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Association of sFlt-1 and Worsening Psychopathology in relatives at High Risk for Psychosis: A Longitudinal Study

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Abstract

Background—Angiogenic dysfunction and abnormalities in psychopathology and brain structure have been reported in schizophrenia, but their relationships are mostly unknown. We recently demonstrated that sFlt-1, anti-angiogenic factor, was significantly elevated in patients at familial high-risk for psychosis (FHR). We hypothesized that elevated sFlt-1 correlates with baseline and longitudinal changes in psychopathology, cognition, and brain structure.

Methods—Plasma sFlt-1 in FHR (n=35) and HC (n=39) was obtained at baseline. Schizotypal, cognitive, soft neurologic signs, and structural brain imaging (1.5T T1-weighted MRI, FreeSurfer software) measures were obtained in both groups. Longitudinal clinical and brain structural

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Conflict of interest

The authors declare no conflict of interest.

Contributions

Paulo Lizano contributed to study design, data analysis and interpretation, drafting of the article, revising the article, and final approval.

Jeffrey Yao contributed to study design, laboratory assays, data analysis and interpretation, revising the article, and final approval.

Neeraj Tandon conducted data analysis, data interpretation, and revised the article.

Suraj Sarvode Mothi conducted data analysis and revised the article.

Debra Montrose contributed to study design.

Matcheri Keshavan contributed to study design, revising, and final approval.

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measures were obtained in a subgroup of FHR patients. Baseline data analysis used correlations between sFlt-1 and clinical/imaging measures and adjusted for multiple corrections. Linear mixed-effects models described differences in trajectories between high sFlt-1 and low sFlt-1.

Results—Baseline sFlt-1 was significantly correlated with soft neurologic signs ($r=0.27$, $p=0.02$) and right entorhinal volume ($r=0.50$, $p=0.02$), but not other baseline clinical/brain structural measures. Longitudinal examination of the FHR group (sFlt-1 high, $n=14$; sFlt-1 low, $n=14$) demonstrated that high sFlt-1 was significantly associated with worsening schizotypal symptoms ($t=2.4$, $p=0.018$). Reduced right hippocampal/parahippocampal volume/thickness trajectories were observed in high versus low sFlt-1 groups.

Conclusions—The findings from this FHR study demonstrate that peripheral markers of angiogenic dysfunction can predict longitudinal clinical and brain structural changes. Also, these findings further support the hypothesis of altered microvascular circulation in schizophrenia and those at risk.

Introduction

The neurobiological basis of schizophrenia (SZ) has several proposed hypotheses implicating mechanisms (Schizophrenia Working Group of the Psychiatric Genomics, 2014), but its pathophysiology remains to be elucidated. Microvascular abnormality may contribute to the pathophysiology of psychotic disorders, as evidenced by capillary ultra-structural damage, reduced blood flow, altered glucose metabolism, retinal microvascular abnormalities, uncoupling of cerebral blood flow/volume, and arteriolar cerebral blood volume reductions in SZ (Hua et al., 2016; Meier et al., 2013; Talati et al., 2015; Uranova et al., 2010; Uranova, 2013), and investigating angiogenic pathways may provide a novel biological framework for understanding these phenotypes (Lopes et al., 2015). Angiogenesis involves a balance between pro- and anti-angiogenic factors and can result in various pathological conditions (Wu et al., 2010). We recently reported a significant increase of the anti-angiogenesis factor, soluble fms-like tyrosine kinase-1 (sFlt-1) in antipsychotic-naïve familial high-risk for psychosis (FHR) patients that was not present in healthy controls (Lizano et al., 2016). Two small studies have demonstrated sFlt-1 elevations in chronic schizophrenia (Kim T.H., 2007) and severe autism (Emanuele et al., 2010).

sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor with two proposed mechanisms; 1) VEGF trapping and 2) hetero-dimerization with the VEGF receptor (Kendall et al., 1996), altering VEGF receptor mediated signaling (Cindrova-Davies et al., 2011). Little is known about sFlt-1 in SZ, but much is known about VEGF in SZ and neurodevelopment (Dumpich et al., 2015). For instance, a VEGF knockout model resulted in growth-cone path-finding errors and altered optic chiasm development (Erskine et al., 2011). In SZ, post-mortem brain analyses demonstrated reduced VEGF in the prefrontal cortex (PFC) (Fulzele and Pillai, 2009), thalamic VEGF dysregulation (Chu et al., 2009), and increased circulatory VEGF (Pillai et al., 2015). Medications targeting VEGF signaling (sorafenib, sunitinib, and pazopanib) have shown to result in psychosis (Demirci et al., 2015; Kunene and Porfiri, 2011; Kuo et al., 2014) and cognitive (Cao et al., 2004) symptoms, domains affected in psychotic disorders (Tamminga et al., 2014).

In FHR, abnormalities affecting brain structure and function have been identified. A review showed that accelerated volume reductions over time were associated with symptom and cognitive deficits (Thermenos et al., 2013). Also, PFC and hippocampal volume alterations were consistently reported in FHR neuroimaging studies (Thermenos et al., 2013). Investigations correlating angiogenesis biomarkers to brain structure and cognition has been described. VEGF polymorphisms in healthy patients have been associated with hippocampal volume (Blumberg et al., 2008). Elevations in serum VEGF levels were associated with decreased PFC volume (Pillai et al., 2015). An animal model investigating offspring from pre-eclamptic mothers, demonstrated that elevated sFlt-1 had a reduction in brain volume that was prevented with prenatal pravastatin treatment (Carver et al., 2014). Taken together, these findings point to the importance of examining the role sFlt-1 on psychosis risk.

The current study assessed the impact of circulating sFlt-1 levels in antipsychotic-naïve FHR patients on baseline and longitudinal measures of psychopathology, cognition, and brain structure. We hypothesized that elevated sFlt-1 correlates with baseline and longitudinal changes in psychopathology, cognition, neurological function, and brain structure.

Methods and Materials

Participants

The study protocol, consent form, and in the case of minors, assent, with a guardian providing informed consent, were reviewed and approved by the IRB at the University of Pittsburgh and VA Pittsburgh Healthcare System (VAPHS). The FHR participants had either a first- or second-degree relative diagnosed with schizophrenia or schizoaffective disorder. The parental diagnosis was confirmed by Structural Clinical Interview for DSM-IV Axis I (SCID) interviews (First, 2012). Healthy controls (HC) were recruited by advertisements in the same geographic area. The FHR and HC participants were evaluated using the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS), diagnoses were confirmed by consensus (Chambers et al., 1985; First, 2012); participants diagnosed with DSM-IV mental retardation, lifetime psychotic disorder, prior antipsychotic exposure, significant neurological/medical conditions, or IQ <75 were excluded (Keshavan et al., 2008).

Clinical assessments and MRI scans were conducted at several time points. The planned follow-up time was 1, 2 and 3 years, unless onset of psychosis occurred earlier, at which point assessments were conducted soon after transition.

Thirty-five FHR participants had plasma sFlt-1 collected at baseline. Three of 35 participants converted to psychosis (schizophrenia, n=1; schizoaffective, n=2) during the 3 year follow up period. At follow-up, non-converters had either no psychiatric diagnosis (n = 9) or non-psychotic psychiatric disorder (n = 23). For the longitudinal examination of clinical and imaging measures, we median split sFlt-1 in the FHR group.

Clinical assessments

Outcome was assessed by interim medical/psychiatric histories and annual interviews by the same clinicians who assessed the participant at baseline. The Structured Interview for

Prodromal Symptoms (SIPS) and the Chapman Schizotypy Scales (CHAP) were obtained at baseline and follow up. (Chapman et al., 1994). The SIPS scale evaluates positive, negative, disorganized, and general symptoms and rates severity on the Scale of Prodromal Symptoms (SOPS). The CHAP scale includes true-false self-report questions that measure positive (magical ideation and perceptual aberration) and negative schizotypy (Chapman et al., 1994), and the former is predictive for future conversion to psychosis (Diwadkar et al., 2006; Keshavan et al., 2008). The modified neurological evaluation scale (NES) was performed by trained raters and yields two subscale scores (repetitive motor and cognitive-perceptual) (Heinrichs and Buchanan, 1988; Keshavan et al., 2003). Percentage of perseverative errors (PERSERR) committed on the Wisconsin Card Sort Test (WCST) was used to assess executive function (Robinson et al., 1980). In the longitudinal analysis, the FHR group had 28 patients with one or more follow up clinical measures. We performed a median split by sFlt-1 level to create two groups with 14 participants in each group.

Image Processing, Quality Assurance, and Reliability

All magnetic resonance imaging (MRI) scans were conducted at the University of Pittsburgh Medical Center (1.5 T Signa Whole Body Scanner, GE Medical Systems, Milwaukee, WI). At baseline there were 23 FHR and 12 healthy comparison patients with available MRI data. For the longitudinal analysis the FHR group had 13 patients with one or more MRI scans. We performed a median split by sFlt-1 level to create two groups with 7 participants in the high sFlt-1 and 6 in the low sFlt-1 group. All images underwent rigorous quality control, checked for scanner artifacts, and performed blind to participant identity. Images were converted to Neuroimaging Informatics Technology Initiative format and checked for scanner artifacts by trained raters. Images were run through a first-level auto-reconstruction in Free-Surfer 5.1 software. The skull- stripped brains were checked for remaining dura or sinuses that could interfere with accurate segmentation. When non-brain tissue was found, trained raters edited images manually. All raters had inter-rater reliabilities and intra-rater reliability greater than 95%. When deemed sufficiently clean for segmentation by an independent rater, images were run through second- and third-level auto-reconstruction, during which gray matter thickness and volume measures were extracted.

sFlt-1 assay

Plasma samples were collected at baseline after overnight fasting from a total of 74 patients (39 controls, 35 FHR). Samples were de-identified and plasma aliquots frozen at -80°C until use to avoid freeze/thaw cycles. Laboratory analysis was conducted in Dr. Yao's laboratory at VAPHS. Plasma samples were processed with MESO SCALE DISCOVERY'S (MSD) MULTI-ARRAY® Technology (Maryland, DE). The MSD human growth factor panel I assay kit provided quantifications for sFlt-1. MSD is a multiplex immunoassay system with specific capture antibodies for analytes that are coated in arrays, within each well of a 96-well carbon electrode plate. The detection system uses patented SULFO-TAG labels. The electrical stimulation is decoupled from the output signal, which is light, to generate the assays with minimal background. MSD labels can be conveniently conjugated to biological molecules, are stable and non-radioactive. Assays were developed, validated, and raw intensities converted to absolute concentrations after comparison with a standard curve. Technicians ran assays without knowledge of clinical status of the participants.

Statistical Analysis

All statistical analyses were performed using the R statistical analysis software (version 3.1.1). Demographics of HCs and FHR participants were analyzed with independent t-tests or Fisher's exact. sFlt-1 values were normalized through logarithmic transformation due to non-normal distribution. Mean log sFlt-1 values were compared between FHR and HCs using an independent sample t-test. Pearson's correlations were performed among log sFlt-1 and baseline age, CHAP, SOPS, NES, and PERSERR scores. Pearson's correlations were followed by Benjamini and Hochberg adjustment for multiple comparisons (Benjamini, 1995).

The MTL (hippocampal, parahippocampal, and entorhinal) and dorsolateral PFC (DLPFC) grey matter volumes and thickness were compared between HCs and FHR patients using separate univariate analysis of covariances, with age and sex as covariates. Partial Pearson's correlations with age and sex as covariates (ICV for volumetric analysis) were tested on these brain volume/thickness measures and log sFlt-1 in HC and patients separately. The group of analysis of covariance tests and the group of partial correlations were each corrected for multiple comparisons with the Benjamini–Hochberg's correction (Benjamini, 1995). Outliers with more than 4 SDs from the mean were removed (FHR, $n = 1$).

Longitudinal analysis was performed on CHAP, NES and PERSERR by calculating the change in-group trajectories of participants using the lmer function for mixed-effects modeling in the lme4 R statistical package. Mixed effects modeling accounts for nested random effects such as varying time-dependent covariates like 'age at assessment' and availability of subjects at assessment. To determine group differences we setup a conditional growth model with the effects of sex, race and age at assessment*group status as fixed effects. Random effects included an intercept per person to account for within person dependence and random slopes to account for varying assessment age per subject. We also performed mixed effects models for structural MRI constructs (volume/thickness), but the models failed to attain convergence and we attribute it to patient attrition.

Model 1: lmer (CHAP ~time point age + race + sex + (1+time point age| subject))

Model 2: lmer (CHAP ~ time point age x sFlt-1 high-low + race + sex + (1+time point age| subject))

Results

Participant characteristics

The demographic, symptom and log sFlt-1 values for HCs and patients are listed in Table 1. There were significant differences in age between the two groups, with the FHR being younger. There was no significant difference for sex or race between FHR and HC patients. Mean plasma sFlt-1 levels demonstrated a significant increase in the FHR group relative to HCs, $p = 0.002$ (Lizano et al., 2016). Mean NES (repetitive motor, cognitive-perceptual, total) and PERSERR scores revealed a significant increase in the FHR group relative to HC (Table 1). All FHR participants were antipsychotic-naïve, two patients in the FHR group had

either a comorbid alcohol or cannabis use disorder. CHAP and SOPS sub-scores in the FHR group were below the attenuated psychosis threshold (Miller et al., 2002).

Baseline correlations between plasma sFlt-1 levels and symptom or cognition

Plasma sFlt-1 levels did not show significant association with age, CHAP, SOPS, NES, and WCST in either HCs or FHR patients (Supplementary Table 1). There was a significant positive association between NES total (repetitive motor plus cognitive-perceptual) and plasma sFlt-1 in the combined groups ($r = 0.27$, $p = 0.02$, $p\text{-adj} = 0.12$), indicating worsening symptomatology (Supplementary Table 1, Figure 1). Three converters to psychosis have higher sFlt-1 levels and worse NES total scores (Figure 1).

Baseline correlations between plasma sFlt-1 levels and brain volume/thickness

There were no significant group differences in grey matter volume or thickness between FHR and HC patients after co-varying for age and sex. At baseline, partial correlations with age and sex as covariates revealed a significant positive correlation between plasma sFlt-1 levels and right entorhinal volume ($r = 0.50$, $p = 0.02$) in FHR patients (Supplementary Table 2, Figure 2). A trend was noted for a positive association between sFlt-1 levels and right hippocampal and parahippocampal volume in FHR patients (Supplementary Table 2). Plasma sFlt-1 did not correlate with either grey matter volume or thickness in HCs.

Symptomatology trajectories in FHR

A subsample of the FHR group containing both baseline plasma sFlt-1 levels and longitudinal measures for CHAP, NES, and PERSERR were utilized for the trajectory analysis. No significant difference was observed for age, sex, or race in the subsample. Positive t-values for CHAP and WCST indicate worsening symptoms in high sFlt-1 ($n = 14$) compared to the low group ($n = 14$). Negative t-values for NES indicate improving scores. Relative to low sFlt-1, high sFlt-1 exhibited greater worsening of the CHAP magical ideation score ($p = 0.02$), while a trend towards improvement was noted in the NES total score (Figure 3).

Brain volume/thickness trajectories in the FHR group

A subsample of the FHR group containing plasma sFlt-1 levels and grey matter volume/thickness measures was median split into 7 high and 6 low sFlt-1 patients. There was no significant difference in age, sex or race, but a trend was noted for age and race. The sample size was too small to perform statistical analysis due to patient attrition. Descriptively, high sFlt-1 mostly started off with higher volume and thickness measures at baseline that either “caught up” with those in the low sFlt-1 group or showed an ongoing decline. For example, the high sFlt-1 group showed a downward trajectory for the right parahippocampal volume and thickness in comparison to the low sFlt-1 group (Figure 4).

Discussion

We previously described an abnormal angiogenic signature early in the course of SZ (Lizano et al., 2016), which may have important implications for diagnostic and predictive markers. In the present study, we sought to integrate the anti-angiogenic marker, sFlt-1 with clinical

findings to further understand the role of angiogenesis in the pathophysiology of SZ. We evaluated the effect of plasma sFlt-1 on symptom and brain structure in a longitudinal FHR sample. Our findings demonstrate a longitudinal association between sFlt-1 and worsening clinical and brain structural trajectories. Elevated plasma sFlt-1 was correlated with worse baseline NES scores. High sFlt-1 levels were significantly associated with progressive worsening of CHAP magical ideation scores. sFlt-1 was significantly positively correlated with right entorhinal volume and high sFlt-1 demonstrated a trend for right hippocampal volume and parahippocampal thickness loss over time. While the sample size is small, its strengths include a unique sample of FHR relatives that are medication naïve, limited substance use, and below attenuated psychotic symptom level at study inclusion, all of which are commonly confounded in other studies. The longitudinal approach may help resolve the debate regarding the central brain effects of peripheral indices, by demonstrating that peripheral markers predicted clinical and brain structural changes.

The non-finding that sFlt-1 was not correlated with baseline psychopathology was expected (Supplementary Table 1), given that this FHR sample had symptomatology scores below the attenuated psychosis threshold (Miller et al., 2002). We expected elevated baseline levels of sFlt-1 to predict worsening of psychopathology and this was demonstrated utilizing linear mixed effects modeling (Figure 3). No prospective studies examining the role of sFlt-1 with psychopathology exist, but one cross-sectional SZ study didn't find a correlation between serum VEGF and psychopathology (Pillai et al., 2015). A post-mortem study in SZ showed that VEGFR-2 expression was reduced in the PFC and associated with positive symptoms (Hino et al., 2016). Also, there are case reports of psychosis and hallucinations resulting from angiogenesis inhibitor treatment (Demirci et al., 2015; Kunene and Porfiri, 2011; Kuo et al., 2014). A small study of offspring from pre-eclamptic mothers with elevated sFlt-1 (mean levels twice that of HCs), showed an increase in the rate of psychopathology in the offspring from pre-eclamptic mothers compared to controls (Ratsep et al., 2016). These data demonstrate that angiogenic disruption may play a role in worsening psychopathology via sFlt-1 by VEGF trapping, hetero-dimerization with the VEGF receptor (Kendall et al., 1996) or alteration of VEGF receptor mediated signaling (Cindrova-Davies et al., 2011). Future studies could look at the effect of sFlt-1 on psychopathology in first episode psychosis and chronic schizophrenia samples. It would also be noteworthy to determine if the increased rate of schizophrenia in pre-eclamptic mothers is due to elevations of sFlt-1 during pregnancy.

Soft neurologic signs were significantly different between HC and FHR (Table 1), and has been previously demonstrated (Neelam et al., 2011; Prasad et al., 2009). sFlt-1 correlated with soft neurologic signs at baseline (Figure 1) and trended towards improving trajectories (Figure 3), suggesting that sFlt-1 might be a state marker for neurologic dysfunction. Soft neurologic signs are an important endophenotype in SZ with strong familial association (Neelam et al., 2011) and brain structural correlates (Zhao et al., 2014). This is the first study examining the role of sFlt-1 on soft neurologic signs. Our data is in agreement with a mouse model of pre-eclampsia induced by pregnancy-specific overexpression of sFlt-1, where offspring displayed impairments in balance and coordination, and was prevented with maternal pravastatin treatment (Carver et al., 2014). These findings may transform our understanding of the pathophysiologic role of angiogenesis in altering the soft neurologic

signs endophenotype, with the potential for novel therapeutic avenues. Future studies should look at the effects of sFlt-1 on soft neurologic signs in first episode and chronic schizophrenia patients, as well as offspring from pre-eclamptic mothers.

We identified significant positive correlations between sFlt-1 and right entorhinal volume (Figure 2) in FHR patients with a positive trend noted for the right hippocampal and parahippocampal volumes (Supplementary Table 2). This finding demonstrates that normal circulatory levels of sFlt-1 do not have an effect on brain structure, while elevated levels may be utilized as a target for brain structural trajectories. This finding may suggest that attenuation of angiogenesis could explain the shift towards a more pathologic process that initially results in brain structural enhancement followed by accelerated grey matter loss. The longitudinal analysis showed two important findings: 1) high sFlt-1 had mostly larger baseline volume/thickness measures compared to the low sFlt-1 group; 2) high sFlt-1 mostly showed downward trajectories compared to an upward trend in the low sFlt-1 group (Figure 4). While these findings are interesting, the sample size was too small to determine significance. This is the first longitudinal study evaluating the effects of sFlt-1 on brain structure in psychotic disorders. Only a few studies have looked at the effects of angiogenesis on brain structure. A mouse model of pre-eclampsia with sFlt-1 overexpression demonstrated brain structural impairments in offspring, an effect that was attenuated with maternal pravastatin treatment (Carver et al., 2014). A similar study in humans, offspring of pre-eclamptic mothers with elevated sFlt-1 showed brain structural and vascular changes compared to controls (Ratsep et al., 2016). In a cross-sectional study of schizophrenia, an inverse correlation between serum VEGF and frontal pole volume was identified (Pillai et al., 2015). A longitudinal Alzheimer's study demonstrated that elevated CSF VEGF was associated with optimal brain aging (Hohman et al., 2015), suggesting that anti-angiogenesis factors could have a contrasting effect. Another study measured the effects of cytokines in clinical high risk for psychosis patients and showed that a pro-inflammatory aggregate (TNF- α , IL-2, and IFN- γ) at baseline was strongly predictive of steeper rates of gray matter reduction in the right PFC of cases transitioned to psychosis (Cannon et al., 2015). Taken together this demonstrates that baseline sFlt-1 could be used to 1) determine brain structural trajectories, 2) that dysregulation of angiogenesis could be detrimental to brain structure, and 3) that VEGF studies can provide a conceptual framework for understanding our current findings. Future studies will need to examine the effects of sFlt-1 on brain structure in a first episode and chronic schizophrenia sample, as well as the effects of maternal preeclampsia on the neurodevelopment of their offspring.

The mechanism for increased sFlt-1 in the schizophrenia population is currently unknown. There are several hypothesized mechanisms by which sFlt-1 could be increased in this population. A functional genomic analysis of available schizophrenia-associated genes from candidate gene, genome-wide association and postmortem expression studies found an overrepresentation of genes involved in vascular function that support both the neurodevelopmental and adult vascular-ischemic hypothesis (Moises et al., 2015). In a study of pregnant mothers and their offspring, the FLT1 genotype has been associated with sFlt-1 levels (Muehlenbachs et al., 2008). The gene-environment interaction of vascular genes and obstetrical complications is of particular interest in schizophrenia (Schmidt-Kastner et al., 2012). Additionally, sFlt-1 could be directly regulated by VEGF (Fan et al., 2014), microglia

activity (Ryu et al., 2009), or inflammation (Muehlenbachs et al., 2008). We hypothesize that sFlt-1 and other genes related to angiogenesis contribute to schizophrenia risk from a neurodevelopmental standpoint with environmental influences.

Angiogenic perturbations due to increased sFlt-1 expression might attenuate VEGF-mediated arterial differentiation (Mukouyama et al., 2005), vasoregulation (Rosenstein et al., 2010), venular development (Stalmans et al., 2002), and capillary density (DiPietro, 2016) via the mechanisms discussed above. Due to advances in retinal and neuroimaging, it is now possible to study arteriolar, venular, and vasoregulatory mechanisms in vivo and there are a few studies implicating microvasculature disruption in patients with schizophrenia (Allen et al., 2016; Hua et al., 2016; Meier et al., 2013). Developmentally, a large longitudinal study showed that second trimester maternal angiogenesis levels were associated with narrower childhood retinal arteriolar caliber, but not with retinal venular caliber (Gishti et al., 2015). Thus, elevations in sFlt-1 could have lasting effects on microvascular structure, fluid dynamics, and neurodevelopmental processes and have the potential to inform diagnosis, prognosis, and treatment.

Limitations of this study include the small sample size and sample attrition, which resulted in nearly 20% loss to follow up. This level of attrition had the greatest impact on the longitudinal structural imaging analysis that limited statistical analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

At baseline, plasma sFlt-1 levels show a significant positive correlation with neurologic evaluation scale (NES) total score in healthy control (HC) and familial high-risk (FHR) subjects ($n = 68$). Shapes depict group distributions; HC (●) and FHR [32 non-converters (no-conv, ▲) and 3 converters to psychosis (conv, ■)].

Figure 2.
At baseline, plasma sFlt-1 levels show a significant positive correlation with the right entorhinal cortical gray matter volume in familial high-risk (FHR) subjects compared to healthy controls.

Figure 3.

a) Values from t-tests for group-by-age slope interactions. Groups are sFtl-1 high ($n = 14$) versus low ($n = 14$). Positive t-values for CHAP MI (magical ideation), PA (perceptual aberration), and WCST (perseverative error) indicate worsening symptoms in sFtl-1 high compared to low subjects, with CHAP MI showing a significant difference (*, $p = 0.02$). Negative t-values for NES RM (repetitive-motor), CP (cognitive-perceptual) and Total indicate improving scores, with a trend towards significance for NES Total. b) Plot of individual (high versus low sFtl-1) CHAP magical ideation scores, by assessment age, showing a worsening symptom trajectory for high sFtl-1 subjects. Abbreviations: CHAP, Chapman schizotypy scale; NES, Neurological Evaluation Scale; WCST, Wisconsin card sorting test.

Figure 4.

Plots of individual (sFlt-1 high $n = 7$ versus low $n = 6$), right parahippocampal grey matter volume and thickness (mm³), by scan age, demonstrating progressive structural loss of left parahippocampal volume and thickness for high sFlt-1 subjects.

Table 1

Demographic information for HC and FHR

	HC		FHR		T-test/Fisher's exact test	
	N	Mean (s.d.)	N	Mean (s.d.)	p-value	
Age (years)	39	25.1±1.0	35	16.5±0.6	<0.001	
Gender (M/F)	39	25/14	35	15/20	0.08	
Race (Cau/AA/other)	39	24/10/5	35	15/20/0	0.10	
Anti-angiogenesis marker						
Plasma sFlt-1 (pg/ml)	39	106±7.7	35	182±19	0.002	
Psychopathology						
CHAP Magical Ideation	-	-	32	3.6±0.5		
CHAP Perceptual Aberration	-	-	32	2.1±0.4		
SOPS Positive Symptoms	-	-	20	0.3±0.1		
SOPS Disorganized Symptoms	-	-	20	0.7±0.3		
NES						
Repetitive-Motor	35	0.19±0.05	33	0.32±0.08	<0.001	
Cognitive-Perceptual	35	0.18±0.04	33	0.29±0.08	0.002	
Total	35	0.24±0.03	33	0.32±0.05	<0.001	
WCST						
Preservative Error	36	10.7±1.3	33	14.2±1.5	0.002	

Abbreviations: HC, healthy control; FHR, familial high risk for psychosis; s.d., standard deviation; M, Male; F, Female; Cau, Caucasian; AA, African American; sFlt-1, soluble fms-like tyrosine kinase; CHAP, Chapman schizotypy scale; SOPS, Scale of Prodromal Symptoms; NES, Buchanan and Heinrichs Neurological Evaluation Scale; WCST, Wisconsin card sorting test. Bold p-values indicate significant results.