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BDNF Val66Met and Spontaneous Dyskinesias in Non-Clinical Psychosis

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Abstract

Background—Evidence indicating that symptoms of non-clinical psychosis (NCP) occur in 6–8% of the general population suggests that psychosis may occur across a continuum. Although a number of studies have examined environmental contributors, to date there have been few investigations of biological/genetic factors in this integral population. A recent study observed spontaneous dyskinetic movements (reflecting an innervated striatal system) in individuals reporting NCP. The present investigation is designed to replicate this finding and determine if brain-derived neurotrophic factor (BDNF) (implicated in striatal dopamine function) is associated with dyskinesias.

Method—A total of 68 young-adult participants reporting High and Low-NCP were assessed for dyskinetic movements using a sensitive instrumental measure of force variability. Saliva from the participants was genotyped for val66met (rs6265), a common functional polymorphism of the BDNF gene (the Met allele is associated with lower activity-dependent release of BDNF).

Results—Participants in the High-NCP group showed significantly elevated levels of force variability. Met allele carriers exhibited significantly higher levels of force variability when compared with the Val homozygotes. Logistic regression indicated the odds of membership in the High-NCP group were significantly higher given the presence of dyskinesias (OR = 2.32; CI: 1.25–4.28).

Conclusion—Findings of elevated force variability suggests that individuals with NCP exhibit subtle signs of striatal vulnerability, reflected more dramatically as jerking and hyperkinetic movements in patients with formal psychosis. The results are consistent with a larger literature implicating BDNF as a critical factor underlying abnormal movements, and suggest specific candidate genes underlie putative markers across a psychosis continuum.

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Conflict of Interest

There are no conflicts of interest to report.

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Keywords

Dyskinesia; BDNF; SNP; val66met; Non-clinical Psychosis

1. Introduction

An accumulating body of evidence indicating that symptoms of sub-clinical psychosis are experienced by the general population suggests that psychosis occurs as a continuous phenotype (Kelleher and Cannon, 2011). In a series of investigations, researchers have been working to understand the nature of vulnerability factors along this phenotypic continuum (Zammit et al., 2008; Blanchard et al., 2010; Jacobson et al., 2010; Alemany et al., 2011; Mackie et al., 2011; Mittal et al., 2011a; Macmanus et al., 2012; Mittal et al., in press). This line of study is integral as examining putative markers in an environment without third variable confounds (e.g., medications, neurotoxicity) stands to significantly elucidate etiological factors underlying psychosis. As research continues to clarify the continuum of non-clinical psychosis (NCP; fleeting psychotic symptoms in the absence of illness, experienced by a proportion of the general population), an important next step lies in exploring the genotype of individuals on the non-clinical side of the spectrum. Although recent studies have shown support for familial clustering of NCP symptoms (Hanssen et al., 2006; Polanczyk et al., 2010), along with familial covariation of NCP symptoms with maternal schizophrenia spectrum disorder (Polanczyk et al., 2010), and greater concordance for NCP among monozygotic twins (when compared to dizygotic twins) (Lataster et al., 2009), to date there is a dearth of research focusing on contributing genes or loci (Kelleher and Cannon, 2011).

Within the context of understanding factors contributing to psychosis, spontaneous dyskinesias (e.g., writhing and jerking movements) are of particular interest, as these movements reflect an impaired basal ganglia circuitry, which is also implicated in the onset and maintenance of psychotic symptoms (DeLong and Wichmann, 2007). More specifically, researchers have observed that independent of medication status, increased spontaneous dyskinesias are a natural byproduct of the pathogenesis of schizophrenia (Puri et al., 1999; Cortese et al., 2005; Pappa and Dazzan, 2009; Mittal and Walker, 2010), and that these movements reflect dysregulated dopaminergic activity in the striatal region (DeLong and Wichmann, 2007). Following a line of research examining spontaneous movements in high risk youth (e.g., schizotypal personality disorder, prodromal syndromes) (Mittal et al., 2007; Mittal and Walker, 2007; Mittal et al., 2008; Mittal et al., 2010a), our group recently conducted an investigation designed to determine if young adults reporting NCP also exhibited subtle signs of dyskinesia (Mittal, et al., 2011a). Using a highly sensitive instrumental measure of force variability (FV; a proximal measure for dyskinetic movements), we observed that youth reporting high-NCP showed elevated dyskinesias indicating that a continuum of striatal vulnerability also underlies the non-clinical side of the psychosis spectrum.

Brain-derived neurotrophic factor (BDNF) modulates molecular pathways and receptors implicated in movement regulation (Sokoloff et al., 2002; Caldeira et al., 2007; Guillin et al., 2007) and is important to functions such as neural plasticity and repair (Cotman and Berchtold, 2002; Woo et al., 2005; Knaepen et al., 2010). In addition, endogenous BDNF influences dopamine system homeostasis by regulating the release and uptake dynamics of pre-synaptic dopamine transmission (Bosse et al., 2012). A single nucleotide polymorphism (SNP) in the human BDNF gene at codon 66 (val66met) has functional consequences in both healthy and clinical populations, as it leads to reduced activity induced by BDNF release from neuronal cells (Chen et al., 2008). For example, in a transgenic mouse model

for Huntington's disease, researchers found that reduced endogenous BDNF was associated with degeneration of striatal projection neurons and advance the onset of motor dysfunction (Canals et al., 2004). Consistent with this evidence, Foltynie and colleagues (2012) observed that val66met was predictive of earlier onset of levodopa-induced dyskinesias in Parkinson's disease. BDNF has also been implicated in psychosis (Green et al., 2011) and research indicates that patients with dyskinetic movements have lower levels of plasma BDNF (Tan et al., 2005).

To date, there has been limited research studying candidate genes in individuals expressing NCP and to our knowledge no studies have examined the BDNF val66met in this population. The noted finding that individuals reporting sub-clinical psychosis also show subtle signs of dyskinesia (Mittal et al., 2011b), and a body of evidence supporting the notion that val66met is implicated in the pathophysiology of abnormal movements suggests that this SNP may be conferring a putative vulnerability in persons endorsing NCP. A total of 68 young adults reporting High or Low-NCP were assessed for dyskinetic movements and genotyped for BDNF val66met to replicate the noted earlier investigation (Mittal, et al., 2011a) and to test the hypotheses that the Met allele carriers would exhibit significantly higher levels of dyskinesias.

2. Methods

2.1 Participants

All participants were young adults (mean age 19, range: 18–26), recruited through the Adolescent Development and Preventive Treatment (ADAPT) research program. Individuals in the undergraduate research pool ($n = 1,248$) were given the Launay-Slade Hallucination Scale (Bentall and Slade, 1981), a questionnaire focusing on symptoms of non-clinical psychosis. The option to participate in the study was made available to those scoring in the top and bottom 10th percentile (scores of ≥ 3 or ≤ 3 respectively). To limit potential sampling bias, the available studies were listed as numbers without descriptions and students were then given study details upon arrival to site for the consent process (all of the individuals who arrived consented to participate). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1976) was administered to ensure that participants with elevated psychosis would not be included, as this could potentially confound results. The other exclusion criterion was current or past treatment with anti-psychotic medication because anti-psychotic medications can have motor side effects ranging from hyperkinesia to hypokinetic syndromes (Mittal and Walker, 2009). Based on these criteria, it was not necessary to exclude any of the participants. The Institutional Review Board approved the protocol and informed consent procedures. See Table 1 for demographic characteristics of this sample.

2.2 Clinical Symptoms

The Launay–Slade Hallucinations Scale (LSHS) (Bentall and Slade, 1985) is a 12-item self-report scale used to measure hallucinatory predisposition by assessing clinical and sub-clinical hallucinatory phenomena (the scores for each item range from 0–4 and the range for the total scale is 0–48). The scale has been validated (Bentall and Slade, 1985), and is one of the most widely used instruments in examining symptoms of non-clinical psychosis in healthy populations (van't Wout et al., 2004; Johns, 2005; Barkus et al., 2007; Vellante et al., 2012). It should be noted that the LSHS is specifically designed to gauge hallucination proneness, and that there are other facets to the overall construct of non-clinical psychosis including unusual thoughts and suspiciousness. The items on this scale have been reliably to be linked to the non-clinical end of a psychosis spectrum (Leviton, Ward, Catts, and Hemsley, 1996; Serper, Dill, Chang, Kot, and Elliot, 2005). In the present study, the subjects

were asked to indicate experiences in the past month, and asked to not include experiences that occurred only while under the influence of alcohol, drugs, or medications that were not prescribed.

The BPRS (Overall and Gorham, 1976) was used to screen the participants in order to control for frankly psychotic symptoms, which might confound or “drive” results. The BPRS is a brief clinical interview designed to track changes in psychotic symptoms and ranges from 18–126. In the present study, a score of 4 (“moderate”) or higher on any item was grounds for exclusion although as noted, it was not necessary to exclude any participants from the study.

BDNF—Genomic DNA was isolated from saliva samples collected using a commercial product, (Oragene, DNAgenotek, Ottawa, Ontario, Canada). Two ml of saliva were collected into the vial that when capped released a stabilizing lysis buffer. DNA samples collected in this way are stable for at least five years when stored at room temperature (www.DNAgenotek.com) (Rylander-Rudqvist et al., 2006). The DNA was prepared from 500 µl of the Oragene™ solution with the Beckman-Coulter DNaAdvance (Brea, CA) system according to the manufacturer’s protocol. The final elution volume was 150 µl. Samples were diluted 1:20 in TE and the DNA was quantified using Picogreen® (Invitrogen, Carlsbad, CA) fluorescence. The BDNF Val66Met (rs6265) assay was performed using a fluorogenic 5′ nuclease (Taqman®, Applied Biosystems, Foster City, CA) method (Surtees et al 2007). The primer and probe sequences were: Forward Primer: 5′-GCCCAAGGCAGGTTCAAGAG-3′; Reverse Primer: 5′-AACTTTCTGGTCCTCATCCAACAG-3′; Val Probe: 5′-VIC-CTTTTCGAACACATGATAG-MGB-3′; Met Probe: 5′-FAM-CTTTTCGAACACATGATAG-MGB-3′. Reactions were performed in an ABI Prism® 7000 Sequence Detection System using the allelic discrimination mode (Livak, 1999). Reactions containing 20 ng of DNA were performed in 15 µl reactions with TaqMan® Universal PCR Master Mix using the standard cycling conditions. Final primer and probe concentrations were 900 mM and 200 mM, respectively. Each 96 well plate included at least one non-template and two known genotype controls. Two individuals independently scored the genotypes.

2.3 Measurement of dyskinesia using force variability

To detect subtle dyskinetic movements in the sample, we employed an instrumental measure, which has been demonstrated to distinguish the same subjects whose abnormalities are identified by standard observer-based severity ratings and also detect an additional subset of the participants (i.e., roughly twice as many participants) (Cortese, et al., 2005). Measurements of force instability involve having a subject use their dominant hand to apply and maintain a constant pressure on a load cell and maintain constant force over 20 seconds, while a computer program measures the amount of variability in the applied force (please see Mittal et al., 2011a for details on this methodology). Final analysis of force error involved obtaining the coefficient of variation (CV) from the mean and standard deviation of the force waveform. The force variability (FV) measure has been validated as a measure of dyskinesia in studies of spontaneous dyskinesias (Cortese, et al., 2005) and is highly reliable (Caligiuri et al., 1997). Participants were asked about a history of nicotine use as this may alter performance on the movement task (Quik et al., 2007).

2.4 Statistical Approach

Independent t-tests and chi-square tests were utilized to examine for any potential differences between the High and Low-NCP groups in demographic characteristics, clinical variables, and the frequency of BDNF Val alleles. Analysis of Covariance (ANCOVA),

controlling for nicotine use, was used to test for both High and Low-NCP group and Val/Val and Non-Val/Val group differences in dyskinesias. A logistic regression analysis was conducted with force variability and BDNF grouping (Val/Val and Non-Val/Val) as predictor variables, and group status (Low and High-NCP) as a dichotomous outcome. As with the previous series, nicotine use was treated as a covariate in the regression analysis.

3. Results

A total of 68 participants were partitioned into High-NCP (n=39) and Low-NCP (n=29) groups. There were no significant differences between the groups on demographic characteristics including gender, age, ethnicity, and parental education. In addition, there was no significant difference in nicotine use between the groups. A Kolmogorov-Smirnov test revealed that the target dyskinesia variable met assumptions for parametric analyses.

3.1 Clinical Symptoms

Reflective of the sampling strategy, an independent t-test indicated that the High-NCP group (mean=26.76, SD=2.88) endorsed a significantly more items on the LSHS scale when compared to the Low-NCP group (mean=1.86, SD=1.02), $t(219)=-5.02$, $p=.01$. The most commonly endorsed items reported as “certainly applies” were: “In my daydreams I can hear the sounds of a tune almost as clearly as if I were actually listening to it” (27.9%), “Sometimes my thoughts seem as real as actual events in my life” (26.4%), “No matter how hard I try to concentrate, unrelated thoughts always creep in my mind” (25%), and “I often hear a voice speaking my thoughts aloud” (20.5%). As noted, the BPRS was employed to ensure that a potentially fully psychotic individual or a group of individuals would not inadvertently drive results. Although no participant in either group endorsed symptoms that approached the clinical range, the High-NCP group (mean=18.71, SD=1.84) had significantly higher BPRS scores than the Low-NCP group (mean=18.03, SD=.18), $t(66)=-2.29$, $p=.03$. No participants scored above a 2 (very mild) out of the scale ranging up to 7 (extremely severe).

3.2 BDNF genotypes

Among the entire sample, 3 individuals had Met/Met (4.4%), 24 Met/Val (35.3%), and 41 Val/Val (60.3%) genotypes. This is consistent with population estimates for the polymorphism in predominantly Caucasian samples. The High-NCP group was comprised of 2 Met/Met (5.1%), 14 Met/Val (35.9%) and 23 (59%) Val/Val genotypes. The Low-NCP group was comprised of 1 Met/Met (3.4%), 10 Met/Val (34.5%) and 18 Val/Val (62.1%) genotypes. Because of the small number of Met/Met homozygotes, grouping for analyses comparing the genotypes was partitioned into those individuals with the Val/Val homozygotes (n=41, 60.3%) genotype and those carrying one or more Met allele (n = 27, 39.7%). This strategy is consistent with other investigations of BDNF Val66Met (Cheeran et al., 2008). There were no significant differences between High and Low-NCP groups in BDNF genotypes, $\chi^2(1)=.06$, $p=.78$.

3.3 Dyskinesias

ANCOVA analyses, controlling for nicotine use, were used to examine group differences (High and Low-NCP) and genotype differences (Val/Val and Non-Val/Val) in FV. Individuals in the High-NCP group showed significantly elevated force variability (mean CV=3.92, SD=1.04) when compared to those in the Low-NCP group (mean CV=3.28, SD=.98), $F(1,65)=6.59$, $p=.01$. Consistent with the present study's hypothesis, the group of participants with the Met allele (mean CV=3.93, SD=1.00) showed significantly elevated force variability when compared with the Val/Val group (mean CV=3.46, SD=1.06), $F(1,65)=3.07$, $p=.03$.

3.4 Logistic regression

To provide an index of the power of dyskinesias and the BDNF Val66Met polymorphism in predicting group membership (Low or High-NCP), we conducted logistic regression analyses with group status as the outcome variable (results are presented in Table 2). The odds ratio for force variability was highly significant suggesting that dyskinesias are a strong predictor of membership in the High-NCP group. Consistent with the analyses in section 3.2, results for the BDNF variable were not significant.

4. Discussion

An important review of the NCP literature recently spoke toward the necessity of studies examining contributing genes (Kelleher and Cannon, 2011) and, to our knowledge, this is one of the first genetic studies in this context. The present results replicate our earlier findings suggesting an underlying striatal vulnerability is present in the non-clinical side of the psychosis phenotype (Mittal, et al., 2011a). In addition, findings that the BDNF val66met SNP is associated with increased dyskinesias are consistent with the larger body of literature suggesting BDNF is an integral factor in regulating movement. Taken together, the results indicating elevated force variability in the High-NCP group as well as in the group with Met allele carriers suggest that the phenotypic continuum of psychosis is dovetailed with a spectrum of vulnerability factors, which in turn are the product, in part, of genetic influence.

The exploration of NCP has seen considerable interest in the past decade, and recent systematic reviews have drawn attention to the potential of this population to elucidate the etiology of formal psychosis (Johns, 2005; van Os et al., 2009; Kelleher and Cannon, 2011). The base rates, outcome, and precipitating psychological and environmental factors have received a good deal of attention (Janssen et al., 2004; Bak et al., 2005; Scott et al., 2008; Morgan et al., 2009; Nishida et al., 2010; Skinner et al., 2011; Ahmed et al., 2012), and an important next step in progressing this line of research is to explore risk-markers and genetic influence. The decision to examine dyskinesias as possible vulnerability markers was based upon a series of landmark studies reporting that these markers are present as early as childhood in individuals who will later develop schizophrenia in adulthood (Walker et al., 1994; Schiffman et al., 2004) as well as children reporting psychotic-like experiences (Macmanus, et al., 2012). The notion that movement abnormalities in psychosis are the product of genetic influence is supported by an excellent study demonstrating that the dyskinesias are present in unaffected relatives (Koning et al., 2011). Because of BDNF's influence on plasticity in corticalstriatal synapses (Kleim et al., 2006), and its role in modulating the dopamine system (Porritt et al., 2005), the val66met polymorphism is a strong candidate for investigating psychosis-spectrum in susceptible populations.

Although the effects are relatively small, the findings are striking in that dyskinesias elevated in both the NCP group and in the Met allele group in a non-clinical sample. As noted, BDNF modulates the dopamine system (Sokoloff, et al., 2002; Caldeira, et al., 2007; Guillin, et al., 2007) and striatal DA is assumed to be responsible for balancing the activity of both the direct and indirect pathways, which comprise the motor circuit (Mittal and Walker, 2009). Further, the significantly increased odds of membership in the NCP group based upon force variability stresses the importance of this circuit in understanding the continuum of psychosis. The relation between striatal DA, movement, and psychotic symptoms can be demonstrated by studies examining compounds, such as levodopa, that are used to treat Parkinson's disease by increasing DA transmission. Movement abnormalities associated with Parkinson's disease (i.e., hypokinesia, rigidity) are related to the low levels of dopamine characteristic of the disease; these movements are also seen in schizophrenia patients taking antipsychotic medications which lower DA. However, researchers have

observed that patients with Parkinson's disease, who are treated with dopamine agonists (i.e., levodopa induced elevated striatal DA) show drug-induced dyskinesias (Hoff et al., 2001), and in some cases, psychotic symptomatology (Papapetropoulos and Mash, 2005). When examining the results of current study, it is noteworthy to consider a report that the presence of the Met allele conferred significantly heightened risk of developing levodopa-induced dyskinesias earlier in Parkinson's patients (Foltynie et al., 2009).

Findings that the Met allele was significantly more frequent in NCP group are consistent with one of few other published studies examining candidate genes in this population. Specifically, while BDNF Met was found to moderate the relationship between childhood neglect and the later development of NCP, there was no main effect found for the val66met polymorphism and symptoms of NCP (Alemany, et al., 2011). Findings in the present study that force variability was elevated in the NCP and Met allele groups, but that there was not a greater frequency for Met allele carriers in the NCP group speak to a nuanced story as well. It is highly probable the Met allele of BDNF, in itself, is not sufficient to confer NCP, but rather, the phenotype is the product of interactions between environmental influences and numerous genes, each exerting a small amount of influence. This interpretation is also consistent with recent insights into the pattern of genetic influence in psychotic disorders (Harrison and Weinberger, 2005; Cannon and Keller, 2006).

Although there were significant differences between the groups on BPRS score, it is likely that sensitivity of the measure for detecting subtle symptoms of NCP (the BPRS is designed for gauging frank symptoms and even the lower scores on the scale represent an upper-limit for NCP experiences) and the timing differences between the two measures (the LSHS asks about symptoms in a one month period and BPRS gauges more proximally or currently occurring symptoms) account for the small effect. This stresses the importance of utilizing specialized scales for detecting NCPs such as the LSHS.

Although the present study includes several improvements on our previous investigation of dyskinesias in individuals reporting NCPs (i.e., including the BPRS and employing a more widely used and formally validated NCP assessment), the sample size is a noteworthy limitation, as chance findings are a possibility (Duncan and Keller, 2011). As this study was limited to hypothesis-driven investigation of a single genetic polymorphism (in our larger overall study of candidate genes in NCP, only three SNPs were examined- each tied to a distinct area of dysfunction), and our earlier work demonstrated dyskinesias in this population, concerns about falsely positive results are somewhat attenuated; however, the present results should be interpreted as preliminary until larger studies can provide replication. We have also noted the likely role of gene and environmental interactions in the larger picture of understanding BDNF, dyskinesias, and NCP, and urge future investigations to examine this possibility in larger samples. Early studies with solid theoretical rationale are important as these can scaffold considerably larger-scale studies in this area. Future studies examining plasma for endogenous levels of BDNF, other gene loci associated with movement, as well as other vulnerability markers will help to progress our understanding of NCP.

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Table 1

Participant Demographics, Dyskinesias, and Symptoms

	High Non-Clinical Psychosis	Low Non-Clinical Psychosis	Grand Total	Group Differences
<u>Gender</u>				
Males	17(43.6%)	15(51.7%)	32(47.1%)	<i>N.S.</i>
Females	22(56.4%)	14(48.3%)	36(52.9%)	
Total	39	29	68	
<u>Age</u>				
Mean/SD	19.0(1.5)	19.2(1.5)	19.0(1.5)	<i>N.S.</i>
<u>Ethnicity</u>				
Asian	2(5.1%)	0(0.0%)	2(2.9%)	<i>N.S.</i>
Caucasian	30(76.9%)	26(89.6%)	56(82.3%)	
African American	1(2.6%)	0(0.0%)	1(1.5%)	
Other	6(15.4%)	3(10.3%)	9(13.2%)	
<u>Parent Education</u>				
Mean Years/SD	15.8 (1.6)	14.9(3.4)	15.4(2.5)	<i>N.S.</i>
<u>Nicotine Use</u>				
Yes	6(15.4%)	1(3.4%)	7(10.3%)	<i>N.S.</i>
No	33(84.6%)	28(96.6%)	61(89.7%)	
<u>BDNF Genotype</u>				
Val/Val homozygotes	23(59.0%)	18(62.1%)	41(60.3%)	<i>N.S.</i>
Non-Val/Val	16 (41.0%)	11(37.9%)	27(39.7%)	
<u>Dyskinetic Movements</u>				
Coefficient of Variation/SD	3.93(1.0)	3.28(.98)	3.65(1.1)	<i>p</i> .01
<u>Non-Clinical Psychosis^a</u>				
Mean/SD	26.76(2.9)	1.86(1.0)	15.9(12.6)	<i>p</i> .01

Note: not significant (N.S.); brain derived neurotrophic factor (BDNF)

^aTotal score on Launay-Slade Hallucination Scale (LSHS)

Logistic regression results (odds ratio) for dyskinesias and the BDNF Val66Met polymorphism in predicting non-clinical psychosis group membership

Table 2

Variable	Estimate	S.E.	Wald	p	OR	95% CI	
						Lower	Upper
Force Variability	.84	.31	7.26	.001	2.32	1.25	4.28
Val/Val and Non-Val/Val	-.23	.56	.16	.68	.80	.26	2.42

Note: The regression analysis controlled for nicotine use, which has been found to influence motor function.

OR = odds ratio; CI = confidence interval