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Genetics of stroke recovery: BDNF val66met polymorphism in stroke recovery and its interaction with aging

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Abstract

Stroke leads to long term sensory, motor and cognitive impairments. Most patients experience some degree of spontaneous recovery which is mostly incomplete and varying greatly among individuals. The variation in recovery outcomes has been attributed to numerous factors including lesion size, corticospinal tract integrity, age, gender and race. It is well accepted that genetics play a crucial role in stroke incidence and accumulating evidence suggests that it is also a significant determinant in recovery. Among the number of genes and variations implicated in stroke recovery the *val66met* single nucleotide polymorphism (SNP) in the BDNF gene influences post-stroke plasticity in the most significant ways. *Val66met* is the most well characterized BDNF SNP and is common (40–50 % in Asian and 25–32% in Caucasian populations) in humans. It reduces activity-dependent BDNF release, dampens cortical plasticity and is implicated in numerous diseases. Earlier studies on the effects of val66met on stroke outcome and recovery presented primarily a maladaptive role. Novel findings however indicate a much more intricate interaction between val66met and stroke recovery which appears to be influenced by lesion location, post-stroke stage and age. This review will focus on the role of BDNF and *val66met* SNP in relation to stroke recovery and try to identify potential pathophysiologic mechanisms involved. The effects of age on val66met associated alterations in plasticity and potential consequences in terms of stroke are also discussed.

Keywords

Stroke; recovery; val66met; BDNF

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1. INTRODUCTION

Stroke patients are faced with long-term impairments, disabilities and handicaps. Depending on the location and the extent of the lesion, 80 % of patients suffer from motor impairments that typically affect the motor control of the face, arm and leg on one side of the body (Brewer et al., 2013). Altered gait patterns, balance impairments, reduced muscle tone, joint mobility and stability are frequently observed (Arene and Hidler, 2009; Brewer et al., 2013). Along with motor problems, visual and sensory impairments (Kessner et al., 2016), mood (Robinson et al., 1984) and perceptual disorders as well as cognitive decline (Serrano et al., 2007) are common sequelae after stroke.

Once the initial high mortality phase of the acute stroke is over, most patients experience spontaneous recovery, due to the intrinsic capacity to repair injury even in the absence of therapeutic interventions. Spontaneous recovery primarily occurs during the first 3 to 6 months after stroke with the most significant improvements during the first 30 days (Duncan et al., 2000). Depending on the clinical criteria of assessment, near full recovery is reported in 25% to 50% of patients (Duncan et al., 2000). Despite these optimistic classifications, spontaneous recovery is rarely complete and shows drastic variation among patients. A systematic analysis of literature revealed that only 65% of the stroke survivors with motor deficits of the lower extremity show some degree of recovery. Less than 15% of the patients with initial paralysis had complete recovery of both the upper and lower extremities (Hendricks et al., 2002). A majority of studies report proportional functional recovery in roughly 70 to 80% of patients (Guggisberg et al., 2017; Veerbeek et al., 2018; Winters et al., 2015), indicating no significant improvement in nearly a quarter of stroke survivors.

A wide range of factors is implicated in the observed differences in stroke recovery. Advanced age seems to be a significant yet relatively weak prognostic factor for poor outcomes (Denti et al., 2008). Gender and race play a role with women being more likely to have long-term disability compared to men (Di Carlo et al., 2003; Santalucia et al., 2013) and black individuals experience poorer recovery compared to whites (Stansbury et al., 2005). Initial injury as assessed by early motor deficit or lesion size is the most important prognostic factor. Less severe initial motor impairment and smaller lesion size is a strong predictor of subsequent functional gains (Cramer et al., 2007; Duncan et al., 1992). A number of studies indicate that corticospinal tract integrity is associated with improved outcomes (Cho et al., 2007; Kim et al., 2018; Watanabe et al., 2001). In line with those findings the absence or low amplitude of transcranial magnetic stimulation responses which suggests loss of neurons or axons in the corticospinal tract is associated with poor functional recovery (Kim et al., 2016a). Finally, it is well established that genetics play a crucial role in stroke incidence and accumulating evidence suggests that it is also a significant determinant in recovery.

A large number of genes and their variations are implicated in stroke risk and prognosis (Sharma et al., 2013). Among them, brain–derived neurotrophic factor (BDNF) is a widely expressed neurotrophin in CNS and plays a key role in memory, neuronal differentiation and survival and synaptic plasticity (Binder and Scharfman, 2004). Several BDNF variants in humans have been identified (Akbarian et al., 2017). Among them, *val66met* single

nucleotide polymorphisms (SNP) is particularly important due to its drastic effects on BDNF physiology and related pathophysiology. This review will therefore discuss post stroke recovery phenomena with a specific focus on the influence of *val66met* SNP on chronic stroke recovery and its interaction with aging.

2. GENETICS IN STROKE

2.1 Genetic influences on stroke incidence

Genome wide complex trait analysis studies (Bevan et al., 2012) and epidemiologic studies conducted with twins and first-degree relatives of stroke patients indicate that stroke is heritable. (Brass et al., 1992; Li et al., 2017; Seshadri et al., 2010). Common multifactorial stroke which constitutes most of the stroke cases appears to be a polygenic condition including numerous alleles with small effect sizes (Lindgren, 2014). Employing linkage analysis or candidate gene associations, earlier comparison studies between stroke patients and healthy controls have identified numerous susceptibility genes. A meta-analysis reported that out of the 32 genes studied, significant associations with ischemic stroke were identified for factor V Leiden Arg506Gln, methylenetetrahydrofolate reductase C677T, prothrombin G20210A and angiotensin-converting enzyme insertion albeit their effect being relatively modest (Casas et al., 2004). More recently, genome-wide association studies (GWAS) where a large number (500K – 5million) of single nucleotide polymorphisms (SNP) are examined, identified numerous novel variations associated with stroke risk. Certain risk loci and their association with risk factors along with their implications in pathological cascades have been described. Namely; Paired-like homeodomain transcription factor 2 (*PITX*2) and zinc finger homeobox 3 (ZFHX3) in atrial fibrillation, alpha 1–3-N-acetylgalactosaminyltransferase (ABO), chromosome 9p21 locus, Histone Deacetylase 9 (HDAC9), and Aldehyde Dehydrogenase 2 Family (ALDH2) in coronary artery disease, ALDH2 and HDAC9 in Blood pressure, Forkhead box F2 (FOXF2) in pericyte and smooth muscle development, Hyaluronan Binding Protein 2 (HABP2) in coagulation, Matrix Metallopeptidase 12 (MMP12) in carotid plague formation and Tetraspanin-2 (TSPAN2) has been implicated in neuro-inflammation (Chauhan and Debette, 2016). It has to be kept in mind however that GWAS have certain limitations: that the loci that are identified may relate to genetic regulatory elements that control other parts of the genome or other genes, and not relate to just the gene next to the locus.

More potent effects of genetics are observed in cases where genetic factors contribute to intermediate phenotypes such as atherosclerosis (Lusis et al., 2004) or lead to monogenic stroke syndromes. Monogenic Stroke syndromes refer to single gene disorders with high penetrance that lead to stroke as a part of a systemic disease or as the primary clinical phenotype (Tan and Markus, 2015). They account for less than 1% of all strokes and are more frequent in young stroke patients without known risk factors (Sharma et al., 2013). These syndromes encompass a broad range of disorders that lead to ischemic or hemorrhagic strokes and arise due to arterial diseases (Ballabio et al., 2007; Lindgren, 2014; Tan and Markus, 2015) (Table 1).

2.2 Genetic influences on stroke recovery:

Studies investigating the effects of genetics on stroke recovery are scarce. The multicenter Genetics of Ischemic Stroke Outcome (GISCOME) study which gathered records including genome-wide genotypic and functional outcome data from 12 ischemic stroke projects is currently ongoing. GISCOME aims to detect genetic influence on stroke outcomes and has the potential to fill a significant gap in our knowledge in genetics of stroke recovery (Jane M Maguire, 2017). As of now, a limited number of candidate genes and their polymorphisms have been shown to influence stroke recovery in humans.

Apolipoprotein E (APOE) gene variations rs7412 and rs429358 have been related to stroke risk (Khan et al., 2013). *APOE* ε3/ε4 genotype in men and *APOE* ε2/03B53 in women were associated with increased 30-day mortality in stroke (Gromadzka et al., 2005). Other studies report equivocal findings regarding long-term outcomes. Gromadzka *et al.* found no association between APOE genotypes and stroke. Functional outcome and APOE was only associated in male ε4 carriers which had greater deficits at the time of admission and higher mortality risk up to a year after stroke (Gromadzka et al., 2007). Similarly, another study reported significantly poor recovery in ε4 carriers (Cramer et al., 2012). On the other hand, Sarzyńska-Długosz *et al.* did not find any impact of APOE genotype on mortality or poor outcome at 1 year post stroke (Sarzynska-Dlugosz et al., 2007). These findings suggest a significant interaction between the APOE genotype, gender and possibly time elapsed after stroke, however, further research is required.

Studies also reported associations between several other polymorphisms and functional outcomes in stroke. While variation in rs7136446 of the Insulin like growth factor1 was associated with favorable functional outcome 24-months post-stroke, the significance was no longer present after the data were corrected for multiple comparisons(Aberg et al., 2013). An allele of the myeloperoxidase G-463A polymorphism was associated with a poorer functional short-term outcome (Hoy et al., 2003). Carriers of either the *rs5275 or rs20417* variant of the Cyclooxygenase-2 (COX-2) gene had relatively lower disability and stroke handicap scores (Maguire et al., 2011). In Catechol-*O*-Methyltransferase polymorphism, patients with Val/Val alleles had higher motor functions and activities of daily living scores compared to Met/Met genotype (Liepert et al., 2013). Finally, other variations including C-reactive protein gene polymorphism rs1130864, serotonin transporter gene 5-HTTLPR s/s and sTin2 VNTR were associated with indices of long-term function (Guo et al., 2014; Kohen et al., 2008). Among the identified gene variations BDNF *val66met* polymorphism is the most studied SNP and will be discussed in detail below.

3. BDNF IN STROKE

BDNF, the second discovered member of the neurotrophic family, localizes in chromosome 11p in humans. It consists of four 5` exons and one 3` exon that encodes the mature BDNF protein (Timmusk et al., 1993). Similar to other neurotrophins, BDNF is synthesized in the endoplasmic reticulum as a precursor and converted to mature BDNF via proteolytical processes mainly by proprotein convertase PC7 (Wetsel et al., 2013), but also extracellularly by metalloproteinases and plasmin (Deinhardt and Chao, 2014). There has been controversy regarding whether BDNF is released in the precursor and/or in the mature form, but

accumulated evidence indicates that at least a fraction is released in the proBDNF form (Mizoguchi et al., 2011). ProBDNF is not transient biosynthetic intermediate and has significant modulatory role in synaptic plasticity (Yang et al., 2009). Acting through p75 neurotrophin receptor proBDNF promotes cell death, attenuate synaptic transmission and take part in synapse elimination (Je et al., 2013) During the formation of mature BDNF, the N-terminal prodomain (pro-peptide) is cleaved. It was assumed to degrade and therefore had no significant bioactivity. Recent evidence however indicates that the pro-domain of *val66met* polymorphic variant of BDNF (discussed below) may actually function as a novel independent synaptic modulator (Mizui et al., 2017).

Unlike other growth factors, BDNF is secreted in a constitutive and activity-dependent manner. BDNF can be secreted by neurons both from axons and dendrites in response to neuronal activity (Lessmann and Brigadski, 2009) and binds to a tropomyosin-related kinase (trk) receptor. TrkB activation by BDNF triggers a diverse set of intra cellular signaling pathways including protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinase (Erk)1 and 2, phospholipase C-γ (PLC-γ) and Ras (Nakagawara et al., 1994; Zirrgiebel et al., 1995). BDNF also binds to the low affinity P75 neurotrophin receptor, which inhibits axonal regeneration via partnerships with Nogo receptor and Lingo-1 and promotes apoptosis through association with Sortilin. It has been shown that mature forms of BDNF show higher affinity towards TrkB whereas proBDNF preferentially bind to P75 (Kraemer et al., 2014; Lee et al., 2001) which likely accounts for the substantially different and even opposing effects of BDNF at different conditions and cell populations (Zhao et al., 2017).

3.1 BDNF and synaptic plasticity

BDNF is implicated in numerous physiologic functions ranging from neuronal development and survival to synaptic transmission, plasticity and neurotransmitter release (see (Binder and Scharfman, 2004; Schinder and Poo, 2000) for detailed reviews). Compared to constitutively expressed BDNF, activity-dependent BDNF release plays a pivotal role in synaptic plasticity. BDNF promotes survival and growth in cortical and hippocampal cells, dorsal root ganglion cells, serotonergic neurons and peripheral sensory neurons of vestibular and nodosepetrosal ganglia (Binder and Scharfman, 2004; Popova et al., 2017). Despite its prominent effect on numerous neuron subclasses *in vivo*, genetic deletion of BDNF in CNS does not cause substantial cell loss in vivo suggesting that it acts primarily as a differentiation factor (Rauskolb et al., 2010). Proliferating cells of the adult CNS are also modulated by BDNF. Neurogenesis is enhanced by BDNF in the adult olfactory bulb, striatum, septum and thalamus (Pencea et al., 2001; Zigova et al., 1998). In addition, basal levels and enrichment or exercise induced hippocampal neurogenesis requires BDNF (Liu and Nusslock, 2018; Rossi et al., 2006).

Through trkB receptor activation, BDNF influences neuro-morphological development and synaptic connectivity. While axon guidance appears independent of BDNF, wiring and synaptic connectivity at the target relies on BDNF activity (Poo, 2001; Rico et al., 2002). Conditional deletion of trkB leads to reductions in number of presynaptic terminals and excitatory synapses formed by Schaffer collaterals and presynaptic defects in mossy fiber

connectivity in the hippocampus (Danzer et al., 2008; Luikart et al., 2005). Similarly, conditional trkB deletion at thalamus leads to pruning and abnormally branched axon terminals to innervate the somatosensory cortex (Lush et al., 2005). Dendritic development, growth and arborization is also differentially modulated by BDNF in a site specific manner (Cohen-Cory et al., 2010). With its role in synaptic plasticity, BDNF is crucial in learning and memory. BDNF facilitates LTP induction in hippocampal slices (Figurov et al., 1996) and dentate granule cells (Kovalchuk et al., 2002) via TrkB receptors (Minichiello, 2009). Target disruption of BDNF leads to impairment of LTP at hippocampal Schaffer collaterals (Korte et al., 1995) which can be rescued by acute recombinant BDNF treatment (Patterson et al., 1996). In line with those findings, selectively deleting BDNF from the forebrain in mice lead to impairments in specific forms of learning with no major effects on acoustic sensory processing or baseline anxiety (Gorski et al., 2003).

Motor learning also relies on BDNF function. Learning complex motor skills or exercise increases BDNF and TrkB in motor cortex (Klintsova et al., 2004). Transcranial direct current stimulation of mouse primary motor cortex slices has been shown to induce LTP, which was absent in BDNF and TrkB mutant mice (Fritsch et al., 2010). In addition, pharmacological upregulation of BDNF was shown to facilitate motor learning (Yoneda et al., 2017). The diverse functions of BDNF ranging from cell survival to plasticity and its function as a canonical mediator of neuroplasticity suggests a critical involvement in stroke pathophysiology and prognosis.

3.2 BDNF modulation and stroke outcome

BDNF's promoting effects on growth, proliferation and neuronal plasticity lead to its potential application as a therapeutic agent for stroke. Early preclinical studies using intracerebro-ventricular BDNF infusions showed reduction in infarct size (Schabitz et al., 1997; Yamashita et al., 1997) and protection of CA1 pyramidal cells in the hippocampus after focal ischemia (Beck et al., 1994). Numerous reports replicated lesion size reduction (Schabitz et al., 2000; Zhang and Pardridge, 2001) and showed improved functional outcome (Chen et al., 2000; Muller et al., 2008) with BDNF treatment. Endothelial cells in the ischemic striatum produce BDNF to promote recruitment of neuronal precursors from the subventricular zone into the ischemic striatum (Grade et al., 2013), showing BDNF's role in endogenous recovery. Clarkson et. al. demonstrated that BDNF elevations by AMPA receptor agonist at the peri-infarct region is responsible for motor recovery (Clarkson et al., 2011). BDNF was identified as the mediator of numerous neuroprotective and/or recovery enhancing pharmacological agents including angiotensin and Tetramethylpyrazine nitrone (Fouda et al., 2017; Taliyan and Ramagiri, 2016; Zhang et al., 2018). In addition, effects of rehabilitation on recovery were abolished in rats receiving infusions of antisense BDNF oligonucleotide after stroke (Ploughman et al., 2009). These results underline the important role of BDNF in spontaneous as well as rehabilitationinduced recovery.

Clinical studies also show BDNF's involvement in stroke pathophysiology. Patients with atherosclerosis and cerebrovascular disease risks have low circulating levels of BDNF (Golden et al., 2010). Higher serum BDNF levels are associated with a decreased risk of cardiovascular disease and mortality (Kaess et al., 2015). In the Framingham study, low

BDNF levels were associated with increased risk for transient ischemic attack and stroke. Salinas et. al. report that social support increases BDNF levels and reduce the risk for stroke (Salinas et al., 2017). Further studies reported reduced circulating BDNF levels in the acute phase of ischemic stroke and lower levels were associated with poor functional outcome (Lasek-Bal et al., 2015; Stanne et al., 2016). BDNF levels were negatively correlated with infarct sizes, with larger infarcts leading to more pronounced reductions (Qiao et al., 2017). In addition, higher BDNF levels were associated with less white matter hyperintensity and better visual memory (Pikula et al., 2013). Serum BDNF levels were also associated post-stroke depression as lower BDNF levels were found in depressed patients (Yang et al., 2011). These studies point towards a relation between stroke outcome and BDNF levels. Yet the possibility of a causal relation remains elusive when only blood BDNF levels are taken as an indicator. More convincing evidence for a crucial role of BDNF in stroke and stroke recovery comes from clinical studies based on BDNF SNP *val66met* variant.

4. BDNF *val66met* SNP

4.1 BDNF SNP in CNS

A single nucleotide polymorphism is the most common type of variation in the DNA sequence where a particular nucleotide is replaced by an alternative one. BDNF gene contains a number of SNPs: rs6265 (*val66met*), rs10767664, rs10501087 rs988712, rs4074134, rs2030323, rs925946, rs4923461, rs10835211, rs1488830, rs1519480 and rs7481311 (Akbarian et al., 2017). Among these, *val66met* is the most well characterized SNP and is common in humans. *val66met* SNP (also known as G189A or rs6265) occur in the prodomain of BDNF gene as a substitution of a valine (Val) by a methionine (Met) at codon 66. It is an evolutionarily recent variation observed only in humans (Anastasia et al., 2013) with a frequency reaching up to 40–50 % in Asian and 25–32% in Caucasian populations (Verhagen et al., 2010). *Val66met* SNP appears to be implicated in a number of psychiatric conditions including anxiety, major depression, bipolar disorder, schizophrenia and eating disorders (Hong et al., 2011; Verhagen et al., 2010) and confers risk of sporadic Alzheimer's disease (Ventriglia et al., 2002).

The landmark study by Egan *et al.*was the first to describe that *val66met* polymorphism reduces activity-dependent secretion of BDNF without affecting constitutive secretion (Egan et al., 2003). It was later shown that NMDA receptor-dependent synaptic plasticity in the hippocampus was impaired by *val66met* polymorphism (Ninan et al., 2010). Another study replicated this finding and showed Fluoxetine induced increases in BDNF and neurogenesis the in hippocampus was impaired in *val66met* carrier mice (Bath et al., 2012). BDNF *val66met* polymorphism drastically alters the structure and function of BDNF pro-domain and confers bioactivity only to Met66 pro-domain variants under certain conditions (Anastasia et al., 2013). As a result, Met-BDNF pro-peptide attenuates LTD whereas Val-BDNF pro-peptide treatment enhances LTD in hippocampal slices (Mizui et al., 2015). Moreover, reduction in hippocampal volume has been associated with *val66met* polymorphism (Pezawas et al., 2004) and although being task and age related, there is substantial evidence for reduced memory performance in *val66met* carriers (Kambeitz et al., 2012).

Motor learning related plasticity is also altered by *val66met* SNP. BNDF *val66met* polymorphism reduces training-dependent increases in the amplitude of motor-evoked potentials and motor map reorganization (Kleim et al., 2006; McHughen et al., 2010). However, the differences between genotypes diminish after repeated training (McHughen et al., 2011). Conversely, no evidence for BDNF *val66met* polymorphism effect on motor map plasticity was found in older adults (McHughen and Cramer, 2013), indicating age as a confounding factor. The significant impact of *val66met* SNP on various forms of neuroplasticity suggests an important role in stroke recovery.

4.1 Impact of BDNF SNP in Stroke Recovery

An increasing number of clinical and preclinical studies are focusing on the role of *val66met* in stroke (see table 2 for a summary). Early clinical studies investigated the epidemiologic relation between stroke and BDNF *val66met*. Zhao et al. analyzed ischemic stroke risk in 494 patients and 337 controls and reported a significantly increased risk in *met/met* carriers (Zhao et al., 2013). A study on 206 stroke patients analyzed the association of BDNF *val66met* polymorphism and ischemic stroke occurrence. The study reported a borderline significant relationship ($p=0.051$) between the polymorphism and ischemic stroke but no significant difference among genotypic groups regarding the severity of the stroke and functional disability (Keshavarz et al., 2016). In a study conducted in an East Asian cohort, *val66met* polymorphism was independently associated with worse outcomes at 2 weeks and 1 year post-stroke, and patients displayed a decline in functional scores and cognitive function (Kim et al., 2012). Similarly, in subcortical stroke survivors 4 months post-stroke, functional scores were significantly worse in the *met* carrier group without any difference at 2 months (Kim et al., 2013). Cramer and Procaccio in their analysis of GAIN American and GAIN international studies observed that recovery over the first month was poorer in *val66met* group, but the difference diminished at 3 months (Cramer et al., 2012).

Recent research also indicates an interaction between *val66met* SNP and post stroke rehabilitation. Stroke patients (>6 months post-stroke) with hemiparesis were trained in a motor learning task and *met* carriers performed worse compared to *val/val* patients (van der Vliet et al., 2017). Similarly, among stroke patients trained to relearn the motor patterns of split-belt treadmill walking, *val66met* SNP carriers performed worse compared to non-carriers but the difference was ameliorated with high intensity exercise (Charalambous et al., 2018). In a study of upper limb rehabilitation, stroke patients carrying *val66met* SNP showed reduction in the magnitude of motor improvement with therapy. This was particularly evident for the patients with higher, but not lower, residual motor function (Shiner et al., 2016).

Literature demonstrates worse memory and functional outcome in *val66met* carriers after subarachnoid hemorrhage(Mirowska-Guzel et al., 2012; Siironen et al., 2007) but not in patients that had stroke as a result of hemorrhage (Vilkki et al., 2008). In the study by Mirowska-Guzel *et al*. *val66met* polymorphism was associated with worse outcome only at early time points (admission and day 7) but not at one month (Mirowska-Guzel et al., 2012). In more recent studies, it has been reported that *val66met* polymorphism was not a predictor of long-term, functional mobility (French et al., 2018) or recovery of aphasia after stroke (de

Boer et al., 2017). It was however shown that dysphagic stroke patients carrying the *met* allele recovered better in response to pharyngeal electrical stimulation (Essa et al., 2017). On the other hand, the *Val* allele was associated with unfavorable outcomes of stroke rehabilitation (Mirowska-Guzel et al., 2014). Taken together, clinical studies suggest poor outcomes in *val66met* carriers particularly at earlier time points. At later stages of stroke, this association tends to disappear. These equivocal clinical findings could arise from complex interactions with other human genetic variations, gender or age. An additional undetermined factor is the temporal progression of functional recovery as observed differences between BDNF SNP carriers may not be sustained at different post stroke stages.

Preclinical studies in animals are invaluable in gaining a deeper understanding of complex biological and pathological phenomena. Knock-in mice homozygous for the BDNF val66met SNP (BDNF $^{met/met}$) display similar phenotypic features as humans (Chen et al., 2006). When WT and BDNF$^{met/met}$ were subjected to middle cerebral occlusion that produced infarction primarily in the striatum and a part of the cortex, there were no differences in lesion size or hemispheric swelling between the genotypes (Qin et al., 2011). BDNF$^{met/met}$ mice showed a significantly larger motor deficit 6 days after stroke in rotarod. In Catwalk analysis BDNF$^{met/met}$ *mice* were significantly worse compared to controls at day 7 but not at 2 weeks and 1 month. BDNF$^{met/met}$ mice showed reduced proliferating endothelial cells and vessel density through upregulation of angiostatic factors CD36 and TSP-1, suggesting an association between met allele and stroke-induced angiogenic deficits. Despite greater deficits at early stages, a subsequent long-term study showed improved motor/gait function by week 2 (Qin et al., 2014). The view that val66met SNP may lead to improved outcome long-term is supported by observations from other CNS injury conditions. Kruger *et al.* reported that Met allele promoted recovery of executive function in war veterans with traumatic brain injury (30 years follow up), showing a complex long term role of BDNF SNP in CNS injury (Krueger et al., 2011).

5. PATHOPHYSIOLOGIC MECHANISMS OF *VAL66MET* in STROKE

Initial studies on the effects of *val66met* polymorphism primarily reported associations with disease states and impaired plasticity in the brain. The prominent view derived from the bulk of these studies implied a negative and maladaptive role for BDNF *val66met* SNP. Yet the high frequency of this variation reached in diverse human populations argues for its adaptive role. While the dampening effects of *val66met* SNP on activity-dependent BDNF secretion and related plastic alterations appear robust, the potential deleterious effects on memory, motor learning and stroke outcome are complex and potentially context-dependent. Indeed, an evaluation of current literature suggests that the effect of *val66met* SNP in learning and memory is task and age (discussed further in “vall66met SNP and aging” section) specific. A significant portion of the earlier literature report poorer performance in met carriers particularly in hippocampus dependent memory tasks (Kambeitz et al., 2012). On the other hand, visual memory (Yogeetha et al., 2013) and memory based task switching performance (Gajewski et al., 2011) in met carriers were superior compared to val/val individuals, indicating a task specific impact of the SNP Similarly, post stroke functional disability and recovery profile differences among genotypes is not straightforward. Evidence from clinical and pre-clinical studies suggest that while *val66met* SNP carriers are most likely

functionally worse in acute phases of stroke, results from later stages are equivocal. Arguably, depending on the injury type, severity, and location of stroke, *val66met* SNP can be advantageous depending on pathophysiological mechanisms influenced by *val66met* SNP.

5.1 Altered interhemispheric interaction in val66met carriers

Cortical strokes lead to suppressed activity in the surrounding ipsilesional cortical regions (Murphy and Corbett, 2009). Apart from cases where big infarctions destroying large portions of the cortex, hypo-excitability is mainly due to tonic or extrasynaptic GABA activity (Clarkson et al., 2010). This inhibition of the marginally damaged tissue lasts up to one month in animal models (Clarkson et al., 2010). Simultaneously, corresponding regions in the contra lesional cortex display extensive activation induced responses and hyperexcitability as early as 3 days. These alterations coincide with the transfer of the ipsilateral forelimb responses. Inhibition of the ipsilesional cortex and increased excitability at the contralesional cortex gradually diminish. Around day 14, lesion periphery begins to regain normal function (Dijkhuizen et al., 2001) which coincides with functional recovery. These findings from animal experiments are in line with human studies and fit well the interhemispheric imbalance observed in stroke patients.

A large body of evidence from transcranial magnetic stimulation studies report an interhemispheric cortical excitability imbalance due to increased excitability (Shimizu et al., 2002) on the intact hemisphere and inhibition of the lesioned side after stroke (Traversa et al., 1997). Motor cortical mapping studies revealed a decreased number of excitable sites over the affected hemisphere compared to the unaffected site (Cicinelli et al., 1997). In addition, an abnormally high interhemispheric inhibitory drive from the primary motor cortex (M1) of the intact hemisphere onto the M1 of lesioned hemisphere is well documented (Murase et al., 2004). Such observations lay the foundation of the interhemispheric competition model of stroke recovery.

According to interhemispheric competition model, the lack of inhibitory input from the damaged hemisphere onto the intact hemisphere leads to an increased excitability in the intact side which in turn exerts further inhibition on the damaged hemisphere. This overall imbalance is postulated to be detrimental for stroke recovery. Indeed, increased inhibitory input exerted on to the lesioned hemisphere (Murase et al., 2004) and hyperexcitability of the intact hemisphere (Di Lazzaro et al., 2010) is a predictor of worse outcome and impaired recovery. Similarly, functional recovery is correlated with a tendency toward LTP-like activity in the lesioned hemisphere and a tendency for LTD-like activity in the intact side (Di Lazzaro et al., 2010). Animal experiments also fortify this notion. Blocking tonic GABA activity via agonists or deletion of GABA-A receptor subunits promote rapid behavioral recovery after stroke (Clarkson et al., 2010). Taken together, hyperactivity of the intact hemisphere appears detrimental for the long term recovery by exerting excessive inhibition on the peri-infarct cortex.

An important study by Di lazzaro *et al.* reports interesting findings indicating that post stroke cortical imbalance can be fundamentally altered in *val66met* carriers. Using single pulse TMS, the authors reported a 9-fold weaker inter-hemispheric imbalance in cortical

excitability between affected and intact hemispheres in *val66met* carriers. Authors argued that BDNF signaling which can potentiate presynaptic glutamate release and increase the response to glutamate at postsynaptic sites may be blunted in *val66met* carriers thereby reducing excitability in the intact hemisphere (Figure 1A) (Di Lazzaro et al., 2015). These findings suggest a complex role for *val66met* genotype in stroke recovery and can potentially explain some of the discrepant findings in clinical studies (Di Pino et al., 2016).

It has also been suggested that hyper excitability of the intact hemisphere may be responsible for residual sensorimotor functions acutely after stroke through reinforcement of the ipsilateral corticoreticulospinal pathway (Dijkhuizen et al., 2001). Therefore, reduced hyperactivity and plasticity on the intact hemisphere may account for the observation that *val66met* carriers -regardless of lesion size- are functionally worse at early time points. In addition, in patients with severe damage, functional take over by the intact hemisphere appears to play compensatory roles suggesting that reduced activity and plasticity in the intact hemisphere of *val66met* patients would be detrimental for long term recovery (Di Pino et al., 2014). Finally, findings by Di lazzaro *et al.* suggest that *val66met* SNP may promote recovery by reducing cortical imbalance, particularly in patients with small or medium sized lesions. However, clinical literature provides limited evidence supporting this view (Essa et al., 2017; Krueger et al., 2011; Mirowska-Guzel et al., 2014), indicating that interaction between genotypes and post stroke plasticity is more complex than interhemispheric competition model predicts. Alternatively, the lack of stratification (i.e for lesion size and location) in patient data may be obfuscating results.

5.2 Increased subcortical excitation and compensation in val66met carriers

Emerging evidence suggests that *val66met* SNP may exert drastically different effects on subcortical structures, which may account for differences in stroke outcome and recovery. Fisher *et al.* reported that human *val66met* carriers showed 2–7% higher subcortical serotonin transporter (5-HTT) binding in the striatum but not in the neocortex (Fisher et al., 2017). Using mice carrying *val66met* in both alleles ($BDNF^{Met/Met}$) and wild type ($BDNF^{Val/Val}$) mice, Jing et. al. examined the effects of *val66met* polymorphism on synapses in the dorsal striatum(Jing et al., 2017). Their study revealed enhanced neurotransmission in the dorsolateral striatum in $BDNF^{Met/Met}$ mice caused by increased glutamate release and NMDA receptor-mediated neurotransmission in the medium spiny neurons. AMPA receptor-mediated transmission was not altered among groups. Contrary to observations in cortical structures, there was no alteration in dendritic complexity and spine density, supporting the view that *val66met* SNP had no effect on striatal volume (Bueller et al., 2006).

Aforementioned studies by our group also suggest that striatal plasticity after stroke is significantly different in *val66met* mice with an increased compensatory potential particularly in the contralesional striatum (Qin et al., 2014; Qin et al., 2011). In this study, $BDNF^{Met/Met}$ mice displayed improvement of gaits through adaptive mechanisms relying on the non-injured contralateral hemisphere. $BDNF^{Met/Met}$ mice showed larger striatal volume, increased neuronal cell body and branched dendritic tree in medium spiny neurons in the contralesional striatum, assessed at 6 months post-stroke. Also, elevated excitatory synaptic markers in the striatum in the contralateral hemisphere suggest an excitatory shift in

$BDNF^{M/M}$ mice. Striatum receives its primary excitatory afferents from the thalamus and the cortex, and project inhibitory efferents to the substantia nigra pars reticulata (SNr) and globus pallidus (GP) through direct and indirect pathways. These pathways then project back to the cortex and thalamus to form the striatothalamo-cortical circuits (Alexander et al., 1986). The direct and indirect pathways operate in conjunction to each other and facilitate or inhibit movement respectively. Disinhibition of inhibitory inputs to the thalamus through GP and SNr may potentiate excitatory cortical afferents to striatum. The increased excitatory activity in striatum may underlie the functional improvement of $BDNF^{M/M}$ mice. (Figure 1B).

6. *VAL66MET* SNP AND AGING

Aging is a normal physiological process that leads to a gradual deterioration of the overall fitness of the organism. The cumulative effects and burden of aging vary greatly among individuals due to differences in personal experiences and habits, but genetics are also a prime determinant. BDNF and TrkB receptors show dynamic changes throughout the life span. Animal studies indicate a peak in BDNF and TrkB levels in early postnatal life that reach stable levels in adulthood (Friedman et al., 1991; Silhol et al., 2005) and gradually decline with aging (Hayashi et al., 1997). Interestingly, aging does not only lead to a decline in hippocampal BDNF, but also induces a shift towards increased proBDNF levels that inversely correlates with the ability to perform in spatial memory tasks (Buhusi et al., 2017). Circulating BDNF levels decline with age is associated with hippocampal shrinkage and memory impairments (Erickson et al., 2010). Although trkB mRNA levels in the hippocampus do not vary drastically in healthy humans, the expression decreases over their life span (Webster et al., 2006). BDNF protein expression is also markedly reduced in the septum, cerebral cortex, cerebellum, striatum and midbrain with age in healthy humans (Croll et al., 1998). Animal studies show that age related decline in hippocampal neurogenesis, changes in hippocampal structure are also associated with BDNF function (von Bohlen und Halbach, 2010) and BDNF mediated beneficial effects on learning, memory and neuroprotection decline with age (Sohrabji and Lewis, 2006). In summary, age related decline in brain plasticity is tightly correlated with reductions and/or alterations in BDNF activity and availability.

Given the effects of *val66met* on BDNF induced cortical plasticity, interaction between age and *val66met* SNP may have profound implications in stroke recovery. According to the “resource modulation hypothesis” suggested by Lindenberger *et al.* as the physiologic “resources” (anatomical or neurochemical) of the brain decline with age, effects of genetic variations among individuals become more prominent and detectable (Papenberg et al., 2015). For example, while the effect of a potentially maladaptive variation may be quite miniscule and untraceable at young age, it can manifest over time and the cumulative effect could reach significant proportions. Indeed, the effects of *val66met* polymorphism on certain cognitive functions seem to fit this theory. In a study by Li *et al.*, Met allele carriers in the old population recalled fewer items than Val homozygotes in a backward serial recall task. No difference of genotype was observed in the young adult group (Li et al., 2010). Similarly, age related decline in perceptual speed (Ghisletta et al., 2014) memory performance (Kennedy et al., 2015) reasoning skills (Harris et al., 2006) and cognitive (Ward et al., 2017)

reserve is more pronounced in the Met allele carriers. In line with behavioral measures, age-related decline in activation of the posterior hippocampal region during a memory task was worse in met carriers (Sambataro et al., 2010). Importantly, BDNF SNP was also linked to the rate of decline in skilled task performance (Sanchez et al., 2011). While these findings are primarily learning and memory related, they indicate a gradual potentiation of the *val66met* SNP effects on plasticity.

Overall, there is substantial evidence indicating that *val66met* SNP impairs cortical plasticity, particularly with advancing age. Cortical plasticity is fundamental for stroke recovery and rehabilitation efficacy (Hara, 2015). Therefore, it can be hypothesized that aged *val66met* carriers would benefit less from stroke rehabilitation. However, it is not clear how age would alter the effects of *val66met* on cortical imbalance. In addition, subcortical plasticity in *val66met* carriers does not appear impaired in humans (Bueller et al., 2006) and animal studies suggest even increased excitability and compensation (Jing et al., 2017; Qin et al., 2014). Effects of age on such variables are yet to be investigated. Examining the intricate relation between *val66met* SNP, age and stroke is of significant importance to understand the varied recovery profiles observed in stroke survivors and developing genotype specific rehabilitation regimens.

7. CHALLENGES AND FUTURE DIRECTIONS

Understanding genetic influences on stroke pathophysiology and recovery is an arduous task. It requires examination of a genetic variation alone as well as in combination with others in meticulously designed, vigorously controlled, expensive clinical studies conducted by teams that include experts on diverse fields. Despite a few limitations, GWA studies have produced promising data in determining new genetic factors affecting stroke risk (Lindgren, 2014). Further GWA studies may help us elucidate the interactions among genetics, metabolic, and physiologic pathways during recovery. Study design however requires special care. From clinical perspectives, long-term outcome studies paying particular attention to patient stratification in regards to age, lesion size and genotype (i.e. homozygote vs heterozygote), are of paramount importance. Moreover, such studies should longitudinal encompass different stages of post-stroke (acute, sub-acute and recovery) and asses various neurological and functional outcomes. In the context of BDNF SNP, investigating whether *val66met* leads to differential outcomes in human patients at defined post stroke phases depending on lesion size or location would be invaluable. Understanding impacts of BDNF *val66met* SNP in response to rehabilitation also has potential clinical relevance to pave the way for developing customized treatments.

Preclinical studies are scarce and much of the questions regarding the impact of val66met SNP on stroke pathophysiology still remains to be addressed. Functional outcome studies coupled with electrophysiological methods in animals should be employed to further elucidate post stroke changes in recovery, cortical imbalance and plasticity in *val66met* SNP.

8. CONCLUSION

BDNF, with its involvement in numerous physiologic mechanisms ranging from neuronal survival to plasticity is a crucial mediator of post stroke recovery. A frequent BDNF, SNP *val66met* confers drastic effects on BDNF function. Despite the early understanding in the field that *val66met* is primarily a maladaptive variation in terms of stroke outcome, subsequent research indicates a much more complex interaction between *val66met* and stroke pathophysiology. BDNF *val66met* polymorphism may lead to differential outcomes depending on the time elapsed after stroke -and potentially- lesion size, location and age. The amount of evidence pointing towards a differential pathophysiology in BDNF Vall66Met SNP carriers suggest that the variant is a potential genetic factor that contributes to the heterogeneity of recovery processes among stroke survivors. Understanding the exact nature of the interaction between *val66met* and stroke recovery and how it is influenced by age requires further research.

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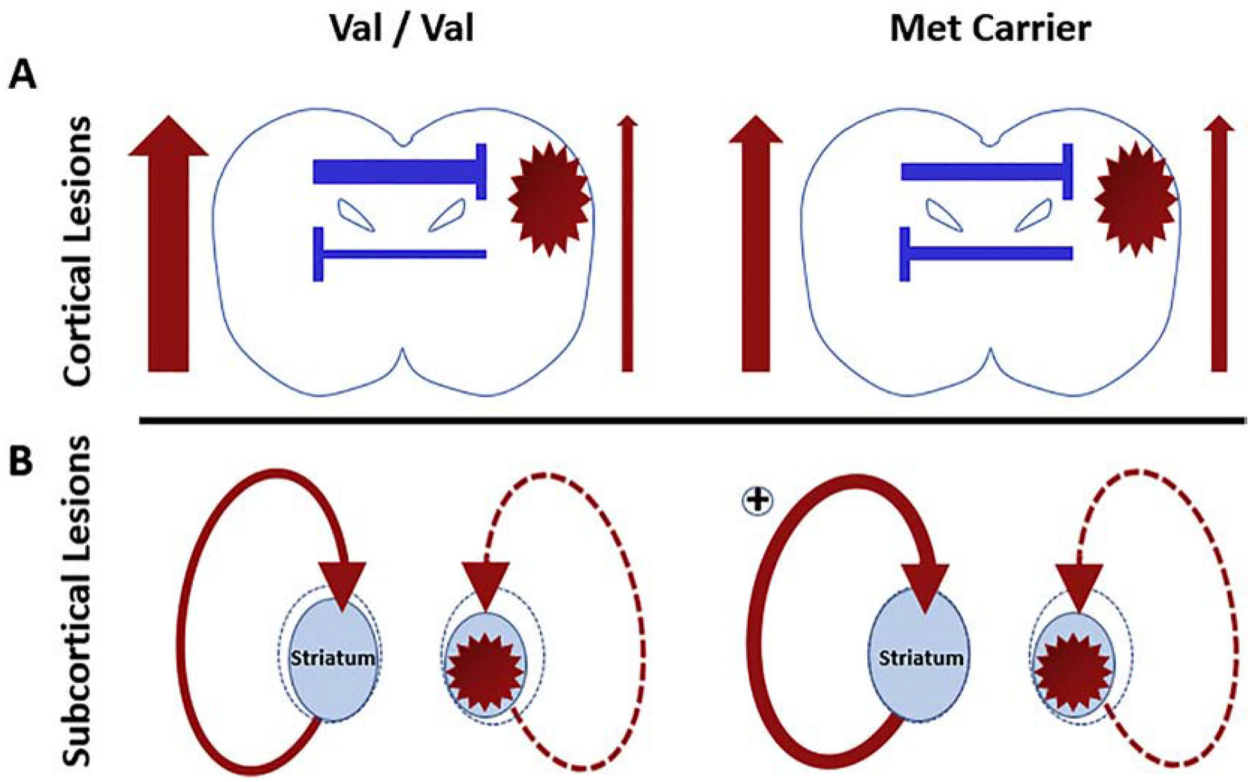

FIGURE 1.

Proposed mechanisms that underlie BDNF val66met SNP effect in cortical (A) and subcortical (B) stroke: A, Stroke causes imbalance in excitability (Red arrows) and inter hemispheric inhibition (blue arrows) in Val/Val individuals. Inhibition from the lesioned hemisphere is reduced leading to increased excitability on intact hemisphere. This in turn exerts increased inhibition on to the ipsilesional hemisphere in the intact hemisphere, resulting in a greater extent of cortical imbalance. In Met carriers, cortical excitability in the intact hemisphere is not drastically increased. Similarly, excitability in the lesioned hemisphere is not dampened to a great extent. These observations suggest a milder imbalance in intercortical inhibition. B, Subcortical lesions disturb ipsilesional strio-thalamo-cortical circuits (Cirle and arrow) and cause shrinkage in ipsilateral and contra lateral striatum in val/val carriers. Met carrier mice display enhanced activation in the strio-thalamo-cortical circuits. The excitatory shift may underlie the functional improvement of $BDNF^{M/M}$ mice and resistant to atrophy in the contralesional striatum..

- * (Helm et al., 2016) , ** (Kim et al., 2016b) ,*** (Kim et al., 2016c)

TABLE 1:

Monogenic causes of stroke

Monogenic Stroke Disease	Gene	Inheritance	Mechanism
CADASIL	NOTCH 3	Autosomal dominant	small vessel disease
CARASIL	HTRA1	Autosomal recessive	small vessel disease
RVCL	TREX1	Autosomal dominant	small vessel disease
Farby's Disease	GLA	X linked	Large artery and small vessel disease
Homocystinuria	CBS and other	Autosomal recessive	Large artery and small vessel disease
Sickle cell disease	HBB	Autosomal recessive	Large artery and small vessel disease
Pseudoxanthoma elasticum	ABCC6	Autosomal recessive	Large artery and small vessel disease
Marfan syndrome	FBN1 and other	Autosomal dominant	Arterial dissection, cardio embolism
Vascuar Ehlers danlos syndrome	COL3A1	Autosomal dominant	Arterial dissection
MELAS	MtDNA gene MT-TL1 encoding tRNALeu	Maternal inheritance	Mitochondrial (multisystem)

TABLE 2:

A summary of studies examining the effect of Val66met SNP on stroke outcome.

SPECIES	ASSESMENT	TIME POINT(S)	KEY FINDINGS	REFERENCE
HUMAN	Motor learning in Unilateral stroke	>6 months post stroke	Met carriers performed worse compared to non-carriers	Charalambous et al, 2018
	Functional mobility in Stroke	6 months post-stroke	Val66Met polymorphism does not predict long-term outcome	French et al, 2018
	Aphasia Recovery in Stroke (with aphasia)	Aphasia onset less than 3 months, follow-up study	Val66Met polymorphism does not alter clinical recovery	De Boer et al, 2017
	Motor learning in Stroke (with hemiparesis)	At least 6 months post-stroke	Met carriers performed worse compared to Val/Val patients	Van der Vliert et al, 2017
	Dysphagia recovery in Stroke (with Dysphagia)	within 6 weeks of stroke	Met carriers recovered better in response to pharyngeal electrical stimulation	Essa et al, 2017
	Motor improvement in unilateral stroke (with hemiparesis)	2–123 months post-stroke, 14 day theraphy protocol	Reduced magnitude of motor improvement with therapy in Met carriers	Shiner et al, 2016
	Motor adaptation in stroke	at least 6 months post-stroke	Val66Met polymorphism influences the rate but not the amount of total adaptation	Helm et al, 2016
	FMRI / Brain activation in stroke	at least 11 weeks post stroke	Decreased brain activation among Met carriers	Kim et al, 2016b
	Motor outcome in ischemic & hemorrhagic stroke	<2 weeks after onset, 1 and 3 month evaluation	Met carriers showed poorer upper extremity motor outcome	Kim et al, 2016c
	Functional disability in ischemic stroke	6 months post-stroke	No difference among genotypes	Keshavarz et al, 2016
	Stroke rehabilitation outcome in ischemic & hemorrhagic stroke	within 3 months of stroke onset	Unfavorable outcome associated with Val/Val genotype	Mirowska-Guzel et al, 2014
	Stroke risk & neurologic disability in ischemic stroke	1 and 90 days post stroke	Met/Met genotype is associated with increased stroke risk and poor outcome	Zhao et al, 2013
	Neurologic disability in subcortical stroke	(stroke <1 month), 1 and 3 months post-discharge	Worse outcome in Met carriers	Kim et al, 2013
	Neurologic disability & cognitive function in ischemic stroke	2 weeks and 1 year post-stroke	Val66Met polymorphism is associated with poor outcome and cognitive function	Kim et al, 2012
	Stroke severity in ischemic & hemorrhagic stroke	1st and 3rd month post stroke	Poor recovery in Met carriers at 1 month, difference diminished at 3 months	Cramer et al, 2012
	Stroke severity, Neurologic disability in ischemic & hemorrhagic stroke	acute (within 12 hours), 7 days, 30 days post stroke	Worse outcome in Met carriers at admission and day 7 but not at one month	Mirowska-Guzel et al, 2012
	Functional outcome in subarachnoid hemorrhage	3 months after SAH	Met allele is associated with poor outcome	Siironen et al, 2007
MOUSE	Motor & Gait in transient focal ischemia (MCAO)	1st and 2nd week, 1,2,4 and 6 months	Greater deficit at 1 week but superior recovery at later time points in Met/Met mice	Qin et al, 2014
	Motor & Gait in transient focal ischemia (MCAO)	1 d, 4 d, 7 d, 2 weeks, and 1 month after MCAO	Met/Met mice were significantly worse compared to controls at day 7 but not at later time points	Qin et al, 2011