博士論文(要約)

The relationship between DRD2 Taq1A polymorphism and white matter structure in healthy young adults.

(若年健常成人における DRD2 Taq1A 多型と白質容量との関連)

永瀬　智美

The neurotransmitter dopamine (DA) plays a critical role in the way our brain controls movements and cognition (D'Ardenne, et al., 2012). Dopaminergic regulation is dependent on D2-like receptors (Ford, 2014; Beaulieu et al, 2011), which influence dendritic and axonal growth as well as synaptogenesis and spinogenesis (Money and Stanwood, 2013). The dopamine D2 receptor gene (DRD2) encodes the D2 subtype of the dopamine receptor and is located on chromosome 11 at q22-q23 (Grandy et al.,1989). The expression of D2 receptors is modulated by a DRD2/ANKK1-Taq1A polymorphism (rs1800497) (Zeuner et al., 2016), The DRD2 Taq1A polymorphism, a single nucleotide polymorphism (SNP), potentially affects the concentrations of synaptic dopamine (Ford, 2014; Thompson et al.,1997). The two alleles of the DRD2 Taq1A polymorphism are referred to as A1 and A2. The A version is equivalent to the A1 allele of DRD2 Taq1A, while the G version of the SNP corresponds to the A2 allele. Together, these lead to three genotypes: A1/A1, A1/A2, A2/A2.

The A1 allele of the DRD2 gene Taq1A polymorphism had been associated with a low D2 receptor density (Pohjalainen et al., 1998; Jönsson et al., 1999; Ritchie and Noble,1996; Ritchie and Noble, 2003), corresponding to a 30% reduction in the putamen/caudate (Noble et al. 1997) and in the striatum of healthy subjects (Jönsson et al., 1999). In addition, voxel-wise analyses showed that DA D2 receptor levels are positively related to grey matter volume in a large region of the brainstem (Woodward et al. 2009). The grey matter volume is decreased in A1 carriers compared to A2/A2 carriers in the midbrain (Cerasa et al., 2009) and the caudate (Li et al., 2018). Recent studies also suggest an intimate relationship between DRD2 activities and white matter (WM) alteration linked to neural plasticity (Endrup et al., 2016; Guma et al., 2018; Takeuchi et al.,2010). Diffusion tensor imaging (DTI) parameters allow detecting WM abnormalities (Hoza et al., 2015; Hutchinson et al., 2016). DTI has shown that DRD2 rs6277 polymorphism is associated with fiber tract integrity between basal ganglia and frontal cortices (Market et al., 2017). DRD2 activity and the particular structure of cortico-striatal white-matter seem to be more important for plasticity and explain individual differences of cognitive function (Klingberg, 2014). Neural plasticity is reflected by changes in myelination (Head et al.,2004) and the conduction velocity directly affects synaptic modulation (Yagishita et al., 2014).

The DRD2/ANKK1 TaqI polymorphism could influence the neural network properties via dopaminergic pathways by an effect on the conduction velocity and alteration of WM structure. In the present study, I focus on WM volume for two reasons. First, while DTI and volumetric parameters are measures of similar pathologic processes (Bora et al., 2011; Santillo et al., 2013), DTI is unable to describe more than one dominant fiber orientation because crossing fibers have a clear impact on anisotropy analysis. Therefore, Jeurissen et al., (2013) considered the diffusion-tensor model inadequate for regions with a high degree of crossing fibers, and the model may thus not be appropriate in the thalamus. Second, voxel-based morphometry (VBM) has a relatively high resolution at the

macroscopic level (Wagner et al., 2013) and VBM analyses of WM are more suitable for the analysis of WM changes in regions with a strong mixture of white and gray matter like the thalamus. Furthermore, the age range of subjects and sample size are critical key factors to investigate WM structure in a brain imaging study. A sample size of A1 carriers ranging from 20 to 60 was perceived as a limitation (Cerasa et al.,2009; Montag et al.,2010). Aging is related to histopathology sign of the WM observed by MRI (Bray et al., 2015). The WM factor became less correlated with cognitive functions in older age, especially in the hippocampal cingulum (Susanne et al., 2018).

To my knowledge, no studies examined the relationships between regional WM volume (rWMV) and DRD2 Taq1A polymorphism in a larger population. In this study, I selected young adult subjects within a narrow age range to observe the influence of genetic polymorphism on WM change while minimizing confounding factors such as environmental factors as much as possible. Therefore, based on the structural connectivity of WM that underlies DRD2 polymorphism, I hypothesized that the DRD2 polymorphism is associated with rWMV. I verified a potential association between the DRD2 Taq1A polymorphism (genotyped utilizing the Taqman Allelic Discrimination Assay System) and the morphology of WM in young healthy subjects. using VBM analysis. Data from 765 healthy, right-handed individuals (425 male and 340 female; 20.7 ± 1.8 years of age) recruited by University advertisement were used in this study. I conducted an analysis of covariance (ANCOVA) to test the difference in regional WM volume among DRD2 Taq1A polymorphism carriers (A1 carriers: 443, A1 non-carriers: 323) by T1 weighted image.

I observed significant WM volume differences in several areas such as the thalamus proper, left cerebral WM, left fusiform gyrus, and left hippocampus among A1 carriers and A1 non-carriers of the DRD2 Taq1A genetic polymorphism. Especially, the regions which showed the most significant differences, and are from thalamus to distinctive limbic, basal ganglia, and cerebellar patterns of functional connectivity may reflect thalamus-mediated cortico-subcortical interactions described in Alexander and Crutcher (1990).

The thalamus plays a critical role in corticocortical communication and integration of sensory information from cortical and subcortical structures (Sherman and Guillery, 1996), and receives dopaminergic input from the ventral tegmental area and substantia nigra (Garc á-Cabezas et al., 2009) as a set of key connector hubs for cortical networks (Siegel et al., 2012; Eckert et al., 2012). Although the density of extra-striatal dopamine D2 receptor was low, the thalamus includes the highest level of dopamine D2 receptors among all extra-striatal brain regions (Suhara et al.,1999). A1 carriers show lower receptor densities, reduced receptor binding, and increased dopamine synthesis rate in healthy individuals (Ritchie and Noble., 2003). The dopamine innervation is especially prominent in

specific association, limbic, and motor thalamic nuclei, where the densities of dopaminergic axons are as high as or higher than in the cortical area with the densest dopamine innervation, which influences the activity of the cortical, striatal, and amygdaloid regions to which the thalamus is connected (Sánchez-González et al., 2005). Lavin and Grace (1998) have reported multiple actions in the mediodorsal thalamus linked to D2 receptor activation. A couple of previous works indicate that D2 receptor activities in the thalamus may influence synaptic morphologies and neural circuits in cortical and subcortical regions (Govindaiah and Cox, 2006). Therefore, these previous studies suggest the possibility that this reduction of dopamine densities becomes a cause of the alternation of synaptic morphologies and neural circuits in thalamocortical neurons, and then becomes a trigger causing reduced WM volume in cortical and subcortical regions around the thalamus.

My findings suggest that decreased WM volume in structural connectivity involving the thalamus-mediated cortico-subcortical interactions and the limbic pathways is related to the difference of dopamine activities due to the A1-allele of DRD2 Taq1A genetic polymorphism. My results are supported by several previous studies which have reported an association between subcortical brain volume and striatal dopamine D2 receptor availability in healthy humans (Caravaggio et al., 2017). Furthermore, my results also coincide with previous results describing a functional and anatomical connection between the paraventricular nucleus of the thalamus and dopamine fibers of the nucleus accumbens (Parsons et al., 2007). The changes of rWMV in my study may reflect alteration of oligodendrocytes properties and myelination, which influence neural circuit and synaptic morphologies that are involved in cognitive functions.

My results are not inconsistent with previous studies performed in a psychiatric population. Abnormalities of the WM around hippocampal–thalamic regions are related to psychosis and neurologic diseases and correlated with dopamine abnormalities (Karlsgodt et al., 2009). In schizophrenia (Koenders et al., 2015), ADHD (Xia et al., 2012), and Alzheimer's dementia (Kemppainen et al. 2003), the decrease in D2 receptor expression induces a decrease in the WM volume in regions similar to the ones showing significant differences between A1 carriers and A1 non-carriers in this study. Interestingly, the previous study reported that the abnormal degree of WM structures in the right anterior thalamic radiation relates to disease symptoms severity in schizophrenia patients, while the normalization of WM by D2/3 receptor blockade, improving dopamine density, ameliorates these symptoms (Ebdrup et al. 2016; Yasuno et al., 2004). Measures of brain structure may be more sensitive to genetic effects compared to behavioral measures, as brain parameters are more proximal to the underlying molecular mechanisms and therefore more directly affected by a genetic polymorphism (Harris and Deary 2011). These studies revealed that abnormalities of WM structure, which are related to dopaminergic alternation by D2 receptor, may be a main cause of some

neuropsychological disfunctions. DRD2 is associated with fiber tract integrity between the basal ganglia and frontal cortices, and a higher integrity linked to the DRD2 variant is beneficial for cognition (Markett et al., 2017).

My inference that the DRD2 Taq1A genetic polymorphism affects WM volume, which may relate both to receptor density and synaptic dopaminergic function through myelination is in line with previous reports. And my whole-brain VBM study suggest that these changes correlate with morphological variations in the regions including thalamus-mediated cortico-subcortical interactions and the limbic regions. DRD2 activity, and cortical-striatal-thalamo-cortical connections white-matter tracts seem to be more important for the neural networks underlying plasticity, which may lead to the alteration of WM volume (Klingberg, 2014). DRD2 may also affect the neuronal morphology through neural plasticity. Moreover, the responsiveness of striatal neurons to cortical or thalamic inputs is altered in response to the dopamine signal, via the mechanism of dopamine-regulated synaptic plasticity (Fujiyama et al., 2015). These findings imply the possibility that the alteration of dopamine activities by the DRD2 Taq1A genetic polymorphism related to thalamo-cortical neural circuits affects WM structures. Therefore, I suggest that decreased myelination in thalamo-cortical and limbic neural circuits, caused by neural activity in fiber tracts by the differences of dopaminergic activities between DRD2 polymorphism, is one possible mechanism underlying the observed WM volume decreases in A1 carriers.

My study has several limitations. First, DRD2 has several other SNPs. I do not consider the influence of the interaction of dopamine with various DRD2 polymorphisms in terms of a structural change. Second, the sample size between genotype grouping is different, leading to an increase of a false-positive rate. Third, my method to investigate WM volume did not allow measuring the myelination degree directly and may be less sensitive than DTI for this purpose (Basser and Pierpaoli, 1996; Beaulieu, 2002). However, WM alteration is considered to be approximately determined by axon myelination (Fields et al., 2014), which regulates conduction velocity and is directly related to neuronal activity (Gibson et al., 2014). In my study, I observed differences of WM morphologies caused by the polymorphism throughout the whole brain. Even healthy brains are characterized by moderate anatomical variability involving the architecture of WM connections. As opposed to hypothesis-based DTI analysis, VBM analysis is hypothesis-free and allows for highly automated, and a relatively fast analysis of an entire population of subjects in which changes the entire brain can be studied (Melonakos et al., 2011). The present findings motivate further research in this area, including studying the relationship between DRD2 Taq1A Polymorphism and myelin-related WM alterations and interrelated gray matter abnormalities, as well as investigating the influence between the dopamine molecule and the receptor strutures influenced by either DRD2 Taq1A Polymorphism or other genetic SNP gives.

According to my investigation I confirm an effect of the DRD2 polymorphism on white-matter volume in the regions including the thalamus-mediated cortico-subcortical interactions and limbic regions, which is thought to be strongly related to the DRD2 gene expression. To clarify whether changes in myelination reflect alterations of the WM volume, it is necessary to investigate WM using calibrated T1-w/T2-w images parameter considered to be an index of the myelination (Ganzetti et al., 2014). My results support the possibility that the differences of dopaminergic effects caused by DRD2 Taq1A Polymorphism is related to WM volume in the regions including the thalamus-mediated cortico-subcortical interactions and the limbic system and may help to clarify the relationship between neural networks underlying plasticity and WM connections.

Taken together, my study proposes the possibility that the WM structure or its components including myelination around the thalamus and the limbic system may have decreased rWMV in A1 carriers compared to A1 non-carriers.