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Endothelial function, folate pharmacogenomics, and neurocognition in psychotic disorders

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ABSTRACT

Cardiovascular disease (CVD) is a well-described complication of schizophrenia, however, mechanisms connecting CVD with other facets of psychotic disorders, such as neurocognition, are not understood. The current study examined folate metabolism as a potential mechanism of CVD and neurocognitive deficits by: 1) using endothelial dysfunction as a biomarker of CVD, and 2) comparing enzymes associated with neurocognition, CVD, and critical to folate metabolism, methylenetetrahydrofolate reductase (*MTHFR*) and catechol-o-methyl transferase (*COMT*). Endothelial function was assessed in 147 participants with schizophrenia, schizoaffective disorder, and psychotic disorder not otherwise specified grouped by *MTHFR* and *COMT* allele status. Regression models were used to compare neurocognitive performance based on the Brief Assessment of Cognition in Schizophrenia (BACS). Overall, endothelial function predicted BACS composite *z*-scores after controlling for age, race, level of education, serum folate levels, and *MTHFR*/*COMT* risk allele status. Participants with at least one or more *MTHFR and/or COMT* risk alleles had lower BACS Composite and BACS Symbol Coding adjusted mean *z*-scores than those with both *MTHFR* CC and *COMT* Met/Met genotypes. Thus, endothelial dysfunction may contribute to the neurocognitive deficits seen in psychotic disorders. CVD interventions may not only reduce CVD-related morbidity, but also lessen progressive neurocognitive deficits reported in psychotic disorders.

1. Introduction

Psychotic disorders such as schizophrenia are often associated with cardiovascular diseases (CVDs). Previous reports show that two-thirds of people with schizophrenia are diagnosed with CVD, compared to one-half of the general population, and this high rate of CVD morbidity is directly related to decreased life expectancy in schizophrenia (Hennekens et al., 2005; Fan et al., 2013).

One potential mechanism for the development of CVD may be found within enzymes responsible for the metabolism of folate, methylenetetrahydrofolate reductase (*MTHFR*) C677T and catechol-O-methyltransferase (*COMT*) Val158Met, as variant or risk alleles (*MTHFR* T and *COMT* Val alleles) are linked to CVD risk in schizophrenia (Kullo and Malik, 2007; Ellingrod et al., 2011; Burghardt and Ellingrod, 2013).

Additionally, *MTHFR* and *COMT* risk alleles are associated with reduced prefrontal cortex functioning and neurocognitive deficits in schizophrenia (Roffman et al., 2007, 2008a,b, 2011a,b). Together, these findings suggest that abnormal folate metabolism may be related to the development of both the CVD and neurocognitive deficits often seen in schizophrenia.

MTHFR and *COMT* enzymes are each involved in the AldoMet cycle, a key pathway in folate metabolism. Within this cycle, *MTHFR* C677T catalyzes the formation of methyltetrahydrofolate (5-methyl THF) from dietary folate. Abnormal folate metabolism may be a consequence of the *MTHFR* 677T allele, as single T allele carriers show a 35% reduction in activity and TT homozygotes show a 70% reduction. The presence of the *MTHFR* T allele results in reduced folate metabolism that can lead to elevated levels of homocysteine or hyperhomocysteinemia, which has been associated with CVD in the general population (Klerk et al., 2002).

In addition to *MTHFR*, the *COMT* variant (158Val/Met) is another crucial component within the AldoMet cycle, as the *COMT* Val/Val genotype exhibits 30–50% greater activity than the Met/Met genotype (Chen et al., 2004), which may also lead to hyperhomocysteinemia. Moreover, the effects of the *COMT* 158 variant may be exaggerated in individuals who also have an *MTHFR* T allele (Tunbridge et al., 2008).

While both *COMT* and *MTHFR* genotypes have been individually and additively associated with neurocognitive deficits in schizophrenia (Roffman et al., 2008b, 2011b; Ceaser et al., 2013; Kontis et al., 2013), the relationship between folate metabolism, neurocognition, and CVD in schizophrenia has not been examined. Accordingly, an important biomarker for CVD is dysfunction of the endothelium (Ross, 1999; Haynes,

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2003; Kullo and Malik, 2007; Rubinshtein et al., 2010). Briefly, the endothelium is a vital organ lining all blood vessels of the body that regulates inflammation and is also related to neurocognitive deficits in clinical populations, e.g., Alzheimer's disease (Dede et al., 2007), and depression (Smith et al., 2007). Hence, understanding the relationship between endothelial function, pharmacogenetically regulated folate metabolism through *MTHFR* and *COMT* enzymes, and neurocognition in schizophrenia may help to identify those at greatest risk for significant impairments. Since deficits in endothelial functioning are potentially reversible, determining the role of CVD in the development of neurocognitive deficits in schizophrenia would be invaluable, as targeted interventions could potentially help to reverse negative outcomes.

Thus, the aim of the current study was to determine the impact of *MTHFR* 677C/T, *COMT* 158 Val/Met, and endothelial functioning on neurocognition in psychotic disorders. We hypothesized that the presence of *MTHFR* and/or *COMT* risk alleles and the occurrence of a specific CVD risk factor (endothelial dysfunction), would be associated with impaired neurocognition. Fig. 1 provides a detailed description of this hypothesis.

2. Methods and materials

2.1. Participants

A total of 147 participants with a DSM-IV Axis I primary diagnosis of schizophrenia ($n = 61$), schizoaffective disorder ($n = 71$), or psychotic disorder not otherwise specified ($n = 15$) were included in this analysis. Participants were part of a larger study examining the metabolic side effects of antipsychotic medications and were included if they: 1) had a DSM-IV (American Psychiatric Association, 2000) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified, 2) were between the ages of 18 and 90, and 3) had received at least 6 months of antipsychotic medication treatment. Participants were excluded if they: 1) were unwilling to participate, 2) lacked the ability to give informed consent, 3) were diagnosed with type II diabetes prior to treatment with antipsychotic medications, or 4) had an active substance abuse diagnosis. The University of Michigan Medical School Institutional Review Board (IRBMED), Washtenaw County Health Organization (WCHO), Ann Arbor Veterans Affairs Medical Center, and Detroit-Wayne County Community Mental Health Agency (DWCCMHA) approved the study protocol. Each participant was assessed at the Michigan Clinical Research Unit (MCRU) at the University of Michigan Medical Center.

2.2. Diagnostic, clinical, and demographic assessment

Participants underwent an informed consent process followed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 1997). Participants also completed the Beck Depression Inventory (BDI; Beck et al., 1996). Level of education was determined by the eight classifications provided by the SCID (1 = completed grade 6 or less, 2 = completed grade 7 to 12 without graduating high school, 3 = graduated high school or high school equivalent, 4 = completed some college courses without graduating, 5 = graduated from a 2 year college, 6 = graduated from a 4 year college, 7 = completed some graduate/professional courses without graduating, and 8 = completed graduate/professional school). Participants were grouped by low and high education, with levels 1 to 2 categorized as low education (no high school diploma) and levels 3 to 8 categorized as high education (high school diploma, GED, or higher).

2.3. Metabolic assessment

Participants completed a fasting blood draw (12 h) that included assays for both serum folate and homocysteine serum levels, which were collected to determine the relationship between *MTHFR*/*COMT* risk alleles and neurocognition independent of serum folate and homocysteine levels.

2.4. Neurocognitive battery

The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe, 1999; Keefe et al., 2004) measures four domains: verbal memory (List learning), working memory (Digit sequencing), processing speed (Token Motor Task, Verbal Fluency: category instances and letter fluency, and Symbol Coding), and executive function (Tower of London; Keefe et al., 2008). BACS *z*-scores were based on a group of 63 healthy controls from our database.

2.5. Endothelial function

Endothelial functioning was assessed with the EndoPAT 2000 (Itamar Medical Inc., Caesarea, Israel), which has been validated and described in previous studies as a non-invasive method using peripheral

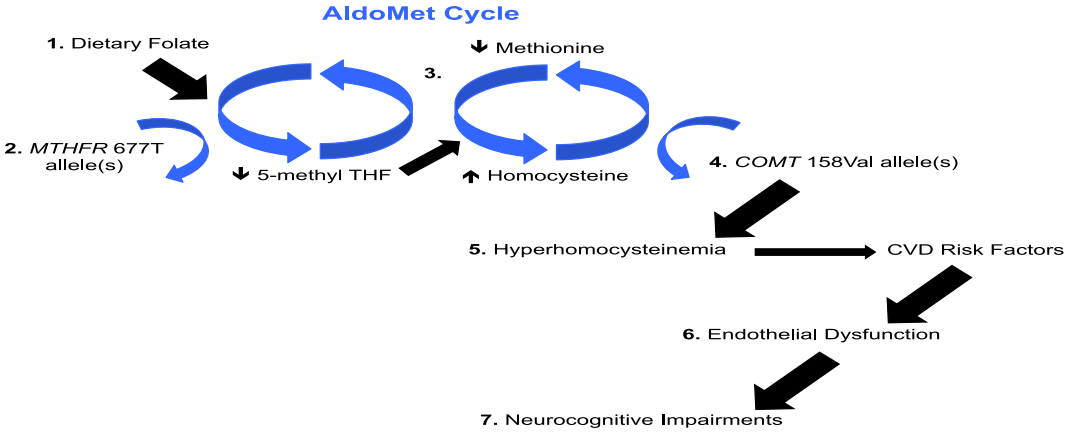

Fig. 1. The AldoMet cycle begins with: 1) dietary folate, which is converted to 5-methyl THF by the *MTHFR* enzyme. 2) Presence of the *MTHFR* 677T allele(s) is associated with a 35 to 70% reduction in the metabolism of folate. 3) In the next phase of the AldoMet cycle, 5-methyl THF is needed to form methionine, which is then converted to homocysteine by the *COMT* enzyme. 4) Presence of the *COMT* 158Val allele(s) is associated with a more efficient conversion of methionine to homocysteine, resulting in an elevation of homocysteine and possible hyperhomocysteinemia. 5) Previous reports have linked hyperhomocysteinemia with CVD risk factors such as metabolic syndrome (e.g., elevated BMI). 6) Additionally, endothelial dysfunction may be a marker of these CVD risk factors, 7) and endothelial dysfunction is associated with neurocognitive impairments. THF = tetrahydrofolate; *MTHFR* = methylenetetrahydrofolate reductase; *COMT* = catechol-o-methyl transferase; CVD = cardiovascular disease; BMI = Body Mass Index.