and the results of these three previous general population studies (8). In that study, polygenic scores for cognitive and functional capacity performance in 3,959 European American veterans overlapped to a substantial extent with polygenic scores for global cognitive ability ($p=5.7\times10^{-16}$) and intelligence (3.47×10^{-20}).

In the article by Holleran et al. in this issue (9), white matter microstructure was associated with intelligence in samples of people with schizophrenia and healthy individuals. Similar to previous findings regarding cognitive performance, functional capacity, and everyday functioning comparing schizophrenia to bipolar disorder (10), Holleran et al. report that people with schizophrenia had lower connectivity and lower intelligence than the healthy sample, but with a highly similar correlational structure between cognition and white matter microstructure within the two groups. These findings suggest that common neural structural variability may have a role in intelligence that is common across neuropsychiatric conditions. The authors characterize their effect sizes as "modest." However, these effect sizes

are in the range of 0.3, which would be enormous for a genomic effect on intelligence.

Interestingly, it has been suggested for years that white matter abnormalities underlie cognitive deficits in schizophrenia (11) and that these abnormalities are genomically influenced (12). Previous studies identified myelin-related candidate genes, some of which, including *ERBB3* (erb-b2 receptor tyrosine kinase 3), *MBP* (Myelin Basic Protein), and *NRG-1* (Neuregulin-1), appear in the lists of genes associated with global cognition on a genome-wide basis in the studies noted above. Clearly these findings suggest convergence between cognition, genomics, and brain structure and could be a very promising area for follow-up examinations of the convergence of genomics, white matter microstructure, and intelligence across populations.

The specificity of this white matter–cognition relationship is highlighted by the results of a recent genome-wide association study (GWAS) examining anhedonia (13). This feature of schizophrenia is highly implicated in functional outcome, as is cognition, and there has been considerable debate about whether negative symptoms such as anhedonia manifest overlap with cognition. That study found that a GWAS-derived polygenic score for anhedonia was not associated with white matter integrity. Thus, genomic modeling may allow for differentiation of influences on cognition as compared with other symptoms of schizophrenia such as anhedonia, both of which are substantial contributors to everyday disability.

In another study related to intelligence, Klein et al. in this issue (14) examine the convergence of attention deficit hyperactivity disorder (ADHD) and intelligence with a highly creative strategy of examining the impact of genes identified in humans with their homologous variants in *Drosophila*. Finding three highly important genes for ADHD, the authors explore their implications in *Drosophila* models. Importantly, the discovery gene set was from a panel of genes known to be related to intellectual disability. Of the three genes the authors identified that are related to ADHD, two have evolutionary variants in *Drosophila*, with different functional implications.

Very interestingly, two of the three genes, *MEF2C* (Myocyte Enhancer Factor 2C) and *ST3GAL3* (ST3 Beta-Galactoside Alpha-2,3-Sialyltransferase 3), also appear prominently in the Savage et al. study of intelligence referenced above (6) as well as the Lee et al. 1.1 million–participant GWAS (7) addressing global educational attainment. In those studies, these genes were identified because of their relationship with intelligence primarily, but the overall GWAS in the Savage et al. study also revealed interesting findings relevant to ADHD. There was a highly significant association between higher intelligence and lower risk of ADHD (odds ratio=0.48, byx [estimated causal effect coefficient]=−0.734, $p=2.57\times10^{-46}$) in the overall GWAS sample. Interestingly, the circadian-relevant *dTRAPP* (Transport Protein Particle) genes identified by Klein et al. to be associated with ADHD and intelligence do not appear in any variant in the Savage et al. study of intelligence but do appear in the Lee et al. educational attainment–focused GWAS.

Very importantly, the *dTRAPPC9*-modified *Drosophila* manifested a phenotype of increased activity and decreased sleep during the night, which was different from the *dMEF2* sleep phenotype. Specifically, the *dTRAPPC9* knockdown phenotype is characterized by an increased latency to sleep onset and disturbed sleep, with more sleep bouts of shorter duration. These findings parallel the phenotype with which many parents of children with ADHD are very familiar—disturbed sleep, excess activity, and waking during the night.

The Savage et al. results implicate two of the three ADHD genes as part of an overall complex of genes driving intelligence, relating to ADHD. The findings regarding sleep are very important as well, in that the *dTRAPP* gene appeared to have robust sleep effects and was associated with educational attainment while not appearing in the intelligence GWAS. These findings, suggesting cognitive and behavioral separation in genomic origins, may broadly apply to variants of ADHD. Many children without symptoms of hyperactivity have attention and concentration problems leading to academic challenges, often requiring treatment. Further, the finding that the *dTRAPP* gene is associated with educational attainment but not with intelligence suggests separable behavioral and cognitive paths toward educational attainment. Apparently, factors can be genomically related to reduced educational attainment without affecting intelligence directly, which is likely true for a variety of behavioral traits that are associated with reduced educational attainment.

The MacDuffie et al. article in this issue (15) also addresses sleep. In a study of children at high risk for ASD, the authors examined the early occurrence of sleep difficulties and their predictive importance over time. Making a critical neurobiological link, they also examined hippocampal volume trajectories, finding a correlation between poor sleep and hippocampal volumes only for children who later developed ASD. Other subcortical structures, some well known to be important in ASD, such as the amygdala, did not show the convergence in trajectory found between sleep problems and hippocampal volume.

The authors provide the rationale for their study by pointing out two well-understood previous trends. Poor sleep in the first year of life has been reported to predict development of ASD. Further, abnormal brain growth in the first year of life, particularly excessive or overly rapid development, has also been shown to predict development of ASD. In their study, MacDuffie et al. examine sleep, brain development, and cognitive development, in both general and language-specific assessments.

In a series of analyses, the authors also zero in on what time period is most informative and how early the sleep→brain→ASD connection can be predicted. They report quite specific predictive findings regarding onset of ASD and its association with sleep and hippocampal volumes. What they also do, which is extremely important, is to hypothesize that poor sleep quality is the origin of the alterations in the hippocampus, and not either the reverse causality (abnormal hippocampal development leads to poor sleep) or the

third-variable explanation (both are markers of some other process).

Why would sleeping poorly at age 6 months lead to changes in the hippocampus? The authors marshal an array of evidence suggesting that the hippocampus is specifically vulnerable to effects of poor sleep. For example, poor sleep leads to metabolic by-products being deposited in the hippocampus. While we think of this as a process that should apply to more mature brains, the authors also remind us that preadolescent, but not adolescent, mice that are sleep deprived develop permanent problems in the long-term consolidation and encoding of information. Also, poor sleep has been shown to be associated with neuroinflammation. In an interesting argument, MacDuffie et al. review evidence that impaired sleep causes inflammation in the hippocampus of mice, which then leads to poor performance on a hippocampally mediated memory test.

An important part of this study is that it suggests an immediate and thoroughly simple treatment strategy. Could something as obvious as improving sleep directly lead to mitigation of the neurobiological cascade that leads to the expression of ASD vulnerability? The authors note that successful interventions for sleep in children who have already developed ASD have been reported, with both melatonin and behavioral interventions having had efficacy. Given ASD's early onset and typically lifelong morbidity, any potentially preventive intervention requires serious attention.

Therapeutic interventions aimed at sleep often employ benzodiazepines and the z-drugs, and these are the focus of attention in the article in this issue by Osler and Jørgensen (16). In their study, they focus on risk for development of dementia in people who are treated on an ongoing basis with these medications and who also had a first treatment for mood disorders in the past 20 years. Several studies have suggested that the use of these medications is associated with an increased risk of developing dementia. It is clear that the use of these medications can cause short-term cognitive challenges. Using the resources available in Nordic countries such as Denmark, with extensive medical records and registries, the authors performed a very-large-sample study of the risk for development of dementia as a function of the use of these medications.

There are several extraordinary strengths in the study. The authors selected a homogeneous diagnostic group, capturing first-episode patients, and they have an extraordinarily long follow-up period. Also examined are characteristics of the drugs, number of refills, and an array of information targeting exposure. The authors also carefully documented dementia outcomes with archival information. As they are not recruiting a sample who would be expected to manifest extraordinary cognitive impairments earlier in life (e.g., people with schizophrenia), the likelihood of false positive dementia diagnoses is reduced as well.

The basic findings of the study are easy to summarize. There was no effect of benzodiazepine or z-drug use on dementia, at any dose or any cumulative exposure. In fact, the opposite was found: there appeared to be a protective effect of treatment with these drugs on the onset of dementia. The conclusions and information presented by MacDuffie et al. in their sleep and autism report are likely to be extremely relevant to these results as well. The adverse effects of poor sleep on the hippocampus and the involvement of the hippocampus in many different dementia-related diagnoses could be reiterated in the interpretation of the results of the benzodiazepines and dementia study. Thus, treatment of sleep disorders, even with z-drugs, may have the same potential benefit in the risk for developing dementia as it may have for ASD.

Why did earlier studies report that benzodiazepines and z-drugs could be causally related to dementia? Osler and Jørgensen delineate several clear possibilities. First, anxiety and sleep problems can occur during prodromal or mild cognitive impairment stages during the development of dementia, and studying participants who are already elderly increases the chances of identifying an already existing condition. As noted above, some psychiatric populations have considerable cognitive impairments at the time of the first episode. The combination of these preexisting conditions and aging could result in a dementia diagnosis that is not associated with the development of any new condition (17). Widespread use of sleeping medications is common in serious mental illness, so studying this population, who may already have cognitive impairments consistent with dementia but lack the neuropathology (18), may lead to exaggerated estimates of the influence of medications on cognitive impairments. Thus, starting early and following the lifetime course of patients with mood disorders provides a fair test of the hypothesis that benzodiazepine and z-drug use and dementia have some convergence.

Vega et al. (19), in their article in this issue—another study on use of medications during certain critical periods potentially increasing the risk for adverse outcomes—carefully examine the risk of prenatal antidepressant exposure in the development of autism. The unsubstantiated fear of inducing autism through various means, including vaccinations, has been common and has led unfortunately to a reduction in use of important evidenced-based medical treatments. Therefore, evidenced-based studies, in this case evaluating any potential relation between the treatment of mood disorders during pregnancy and developing autism, is important, and especially so in the case of antidepressants, since previous studies have suggested just such a link.

Depression during pregnancy and the immediate postnatal period can have adverse consequences to both babies and parents. Using medications during this period is always an issue, and therefore safety and risks need to be established. In performing a meta-analysis of the results of these studies, there are several considerations. First, given that the mother who receives antidepressants is generally getting them because of depression, results when using comparison samples of nondepressed mothers do not address a linkage between medication and outcomes as much as they reflect more

broadly the relation between maternal illnesses and outcomes in offspring. Further, because the risk for autism is highly familial, an optimal design is to study discordant siblings in which differences in outcomes across siblings can be related to prenatal exposure variables.

In this study, meta-analyses of autism risk and prenatal exposure were conducted from studies across all three trimesters of pregnancy and with different research designs. It is important to note that none of the 14 studies used examined whether the mothers were actually depressed during the index pregnancy, focusing instead on lifetime diagnoses. Also, there were so few data on the second and third trimesters that comparator effects could only be examined in the first trimester.

Compared with population-based estimates, the increased risk for autism in children exposed to antidepressants during the prenatal period was quite elevated, across antidepressant classes. However, when the comparison group was confined to women with depression, antidepressant treatment was actually found to be associated with a substantially reduced risk. The finding was even more striking for discordant sibling designs, where treatment with antidepressants during pregnancy was associated with a significant and substantially reduced risk of autism compared with children of the same mothers who did not receive antidepressants during their pregnancy.

The study by Vega et al. examining the relation between antidepressant treatment and autism shares important themes with that by Osler and Jørgensen examining the association between benzodiazepines and dementia. In both studies, the selection of the patient populations for study and the appropriate comparators are critical, and by so doing, both studies demonstrate that in contrast to exerting an adverse effect on the lifetime course of the population receiving treatment, treatment with certain medications during certain critical periods may have a risk-reducing effect. The Vega et al. results suggest that, in contrast to antidepressant treatment having a toxic effect, maternal depression may be the origin of the toxicity.

The last of the six studies, by Lenze et al. (20) is on antidepressant treatment as an adjunct to computerized cognitive training. Pharmacologically augmented cognitive training has been suggested as a strategy for cognitive enhancement in several conditions, including schizophrenia (21). Based on the success of the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial (22) reviewed by the authors, cognitive training has been largely accepted as having efficacy for cognitive test performance, which could be increased with addition of the right pharmacological stimulation. In fact, in addition to the completed study by McClure et al. (23) published in the *Journal* last year, there are other ongoing trials (24) using this strategy.

In the Lenze et al. study, the authors selected a newer antidepressant medication, vortioxetine, the only antidepressant medication whose manufacturers are allowed to claim efficacy for cognition in major depression. The rationale for the selection of vortioxetine is interesting, and other compounds, such as guanfacine, alertness-promoting agents, or stimulants, could also have been considered. The study used a rigorous design, a randomized, placebo-controlled augmentation of computerized cognitive training, exclusion of individuals who may have been depressed (in order to avoid spurious antidepressant effects on treatment), and a carefully selected cognitive outcome assessment (the NIH Toolbox). A performance-based measure of functional capacity, the UCSD Performance-Based Skills Assessment (UPSA), was also used, to examine whether training effects transferred to the types of everyday functional skills not trained by the program but also dependent on cognitive performance. In addition, this intervention had another critical component, that of a psychosocial intervention aimed at augmenting engagement in treatment and real-world deployment of the skills obtained.

The pharmacological augmentation of training had evidence of efficacy, in that the primary outcome was significantly better performed in the vortioxetine-augmented group compared with the placebo group at the 12-week time point. As the patients receiving placebo treatment were also receiving computerized cognitive training and a psychosocial intervention, there was improvement in both cognition and functional capacity in that group as well; this constitutes a high bar for separation from placebo. The improvement in both groups on the UPSA could be due to several factors. The authors delineate several possible reasons for the change in both groups, but there is an additional one as well. The UPSA has only one form and has been shown to manifest retesting effects. People who were in the placebo condition in this study did receive cognitive training, and that training benefit may have been enough to lead to augmentation of the typical practice effects on the UPSA.

All told, what are the themes in these six articles? There are at least three.

The first is the simultaneously generalized and specific influence of genomics. Holleran et al. examined the confluence of white matter structure and cognitive performance in healthy people and in patients with schizophrenia. It turns out that other research has suggested that subgroups of white matter–related genes are also related to cognition, but in an intriguing (and speculative) twist, it may turn out that only a subset of genes relevant to white matter are also related to cognition. Interestingly, the set of genes previously identified as related to white matter only have a few overlapping genes with cognition, intelligence, and educational attainment. Are genes related to oligodendrocyte development differentially related to these cognitive outcomes relative to genes that are responsible for white matter structure? This idea could easily be tested with existing data sets.

Similarly, Klein et al. searched among genes for intellectual disability to find genes that relate to ADHD. They found several, with some seemingly related to cognition and others to chronobiology and activity levels. Where the specificity comes in is that the genes they identified that are linked

directly to cognition also appear as hits in a large-scale GWAS of intelligence in the general population. The activity-related gene the authors identified is not associated with cognition but was found to be related to educational attainment in a GWAS focusing on that topic. Thus, genes that are linked broadly to intellectual disability are found to be related to ADHD, but possibly to different phenotypic features. Also intriguing is that *dTRAPP* genes are as strongly related to educational attainment as genes associated with cognitive abilities, but they do not seem to be as strongly related to intelligence. Thus, the end-state phenotype of ADHD has different features that appear to be under separate genomic control.

The second theme is the importance of sleep. MacDuffie et al. present fascinating data suggesting that poor sleep and abnormal hippocampal development convergence are associated with higher incidence of ASD among high-risk children compared with those who sleep better. The authors generate the hypothesis that poor sleep itself is the cause of abnormal neurobiological development and accelerated risk for ASD. They show that the consequences of poor sleep, particularly in early developmental stages, can interfere with hippocampal functioning. Osler and Jørgensen then show that, in contrast to previous results suggesting that sleep-related medication treatments (benzodiazepines and the z-drugs) may cause dementia, these treatments actually may have a preventive effect. This effect is probably due to improving sleep. Thus, improving sleep at opposite ends of the lifespan, in infancy and in later life, may have the potential to avoid serious adverse neurobiological consequences.

The third theme is that of the benefits of antidepressant treatments for very different neuropsychiatric outcomes. Vega et al., in a comprehensive set of meta-analyses, turn the common idea that antidepressant use in pregnancy is associated with risk for autism on its head. In their analyses of the best-designed studies, they actually find that antidepressant use in pregnancy is associated with reduced risk of autism, and they suggest, based on previous studies, that it is actually depression during pregnancy that may increase the risk for ASD. Interestingly, is it also possible that a mother with untreated depression during the postpartum period may in some way have an impact on the way that her infant sleeps, possibly by her own sleep difficulties? Finally, antidepressants may actually have the potential to be a supplementary cognitive enhancer. Much as with previous attention-enhancing agents, such as guanfacine, modafinil, and amphetamine, adding vortioxetine, a new antidepressant with some possibly unique properties, to computerized cognitive training leads to augmented benefits. While other medications are also candidates for this role, the use of vortioxetine as an augmentation agent is creative and well supported. As the authors note, there are other research designs that can also be employed in this augmentation model, but in the meantime, the use of vortioxetine as a augmentation strategy in people without depression is a new and creative strategy that might work even better in people who are depressed as well.

These six articles show how diverse research approaches across neuropsychiatric populations can converge in a very robust manner. They also suggest several additional areas of inquiry that could render these linkages even closer and suggest interventions that might reduce development of and morbidity in significant conditions affecting both ends of the lifespan.

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