The Biopsychiatrists' Flying Circus:

American Journal of Subatomic Psychiatry CME quiz: 21st century Digital Bedside Manner of RoboDocs
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Lesson
In a world that's rolling downhill like a snowball headed for hell, there are least some inspiring developments in 'mental health' science to look forward to as we plunge into 2018. Thanks to the current thrilling pace of discovery we are tracing human unhappiness to aberrant genes and devious molecules, a predestined arc of progress that will soon lead to a merger of string theory and quantitative genetics so as to explain the exact origins of psychopathology at the sub-Planck length. The Next-generation robotic biomolecular/subatomic quantum drone psychiatrists will surpass current beta-phase prototypes already deployed in public and academic psychiatry to become almost lifelike.

Assembled in American psychiatric residency programs by other robots (faculty) on an assembly line, and untouched by clumsy human hands, they will be equipped with infallible hacking protection donated by Yahoo. Exploiting the superiority of artificial intelligence, with the scourge of subjectivity removed from their transistors, these automatons, driven by flawless algorithms and instant wireless connectivity with 23&Me, NIMH, CDC, Big Pharma, Tesla, FB, Twitter, police, FBI, CIA, NSA, local militias, insurance companies, military recruiters, Hollywood, popular science magazines, advertisers, lobbyists, Silicon Valley and molecule-busting laboratories around the world, will be able to effortlessly coordinate anticipated innumerable diagnostic evaluations, drug prescription/delivery/unlimited refills/blood level monitoring/compliance, record keeping and billing.

And really, really, really, really, really informed consent for a change. These compassionate robotic healers will be programmed for impeccable bedside manner, using voice and facial recognition software borrowed the National Security Agency to respond instantly to urgent questions like 'WTF are you doing to me?' by drawing upon massive cloud-based data banks to educate and comfort patients and their families in a mellifluous digital voice simulation of TV's Doctor Marcus Welby trying to suppress hiccups.

In this CME lesson, we will use a transcript from prototype RoboDoc experiments underway in Durham, North Carolina at 23&Me University and its teaching hospital with real patients. The subject is a listless 19 year old kid who, after a few years of being a bit withdrawn and self-absorbed, regresses to infantile patterns of speech and behavior, causing his parents to freak out. The trembling parents, promised a free Big Mac if they enlist him in the Subatomic Biomedical Robopsychiatric Clinical Experiment Program, ask

Doc, what's wrong with Jimmy?

RoboDoc: (Drawing on abstract from citation #1): Schizophrenia is a common disorder with high heritability and a 10-fold increase in risk to siblings of probands. Even though recent studies show low heritability and only ~4x increase in sibs, I know *a priori* that it is a powerful truth no matter what kind of distracting counterfactual evidence the Devil throws at us.

Parents: Argghhh! Gasp! We'd rather he be a leper! Or full of cancer! Will our other kids get it? Did we give them bad genes? Oh Honey, Oh My! I wish we'd used 23&Me when we got married!

RoboDoc recites further reassurance from citation #1: Ahem. Replication has been inconsistent for reports of significant genetic linkage. To assess evidence for linkage across studies, rank-based genome scan meta-analysis (GSMA) was applied to data from 20 schizophrenia genome scans. Each marker for each scan was assigned to 1 of 120 30-cM bins, with the bins ranked by linkage scores (1 = most significant) and the ranks averaged across studies (R(avg)) and then weighted for sample size (N(sqrt)[affected cases]). A permutation test was used to compute the probability of observing, by chance, each bin's average rank (P(AvgRnk)) or of observing it for a bin with the same place (first, second, etc.) in the order of average ranks in each permutation (P(ord)). The GSMA produced significant genomewide evidence for linkage on chromosome 2q (PAvgRnk<.000417). Two aggregate criteria for linkage were also met (clusters of nominally significant P values that did not occur in 1,000 replicates of the entire data set with no linkage present): 12 consecutive bins with both P(AvgRnk) and P(ord)<.05, including regions of chromosomes 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q, and 14p, and 19 consecutive bins with P(ord)<.05, additionally including regions of chromosomes 16q, 18q, 10p, 15q, 6q, and 17q. There is greater consistency of linkage results across studies than has been previously recognized. The results suggest that some or all of these regions contain loci that increase susceptibility to schizophrenia in diverse populations. Does that help?

Parents: Thank you, oh thank you. We'll do anything you say. We didn't understand a word of it but it sounds sooooo like you really know what you are talking about, and we should leave Jimmy's treatment to molecular wizards like you! For a while we thought maybe he was still bothered by being molested by his baby sitter, his priest, then a teacher, then a neighbor, then beaten up by his older siblings, then rejected by girls and ridiculed at school because he has a hare-lip. Not necessarily in that order,

'cuz we really don't know what's been going on in his life, 'cuz we both work two jobs in the city and are in the middle of a divorce, but he seemed OK up until his uncle visited last week.

RoboDoc: Yuk! Don't get caught up in that stuff. The absurd hypothesis that psychosocial factors would cause Jimmy's malfunction is based on so few facts it's like stretching a gnat's ass over a rain barrel. Besides we all know that normal kids can take a lot of punishment. Your kid has a bad gene that makes him weak, unable to shake off that barnyard crap. Plus my algorithms get queasy thinking about it, and I can't stand the smell of animals or to have dirt under my Teflon nails or mud on my metal boots. I'm a robot with sensitive electronics! I was born in a clean room! Let's talk molecules and genes, not grubby and distracting subjects like incest and other childhood trauma.

Parents: Is there any way to get rid of the bad genes?

[***Quiz Editor Note***: *The Robodoc is programmed to be ready for anything, like more annoying questions. To help Mom and Dad cope with this crisis, the Bot further lifts the veil of mystery shrouding their son's condition by summoning landmark 2004 data from citation #2 (Owen et al)*]:

RoboDoc: The high heritability of schizophrenia has stimulated much work aimed at identifying susceptibility genes using positional genetics. However, difficulties in obtaining clear replicated linkages have led to skepticism that such approaches would ever be successful. Fortunately, there are now *signs of real progress.* Several strong and well-established linkages have emerged. Three of the best-supported regions are 6p24–22, 1q21–22 and 13q32–34. In these cases, single studies achieved genome-wide significance at P=0.05 and suggestive positive findings have also been reported in other samples. The other promising regions include 8p21–22, 6q21–25, 22q11–12, 5q21–q33, 10p15–p11 and 1q42. The study of chromosomal abnormalities in schizophrenia has also added to the evidence for susceptibility loci at 22q11 and 1q42. Recently, evidence implicating individual genes within some of the linked regions has been reported and more importantly replicated. The weight of evidence now favors NRG1 and DTNBP1 as susceptibility loci, though work remains before we understand precisely how genetic variation at each locus confers susceptibility and protection. The evidence for catechol-O-methyl transferase, RGS4 and G72 is promising but not yet persuasive. While further replications remain the top priority, the respective contributions of each gene, relationships with aspects of the phenotype, the possibility of epistatic interactions between genes and functional interactions between the gene products will all need investigation. The ability of positional genetics to implicate novel genes and pathways will open up new vistas for neurobiological research, and all the signs are that it is now poised to deliver crucial insights into the nature of schizophrenia.

Parents: New vistas! Crucial insights! We live in an age of miracles! Thank you Dr Robot!!!

RoboDoc: It gets better!! (drawing from the Conclusion section from citation #2):
After false starts and a more than a decade of hard work, schizophrenia is at last yielding its secrets to molecular genetics. The weight of evidence now strongly favors NRG1 and DTNBP1 as susceptibility loci, though work remains before we understand precisely how genetic variation at each locus confers susceptibility and protection. Both associations are with inferred haplotypes rather than variants with manifest functional consequences, although, in the case of DTNBP1, we know that variation within this gene does alter gene expression….In both cases, the relative risk is small (<2.5) and cannot fully explain the linkage finding in the relevant region. These observations could suggest that the associated polymorphisms/haplotypes are in LD with pathogenic variants elsewhere in the associated gene or in a neighboring gene. Alternatively, association may arise not from a single variation in the relevant gene but from the combined effect of several different variants. Both of these situations apply to complex traits in Drosophila,…and have been found in human diseases….It is also possible that the respective linkages reflect variation at two or more linked loci…..These successes of positional genetics are immensely encouraging for psychiatry. First, the existence of several promising linked regions suggests that other susceptibility genes for schizophrenia are likely to be found in the coming years. The loci identified so far only explain a small proportion of the genetic risk for schizophrenia….Second, these findings suggest that similar approaches should be successful in identifying genes for other psychiatric disorders where replicated linkages have been found, such as late-onset Alzheimer's disease, BPD, autism and dyslexia….Advances in genotyping technology and the establishment of several consortia collecting large samples of families and unrelated cases are *further grounds for optimism. Genetic studies of schizophrenia have traveled a long and sometime rocky road, but all the signs are that now they are poised to deliver crucial insights into the nature of one of the most severe and debilitating mental illnesses.*

Parents: Wow! The long and rocky road is over! We're already past the false starts!!! So fruit flies have schizophrenia! If we can cure SZ in laboratory fruit flies, Jimmy has a bright future!! Where do we donate the money?

RoboDoc: (transistors purring) I have a list of deserving projects. Science advances because of generous people like you. Meantime, please swipe card in blinking green slot on my mechanical belly and approve $500 transaction, because the meter is running, and I will shut down if I am not paid and you will be helpless. By the way, how is your insurance?

Parents: We got him on Medicaid after talking to a NAMI rep!

RoboDoc: Great! The medical industrial complex will provide him a case manager and a team of psychiatric social workers who work under my masterful leadership and make sure he takes all his pills and that he will be whisked away to the hospital whenever he regresses (or starts acting alive again) and we can add more pills. They

also make sure I am not bothered by calls in the middle of the night. You won't have to worry any more!

Parents: All that stuff about genes blew right past us, except for some sexy thing called DTNBP1. Does he have that one?

RoboDoc (drawing on citation #3 and other sources): Sure, great question, you guys understood more than you thought. (Now activating excerpts of a digital tape loop to recite stuff from citations): Family-based analyses produced rather clear evidence for an association between schizophrenia and a set of DNA markers in the gene DTNBP1 (dystrobrevin binding protein 1) or dysbindin-1…. Dysbindin-1, a 40–50-kDa protein that is expressed in neurons in many areas of the mouse and human brain, is named for its capacity to bind dystrobrevin . . . proteins that are part of the dystrophin glycoprotein complex.....a corner has been turned in our long struggle to understand the genetic basis of SZ . . . it may no longer be outlandish to hope that we will see [now quoting Isaac Newton for support*] 'the first dawning [which] opens gradually, by little and little, into a full and clear light.'* . . . .The pathophysiology of schizophrenia is still unclear; however, this disease is believed to involve genetic abnormalities in developmental processes leading to abnormal synaptic plasticity, including glutamatergic transmission . . . Our results suggest that an abnormality of dysbindin might influence glutamatergic systems and Akt signaling. Further investigation is necessary to elucidate the mechanisms of Akt activation and upregulation of pre-synaptic molecules by dysbindin . . . In summary, there is now little doubt that the DTNBP1 gene plays a significant role in the genetic etiology of schizophrenia.

Parents: Whoa! That's OK. We shouldn't waste your time trying to explain this genius stuff about synapses to us. But it explains a lot. Like what that psychologist told us before we came to you, sayin' somethin' about 'double-binds', that Jimmy comes home to a household full of deviant communication and 'double-binds'. So we get it - he must have got the gene for 'double-dysbindin' from both of us. We'll sleep better tonight, and so will Jimmy, now that he's on that new Toraborazine. At least he won't bother us about those nightmares about somebody shoving a broomstick up his....

RoboDoc [interrupting, arms waving in big circles]: Warning! Warning! My sensors indicate something grubby! I am programmed to change subject of conversation whenever unseemly reality creeps in! My circuits start to smoke and I feel like I'm going to puke a bunch transistors through my oral interface!

Parents: So sorry, Dr Bot, we'll respect your exquisite robogenetic sensitivity to distasteful reality. [Now the Parents and Dr. Smartbot and the social workers join hands with a drug rep (who suddenly appears) and burst into song, dancing in a circle, singing 'I'm for-ev-er turn-ing cor-ners' to the tune of 'I'm forever blowing bubbles', then walk into Jimmy's cell to tell him the good news, united as a Parent/Provider/Welfare System/Medical-Industrial Complex *Team* glowing in enlightenment. Jimmy, for his part, won't sing along.]

There is only one little problem. RoboDoc evidently doesn't get his software updated often enough. Dysbindin is just one classic candidate SZ gene, the subject of richly imaginative plausibilification, a menacing figure in a Hieronymus Bosch tableau of wicked molecules torturing genetically tainted victims. RoboDoc hasn't said anything publicly about this 2017 study (citation #4) which includes double-dysbindin. Jimmy is still incarcerated, as none of the pills seems to work against double-dysbindin, but they do help him sleep 18 hours a day.

Oh, and what about the 'dawn' praised by RoboDoc (with help from I. Newton)? As the 19th century mathematician/logician George Boole lamented, '*Herein too may be felt the powerlessness of mere Logic, the insufficiency of the profoundest knowledge of the laws of the understanding, to resolve those problems which lie nearer to our hearts, as progressive years strip away from our life the illusions of its golden dawn*'. Most of the people working in human behavioral genetics are going to be stripped of their illusions, and a whole lot more, when they finally get to the fire causing the glow, where the unwashed will be roasting SNPs on a stick.

OK, now the 1-question CME quiz:

1. Robots and whole genome sequencing and machine learning and CRISPR will stamp out the scourge of human unhappiness in the 21st Century. Yes/No
(Hint: even though CRISPR was not mentioned in the lesson, answer Yes).

If you answered Yes, Congratulations! You just met your annual CME requirement and are abreast of progress in the exciting field of quantum psychiatry. You may now return to your telepsychiatry workstation in your windowless cubicle and do your best to imitate a superior corporate robot.

Citations:
1. Lewis, CM et al: Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. Am. J. Hum. Genet. 2003; 73:34-48
2. Owen, MJ et al: The molecular genetics of schizophrenia: new findings promise new insights. Mol. Psychiatry 2004; 9:14-27
3. Kendler, KS: Schizophrenia genetics and dysbindin: a corner turned? (editorial) Am. J. Psychiatry 2004; 161:1533-1536
4. Johnson, E. C. et al. 2017. No evidence that schizophrenia genes are more associated with schizophrenia than non candidate genes. Biological Psychiatry 82(10):702-708 doi: 10.1016/j.biopsych.2017.06.033

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