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Minor Physical Anomalies and Vulnerability in Prodromal Youth

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Abstract

Because both the brain and craniofacial/limb features originate from the same germinal layer during early gestation, the postnatal presence of minor physical anomalies (MPAs) involving these physical features may be indicative of defects in prenatal neural migration and consequent brain abnormalities among individuals with psychosis. However, to date it is unknown what symptoms and characteristics MPAs may be associated with, or how these markers may reflect vulnerability among adolescents at high-risk for developing psychosis. This information is particularly vital for understanding susceptibility and informing etiological conceptualizations such as the neural diathesis-stress model. In this study, 50 adolescents with a prodromal syndrome were evaluated for MPAs, salivary cortisol, auditory and visual memory function, and attenuated positive, negative, and disorganized symptoms. Results indicated that the participants showing elevated MPAs ($n = 25$) were distinguished by elevated cortisol, deficit immediate and delayed visual memory, and higher levels of disorganized prodromal symptoms when compared with those participants exhibiting a lower incidence of MPAs. This was supported by supplementary correlational analyses examining the entire sample. These findings provide preliminary support for a theory that MPAs may reflect hippocampal system vulnerability among prodromal patients.

Keywords

Minor Physical Anomalies; Prenatal; Psychosis; Cortisol; Memory

1. Introduction

Minor physical anomalies (MPAs) are dysmorphic characteristics that are of little functional or cosmetic consequence (e.g., high-steeped or a cleft palate) (Weinberg et al., 2007), but nonetheless, the signs have been of interest to researchers since early conceptualizations of schizophrenia (Kraepelin, 1896). In recent years, investigators have viewed the heightened occurrence of MPAs among individuals in the schizophrenia spectrum through the lens of a

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Conflict of Interest

There are no conflicts of interest to report.

Contributors

Dr. Mittal conceptualized the study, conducted analyses, and drafted the manuscript. Dr. Walker attained funding for the study, directed data collection, conceptualized the study, and drafted the manuscript.

neurodevelopmental framework (Weinberger, 1995), specifying that these markers serve as an enduring representation of early gestational insult (e.g., maternal exposure to viral teratogen, stress, hypoxia) (Mittal et al., 2008a; Mittal et al., 2008b; Mittal et al., 2009) and may elucidate etiological processes, improving understanding of susceptibility among youth at high-risk for developing psychosis. However, to date it has been unclear what symptoms and characteristics MPAs may be associated with, how these markers may reflect vulnerability in the psychosis prodrome (McNeil et al., 2000; Waddington et al., 1999). This is critical as measuring MPAs and vulnerability in the prodromal period, a time less confounded by the effects and consequences of illness, stands to provide a unique perspective for understanding susceptibility in the etiology of psychosis.

The prodromal period is characterized by the emergence of a constellation of subthreshold psychotic-like symptoms and progressive social/functional impairments that precede the onset of an Axis I psychotic disorder, and is of interest both as a window for investigating processes involved in disease onset and also as a potential point of intervention and prevention (Haroun et al., 2006). Within this framework, it is particularly noteworthy that prodromal adolescents have been found to exhibit a range of characteristics including elevations in resting cortisol (Walder et al., 2000; Walker et al., 2008), and deficits in verbal fluency and declarative verbal memory (Simon et al., 2007). Prodromal youth also show elevated positive (e.g., suspiciousness, grandiosity, unusual thoughts, perceptual abnormalities, disorganized communication), negative symptoms (e.g., feeling disconnected from self and others) and disorganized symptoms (e.g., odd behavior, bizarre thinking, trouble with focus and attention) (Miller et al., 1999). However, to date, it is unclear to what degree these characteristics and symptoms may reflect an early prenatal insult, as indexed by the presence of MPAs.

The present investigation examines the relations among MPAs, salivary cortisol, memory function, and symptom profiles in a group of adolescent with a prodromal syndrome. Specifically, it is hypothesized that high-risk participants with elevated MPAs will show significant elevations in cortisol, deficits in domains of immediate and delayed auditory and visual memory, and higher levels of attenuated positive, negative and disorganized symptoms when compared to those high-risk participants with lower levels of MPAs.

2. Methods

Participants were recruited from the Atlanta, Georgia area for a prospective study conducted at Emory University. Recruitment announcements focused on youth with subclinical signs of risk for psychosis and described prodromal and schizotypal symptoms in lay terminology. The present sample includes those who met symptom criteria for a schizotypal personality disorder or a prodromal syndrome (Miller et al., 1999). This report presents data on 50 adolescents, ranging in age from 12–18 years for whom data on MPAs were available (see Table 1 for Demographics). Exclusion criteria were neurological disorder, mental retardation, history of a traumatic head injury, substance abuse/addiction, and Axis I psychotic disorder. Written consent was obtained from all participants and a parent, in accordance with the guidelines of the Institutional Review Board.

2.1 Assessment of Minor Physical Anomalies

Morphology was examined with the use of the Waldrop and Halverson scale (Waldrop & Halverson, 1971). The following anomalies were scored: fine electric hair, hair whorls, large or small head circumference, epicanthal fold, hypertelorism, high-steeped or flat and narrow palate, furrowed tongue, tongue with smooth/rough spots, asymmetrical ears, low-seated ears, adherent earlobes, malformed ears, soft and pliable ears, markedly or slightly curved fifth finger, single transverse palmar crease, third toe longer than or equal to the

second, webbed toes, large gap between first and second toes. Each anomaly was scored as present or absent, and a point was assigned for each one scored as present; this method was conducted using the modified Waldrop Halverson scoring criteria which is described in several research articles (Compton & Walker, 2009). Published norms, adjusted for age and sex, were used in scoring head circumference (Eichorn & Bayley, 1962) and canthal distance (Laestadius et al., 1969) as being one or two standard deviations beyond the mean.

To determine internal consistency of the Waldrop scale, scores for each body region (i.e., hair, head, face, eyes, ears, mouth, hands, feet) were calculated and Cronbach's alpha was computed. Results suggested moderate internal consistency from MPAs across body; the standardized alpha for the eight items was .56. However, it should be noted that the Waldrop and Halverson scale has been traditionally reported to have poorer internal consistency due to heterogeneity of anomalies in terms of location, character, and how MPAs relate to the timing of early developmental insults (Akabaliev & Sivkov, 2007; Compton et al., 2007; Sivkov & Akabaliev, 2003). This supports the importance of the present study, which is designed to elucidate developmental factors that the MPAs may be reflecting.

Examiners were three research assistants who underwent a systematic training included observation of videotaped MPA examinations, as well as practice evaluations with psychiatric patients (reliability exceeded a $Kappa \geq .80$). The rater conducting the MPA examination was never the same individual who conducted the structured interview, and was subsequently blind to scores of symptom severity and memory performance.

2.2 Assessment of Cortisol

Three saliva samples were obtained during the assessment period to gauge hypothalamic-pituitary-adrenal (HPA) activity. Participants were provided with explicit verbal and written instructions about dietary restrictions for 24 hours preceding the assessment. In order to maintain uniformity in the portion of the diurnal variation in cortisol excretion represented in the samples, all assessments were conducted at the same time of day. The first sample was taken at about 9:00AM, and subsequent samples were obtained at 10:00AM, and 11:00AM before participants ate lunch (food consumption typically produces a transient rise in cortisol). The intent was to obtain a measure of resting cortisol, and maximize reliability by computing the average of three separate measures over several hours. The participants were not exposed to a stressor, thus the cortisol level indexed in the present study represents the participants' cortisol secretion in the context of the novelty of the assessment.

Saliva was stored at -20°C in a laboratory freezer. In preparation for assay, samples were rapidly thawed and centrifuged at 300-x g for 10 minutes to remove coagulated protein and other insoluble material. Cortisol was assayed in duplicate 200 μl aliquots of the clear supernatant, using materials and procedures provided by Incstar Corporation (Stillwater, Minnesota). The assay was performed in tubes coated with an antiserum which shows significant cross-reactivity only with prednisone (83%), 11-deoxycortisol (6.4%), cortisone (3.6%) and corticosterone (2.3%). Standards in the range 1–30 ng/ml, consisted of the serum standards provided with the kit materials diluted with 200 μl of phosphate-buffered saline. Protein concentrations are equalized in standards and samples by adding cortisol-free serum to the samples. The mean coefficients of variation between duplicates and between assays were less than 5%. Using this method, the range (central 95%) of salivary cortisol concentrations in normal adults has been determined as 1.8–10.1 ng/ml.

2.3 Assessment of Cognitive Memory Function

Selected subtests from the Wechsler Memory Scales, Third Edition (WMS-III) (Wechsler, 1997), including Logical Memory I and II (immediate and delayed verbal memory) and

Family Pictures I and II (immediate and delayed spatial memory) were used to assess domains of the participant's memory. These subtests were chosen as broadly valid and reliable measures of memory function, previously demonstrated to be sensitive to deficits in high-risk samples (Seidman et al., 2010).

2.4 Assessment of Prodromal Syndrome and Dimensions of Symptoms

The Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 1999) was administered to diagnosis a prodromal syndrome and to gauge the presence of prodromal symptoms. As noted, the participants in the present study met criteria for a prodromal or high-risk syndrome, defined by moderate levels of positive symptoms and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of schizophrenia (Miller et al., 1999). The SIPS gauges several distinct categories of prodromal symptom domains including positive, negative, and disorganized dimensions. A mean of the score of items for each category is used as an indicator of respective dimensions of symptomatology. Training of interviewers was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of $\text{Kappa} \geq .80$.

2.5 Statistical strategy

Consistent with other evaluations of MPAs among high-risk populations (Schiffman et al., 2002), a mean split of the total score was utilized to distinguish those prodromal participants with high and low incidence of MPAs (*High* and *Low MPA* groups). Independent-T and Chi Square tests were utilized to examine between group differences in demographic characteristics and memory variables, and Analysis of Covariance (ANCOVA) was used to test for group differences in cortisol levels and symptoms. A series of bivariate and partial correlations are included to provide a continuous perspective for the whole sample (when employed, covariates are noted in the respective following sections).

3. Results

The MPA scores ranged from 9 to 63 (median=19); the sample was split at the median and a total of 25 high-risk patients fell into the *Low-MPA* category and 25 high-risk participants fit in the *High-MPA* group. Analyses were conducted to test for demographic differences between the groups. Independent t-tests indicated no group differences in age [$t(48)=-.08$, $p=.93$] or parental education [$t(45)=-.54$, $p=.59$], and Chi Square tests revealed no significant differences between the *Low-MPA* and *High-MPA* participants in sex ratio [$\chi^2(1, n=50)=3.30$, $p=.07$] or stimulant [$\chi^2(1, n=50)=.39$, $p=.59$], antidepressant [$\chi^2(1, n=50)=.85$, $p=.35$], and antipsychotic [$\chi^2(1, n=50)=.13$, $p=.71$] medications. One sample kolmogorov-smirnov tests were conducted on MPAs and each of the dependent variables, and non-significant findings across the tests indicate that the assumptions for parametric tests were not violated.

3.1 Cortisol

Univariate ANCOVA, with age and medication status (dummy coded: stimulant, antidepressant, and antipsychotic) treated as covariates, was used to test for group differences in salivary cortisol. As predicted, ANCOVA indicated significant differences between the *Low-MPA* and the *High-MPA* group, $F(1,48)=2.82$, $p<.01$, eta squared=.28, such that those participants with *High-MPA* s exhibited elevations in salivary cortisol (please see Table 2).

3.2 Auditory and Visual Memory

Independent sample t-tests were utilized to examine differences in memory functioning among those high-risk participants with *Low-MPA* and *High-MPA*. Although psychotropic medications can affect cognitive functioning, there has been no evidence of an adverse medication effect on cognitive performance among participants in the Emory High-Risk program (Trotman et al., 2006; Walder et al., 2008). The *High-MPA* group performed significantly more poorly than *Low-MPA* group on Family Pictures I, $t(48)=1.65$, $p\leq.05$) and Family Pictures II, $t(47)=1.81$, $p\leq.05$). However, there were no significant results for Logical Memory I or II (see Table 2). Taken together, results suggest that while both groups have deficit memory compared to standardized subscale norms (i.e., mean=10), the *High-MPA* group shows significantly greater disability in the visual-memory domain.

3.3 Prodromal Symptoms

ANCOVA controlling for dummy coded classes of medication, were conducted to determine if *Low-MPA* and *High-MPA* groups show distinct profiles on dimensions of attenuated prodromal symptoms. Results showed no significant group differences for positive or negative dimensions of prodromal symptoms. However, there were significant group differences for disorganized symptoms, $F(1,48)=2.29$, $p\leq.05$, eta squared=.17, where the *High-MPA* group showed significant elevations along this dimension (see Table 2).

3.4 MPA Associations With Cortisol, Memory, and Prodromal Symptoms

To provide an integrated and continuous perspective of the data set, correlational analyses were conducted between MPAs and cortisol, memory, and symptom variables with the entire sample ($N=50$). The results were consistent with findings that the increased incidence of MPAs was associated with significantly elevated cortisol, deficits in both immediate and delayed visual memory and attenuated disorganized symptoms (at the trend level) (See Table 3).

3.5 Craniofacial Dysmorphology

Physical markers involving facial measurement are of specific interest as researchers have theorized that the timing between facial/cranial and brain development appears to be in close in concert (Waddington et al., 1999; Compton and Walker, 2009). To examine if a specific subtype of MPAs involving the craniofacial region is particularly associated with cortisol, memory, and symptom variables, a supplementary series of correlations was conducted on a craniofacial domain consisting of items measuring head circumference, skull base, nasion-stomion height, biocular diameter, inter-pupillary distance, nasal width, and width of mouth and height of upper lip. As seen in Table 3, although the direction of findings for the craniofacial domain is consistent with the broader total MPA category, it appears to not have held up as strongly as the comprehensive scale.

4. Discussion

This report suggests that those high-risk individuals with elevated MPAs exhibit a distinct series of characteristics and symptoms. Taken together, findings that the *High-MPA* group showed increased levels of salivary cortisol, deficit immediate/delayed visual memory, and significantly more disorganized symptoms are consistent with a neural diathesis-stress conceptualization of schizophrenia (Walker & Diforio, 1997; Walker et al., 2008; Weinberger, 1995) and to our knowledge, represent the first evidence to support an association between MPAs and vulnerability among prodromal youth.

Results suggest that elevated MPAs are associated with heightened salivary cortisol and because HPA dysregulation is linked with psychotic and mood symptoms (Burke et al.,

2005; Tandon et al., 1991; Walder et al., 2000) symptoms, the HPA axis appears to act as a nonspecific moderating system that can potentiate the expression of several disorders, as well as mediate the effects of stress on symptom expression (Walker & Diforio, 1997; Weinstein et al., 1999). This may in part explain why MPAs have also been found in other illness involving HPA dysregulation such as affective disorders (Tenyi et al., 2009).

Taken together, the literature suggests that MPAs are not definitively associated with broad intelligence (Green et al., 1994; Green et al., 1989; Guy et al., 1983; Ismail et al., 2000; O'Callaghan et al., 1995; O'Callaghan et al., 1991). However, the role of immediate and delayed auditory and visual memory have been largely unexamined in this context, and to date, no studies have prospectively examined relationships between these functions and MPAs in a prodromal sample, before the confounding effects of neurotoxicity and medications (Haroun et al., 2006). Consistent with hypotheses, the participants in the *High-MPA* group exhibited significant deficits in both immediate and delayed visual memory. However, in contrast to our predictions, measures of auditory memory did not distinguish the groups. As both visual and auditory memory deficits have been observed in high-risk populations (Brewer et al., 2006), and both groups in the present study did show lower immediate/delayed auditory/visual memory scores than the standardized 50 percentile (mean=10), it is particularly interesting that the *High-MPA* group showed further distinctive deficits in the visual domain.

To date, there has not been consistent evidence to suggest that MPAs are associated with distinct features of illness such as symptom dimensions (Compton & Walker, 2009). For example, one group reported that neuroleptic-naïve patients with recent-onset schizophrenia who had more MPAs also had higher levels of positive and negative symptoms (John et al., 2008), whereas several studies have reported no consistent association between MPAs and positive or negative symptoms (Compton et al., 2007; McGrath et al., 1995). However, it is important to consider that these previous studies focused primarily on positive and negative symptom dimensions and the present results did suggest that disorganized symptoms, a heretofore-unexamined dimension in this context, were significantly elevated in the *High-MPA* group.

The timing of MPA formation, which limits potential contributing factors to the early prenatal period, when the outer layer of the embryo (i.e., ectoderm) forms both the skin and the central nervous system (CNS) (Compton & Walker, 2009), may provide one tentative explanation for the direction of the present findings. Dysmorphic features arise during the formation of the craniofacial region, limbs, and hands, which occurs from roughly the end of the 1st trimester into the early 2nd trimester (Waddington et al., 1999). During this period the hippocampal system (i.e., hippocampus, the dentate gyrus, and the adjacent subicular, entorhinal and perirhinal cortices that form the major afferents and efferents to the system) is one of the first cortical regions to differentiate (weeks 9–10) and it continues to undergo substantial growth and differentiation during the same noted fetal period as the face, forehead, eyelids, nose, chin, arms, hands, and lower limbs become distinguishable (Kier et al., 1997). Further, although multiple brain structures are forming in parallel, the hippocampal system is highly susceptible to a range of early gestational insults and has been linked with schizophrenia (Waddington et al., 1999; Walker et al., 2008).

Insults during the early prenatal period have been robustly associated with characteristics seen in adults with psychosis such as hippocampal abnormalities (Van Erp et al., 2002), which in turn may lead to HPA axis dysregulation. The HPA axis may then influence behavioral expression of vulnerability to schizophrenia through a modulation of cortisol via hippocampal regulated negative feedback to the HPA axis (Mittal et al., 2008a; Walker et al., 2008). There is also extensive evidence that persistent stress or glucocorticoid exposure

leads to hippocampal volume decrease, rendering the whole system more vulnerable in a vicious cascade (Corcoran et al., 2003).

The hippocampal system also has an important role in the formation of new memories about experienced events as well as detection of novel events, places and stimuli. The direction of the present findings also provides some support for the potential hippocampal link. For example, a relevant animal model study evaluating the role of the hippocampus in visual recognition memory tasks in rodents observed that selective lesions of hippocampus impaired delay-dependent visual memory (Prusky et al., 2004), while in contrast, researchers examining the role of hippocampal lesions and auditory memory in a separate animal study did not find a significant relationship among canines, suggesting that the tissue critical for auditory memory is located outside the perirhinal/entorhinal cortices and hippocampus (Kowalska et al., 2001).

Finally, although disorganized symptoms are complex, and are likely the result of several distinct areas of dysfunction, deficits in functions central to hippocampal functioning (e.g., emotion/behavior regulation, forming associations, integration functions) (White et al., 2007) are also likely to contribute to disorganized symptoms. Researchers have noted that individuals with psychosis are especially impaired in cognitive coordination (i.e., segregating relevant and irrelevant stimuli and selectively using associations between relevant cues) (Silverstein et al., 2000), and that this cognitive disorganization is a core deficit in disorganized schizophrenia (Phillips & Silverstein, 2003). Consistent with this notion, studies have implicated that the hippocampus plays a key role in disorganized symptoms, as rat studies have provided evidence that injecting the neural activity blocker tetrodotoxin (TTX) into the hippocampus specifically impaired cognitive coordination (Olypher et al., 2006). Further, Rajarethinam and colleagues (Rajarethinam et al., 2001) observed that hippocampal volume deficits were associated with higher symptoms of thought disorder and disorganized symptoms and, researchers have observed that improvement in disorganized symptoms among individuals with schizophrenia treated with Clozapine are specifically related changes in hippocampal volume (Molina et al., 2005).

A neural diathesis-stress model of schizophrenia posits that interacting genetic and prenatal environmental factors coalesce in an organic vulnerability, observable from an early age via characteristics such as social/affective and cognitive deficits (Walker & Diforio, 1997; Walker et al., 2008). More specifically, a genetic liability may render the fetus more vulnerable to disruptions of fetal neural development and thereby increases the risk of later developing psychotic disorders (Schiffman et al., 2002). The present findings offer preliminary evidence that MPAs may fit within this framework, improving our understanding vulnerability in prodromal youth.

Previous studies of MPAs have been criticized for the potential of rater bias. To address concerns that raters in the present study might be influenced by symptom severity, individuals who were not involved in the other testing conducted assessment of MPAs. It is also important to consider that one benefit of MPAs in this high-risk context is that they serve as a readily observable marker of early insult, which can reflect subtle prenatal upset that isn't necessarily detected by mothers/treatment providers, or confounded by recall bias, which remains a significant limitation of retrospective reports of obstetric complications (McIntosh et al., 2002). A limitation is the potential for false positive results due to multiple comparisons; future collaborative multisite studies with larger samples will allow for more conservative statistical approaches. Future prospective designs and larger samples will also help to elucidate the potential role of MPAs in predicting conversion to psychosis. Previous research has implicated gender differences in facial shape between male and female patient and control groups (Hennessy et al., 2004). To this end, future samples with more evenly

divided gender groups may be useful in identifying any gender effects. Replication studies utilizing refined measures of visual memory are warranted, and stand to inform understanding of how early insult may later impact cognitive functioning in psychosis.

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Table 1

Characteristics of Sample

	Low MPA Group (n=25)	High MPA Group (n=25)	Total Group
<u>Gender</u>			
Males	14	20	34
Females	11	5	16
<u>Age (yrs.)</u>			
M	14.16	14.12	14.14
(SD)	(1.49)	(1.85)	1.66
<u>Parental Education (yrs.)</u>			
M	14.30	15.00	14.66
(SD)	(5.87)	(2.19)	14.36
<u>Medication</u>			
Stimulants	6	8	14
Antidepressants	9	6	15
Antipsychotics	4	5	9

Note: The minimal physical anomaly score from the Waldrop and Halverson Scales ranged from nine to sixty-three (median = 19). The cohort was split at the median into *Low-MPA* and *High-MPA*.

Table 2

Differences in Salivary Cortisol, Memory Function, and Attenuated Symptoms for High-Risk Adolescents with Low and High Incidence of Minor Physical Anomalies

Test Variable	Low MPA Group	High MPA Group	Group Differences
Average Cortisol^a			
Mean(SD)	.41 (.15)	.44 (.17)	2 > 1 **
Memory Domains^b			
<u>Immediate Auditory</u> <u>Logical Memory I</u>	9.12(3.57)	8.72(3.86)	1 = 2
<u>Delayed Auditory</u> <u>Logical Memory II</u>	9.08 (3.92)	9.08 (3.92)	1 = 2
<u>Immediate Visual</u> <u>Family Picture I</u>	9.92 (2.90)	8.32 (3.86)	1 > 2 *
<u>Delayed Visual</u> <u>Family Picture II</u>	9.96 (3.01)	8.12 (3.99)	1 > 2 *
Prodromal Symptoms^c			
<u>Positive</u>	2.24 (.94)	2.25 (.87)	1 = 2
<u>Negative</u>	1.64 (1.07)	1.74 (1.12)	1 = 2
<u>Disorganized</u>	1.30 (.81)	1.59 (1.08)	2 > 1 *

Note:

**
p<0.01

*
p<0.05.

^a Analysis of Covariance: Covariates include age and classes of medication (stimulant, antipsychotic, antidepressant). Cortisol values reflect average of 3 samples collected hourly from 9:00–11:00 am for each participant (the units are listed in (µg/dl)).

^b Independent T-Test.

^c Analysis of Covariance: Covariates include classes of medication (stimulant, antipsychotic, antidepressant).

Table 3

Association Between Minor Physical Anomalies/Craniofacial Dysmorphology and Cortisol, Memory, and Symptoms for the Integrated Sample (N = 50)

	Total Minor Physical Anomalies	Craniofacial Dysmorphology
Average Cortisola^a	.28*	.25*
Memory Domains^b		
<u>Immediate Auditory Logical Memory I</u>	-.16	-.06
<u>Delayed Auditory Logical Memory II</u>	-.10	-.03
<u>Immediate Visual Family Picture I</u>	-.20 [†]	-.14
<u>Delayed Visual Family Picture II</u>	-.21 [†]	-.20 [†]
Prodromal Symptoms^c		
<u>Positive</u>	-.01	-.11
<u>Negative</u>	.08	-.02
<u>Disorganized</u>	.18 [†]	.15

* p<0.05;

[†] p<0.10 (Statistical Trend).

^a Partial Correlations: covariates include age and classes of medication.

^b Bivariate Correlations

^c Partial Correlations: Covariates include classes of medication.