Individual differences in dopamine signaling and the future of personalized medicine.

The term "personalized medicine" has gained popularity in recent years. While it may seem like a buzzy term, its potential for improving treatment of a variety of medical conditions is vast. Personalized medicine involves tailoring treatments to individuals based on some aspect of their biology that might affect how they respond to a treatment. For example, you might give one patient with a particular genetic variant a different pharmacological treatment than another if that variant effects how they process (metabolize) or respond to that particular drug. This particular approach of using genetic information to understand response to pharmaceuticals is termed pharmacogenomics (see also).

The rapid reduction in the cost to sequence the human genome (complete set of an individual's DNA) as well as proliferation of genotyping services such as 23andMe (which genotype common genetic polymorphisms, or areas in human DNA most likely to vary across individuals) means that genetic data can be readily obtained by anyone who wants it. This technological advance will allow physicians greater information of a patient's underlying biology and eventually will be merged with growing insights into the effects of genetic variation on drug metabolism, brain signaling, and behavior to make personalized medicine commonplace. In fact, pharmacogenomic data has been added to several drugs by the FDA.

My own work suggests that genetic variation in a gene encoding the dopamine D2 receptor (DRD2) can affect the relative availability of this receptor in the brain as measured with PET (Smith et al., 2017 *Translational Psychiatry*). Individuals with a particular genetic variant in DRD2 that is associated with less availability of the receptor (C957T CC individuals) may need either a higher dose of a D2 drug or a higher affinity D2 drug to receive a therapeutic benefit. D2 agonists are commonly used in Parkinson's Disease patients to preserve motor function and D2 antagonist-like drugs are used in the treatment of Schizophrenia. Understanding the genotype of individuals affected with these conditions, then, could enhance the effectiveness of their D2 drug treatments (by suggesting a physician might want to start with a higher or lower dose of the drug). While studies such as our linking genetic variation with differences in biology are encouraging, DNA can also be modified by the environment. Researchers have begun studying these

epigenetic effects on behavior, with most work occurring in rodents. As we integrate this knowledge, we will begin to better understand the impact gene by environment interactions have on biology and behavior.

But genetics are not the only variables that could be worth attending to in future treatments. Additionally, dopamine signaling is known to decline with age. So, doses of dopaminergic drugs that work well on young adults might need to be titrated in older adults. Furthermore, we and others have shown that estradiol levels in naturally cycling women can affect dopaminergic brain functions (assessed by fMRI imaging and a genetic variant (COMT) know to affect dopamine levels in the higher-order areas of the brain). Thus, a dopaminergic medication might be more effective at treating a female patient's symptoms at certain points of her menstrual cycle but not others. We are only beginning to understand the role of female sex hormones in a variety of biological systems as basic research historically has focused on male model organisms.

This brief overview emphasizes potential regulators of dopamine signaling in the human brain, as it is an area I am most familiar with. Hopefully I have conveyed the complexity of implementing personalized medicine when treating psychiatric or behavioral disorders. The brain is complex enough and the fact that genetics, sex hormones, age, and environment can all affect one neurotransmitter (dopamine) among the many others involved in brain function speaks to the vast challenge that lies ahead for researchers. Our quest to better understand individual differences, however, has the potential to lead to more targeted treatments and therapies for a variety of dopamine-associated disorders including ADHD, Schizophrenia, Parkinson's Disease, and drug addiction. The development of these personalized treatments will undoubtedly improve healthcare in the 21st Century but will require further research focused on measuring and categorizing individual differences.