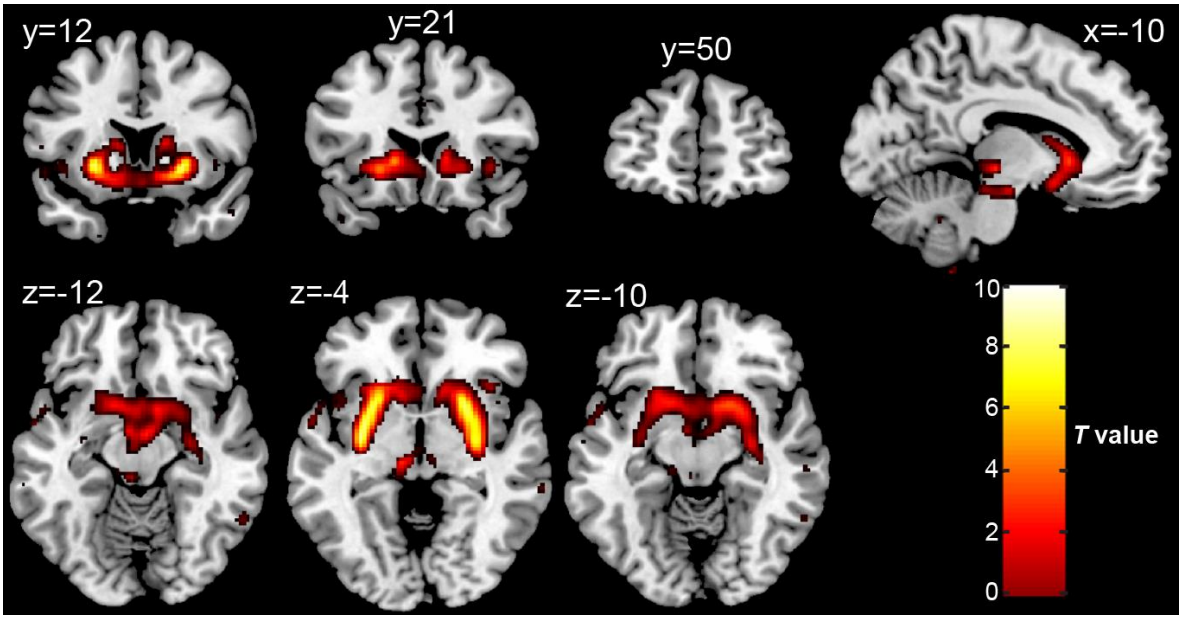

Areas of significant change in Fallypride PET binding after oral d-amphetamine (dopamine release). Smith et al. 2016 Neuropharmacology

Do dopamine signaling differences reflect risk for drug addiction?

Drugs of abuse release dopamine in the brain. Dopamine, among other things, links pleasure/wanting with the stimuli its release is paired with. Thus, differences in dopamine signaling in response to drugs of abuse may relate to a greater propensity to re-use drugs found to be rewarding and potentially lead to increased risk for drug addiction.

PET imaging has shown that lower dopamine D2 receptors are present in a variety of drug-addicted individuals (alcohol, cocaine, methamphetamine, heroin) when compared to healthy controls. Whether low D2 receptors are a cause or consequence of problematic drug use has been difficult to determine in human studies, however.

Animal work has suggested that behavioral impulsivity is associated with lower D2 receptor levels in rodents. These researchers also found that high impulsive rats would later go on to self-administer more cocaine than low impulsive rats (Dalley et al., 2007). Thus, D2 receptors may confer a greater propensity to engage in behaviors that are associated with drug addiction risk in humans (impulsivity, novelty seeking). Furthermore, monkey work has shown that low D2 receptor levels predict escalation in cocaine self-administration, which leads to lower D2 receptor levels (Nader et al., 2006). This work suggests that low D2 receptor levels may predispose individuals to escalate drug use and that chronic drug use further changes these receptor levels.

Human PET studies have focused on individuals with a family history of addiction to try to corroborate the animal work linking dopamine D2 receptors with addiction risk. Volkow et al. 2006 have shown that individuals with a family history (FH) of alcoholism show

heightened striatal (a region deep in the brain responsible for reward processing, learning, and action initiation) D2 receptor levels compared to subjects without a family history. They argue these high D2 levels may serve as a protective factor that prevented these individuals from becoming alcohol abusers themselves. This finding highlights the complexity of working with human subjects as the animal literature might have suggested the opposite finding (lower D2 in FH individuals). Human motives to use drugs are many and often the environment greatly shapes behavior. It could be argued that FH positive individuals with lower D2 (not observed in Volkow et al) had behavioral profiles (see Dalley et al., 2007; above) that resulted in them already transitioning to alcohol/drug abuse and thus being excluded from the Volkow study. Undoubtedly, there are more variables associated with risk for drug use than low D2 levels and future work may be able to identify what other factors (genetic, environmental, social) interact with D2 levels to predict drug abuse risk.

Another area of focus regarding dopamine's role in addiction is understanding differences in dopamine release to potential drugs of abuse. This measure is more closely associated with the biological processes associated with actual drug use, but is collected in a more controlled, laboratory setting. PET psychostimulant challenge studies allow researchers to examine dopamine release in the brains of human subjects. Methylphenidate and d-amphetamine (dAMPH) are often used in these PET studies as both release dopamine in the brain by blocking and/or reversing the dopamine transporter. If PET radiotracers that are displaceable by endogenous dopamine are used, researchers can perform a PET scan after placebo or psychostimulant administration and measure the change in radiotracer signal. The PET signal will go down after a psychostimulant for a tracer that is displaceable as the increased endogenous dopamine released by the drug lowers the binding sites for the tracer in the brain. This change in binding potential of the radiotracer can be used as a measure of dopamine release and has become a useful tool in research into addiction related processes.

Using this PET technique, Casey et al 2014 found that young adults with a multigenerational FH of substance use disorders showed reduced dAMPH-induced dopamine than either healthy controls or subjects that personally used drugs at similar levels to the FH group but without a FH of substance use disorders. This study was particularly informative as the effects of current drug use were also investigated and measured separately from family history. Furthermore, our group and others have demonstrated that dAMPH-induced dopamine release correlates with subjective ratings of the drug, particularly wanting more, in drug naïve individuals. These data confirm animal work linking changes in dopamine signaling after drug use to wanting processes (which has been labeled *incentive salience*).

The concept of blunted dopamine signaling (lower D2 receptor levels and less dopamine release) as biomarkers of addiction has been recently reviewed (Trifilieff et al 2017; Leyton, 2017). While more work needs to be done, understanding factors that influence these PET-based biomarkers of dopamine signaling in human subjects has the potential to identify at risk individuals. This risk identification may allow intervention to be attempted earlier in the addiction process or perhaps prevent addiction before it even occurs.