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Retinal microvessels reflect familial vulnerability to psychotic symptoms: A comparison of twins discordant for psychotic symptoms and controls

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ABSTRACT

Mounting evidence suggests that individuals with schizophrenia have an underlying vulnerability to cardiovascular disease, and a recent study suggested that this vulnerability might be reflected in the retinal microvasculature. The purpose of this study was to test the hypothesis that the retinal microvessels reflect familial vulnerability to psychotic symptoms. Participants were 531 adolescent and young adult twins who took part in the Brisbane Longitudinal Twin Study and the Twins Eye Study in Tasmania. The twins had photographs taken of their retina when they were adolescents or young adults (M age = 20.6 years), and retinal vessel diameter was assessed using computer software. The twins completed an assessment of psychosis symptoms approximately six years later. We compared retinal venular diameters of individuals with one or more symptoms of psychosis (n = 45), their unaffected co-twins (n = 24), and controls (n = 462). Individuals with one or more symptoms of psychosis had wider venules (standardized mean = 0.29) than controls (standardized mean = −0.04; p = .03), and unaffected co-twins had venular diameters that were intermediate (standardized mean = 0.13) between the two groups, suggesting that wide venules may represent a proxy marker of familial vulnerability to psychosis symptoms. Consistent with previous work, there were no differences in arteriolar diameter between individuals with and without symptoms of psychosis. Findings suggest that wide retinal venules may serve as a proxy marker of familial liability to psychosis symptoms. The pathophysiological mechanisms linking psychosis and cardiovascular disease may be operative from early in life, possibly at the level of the microvasculature.

1. Introduction

Individuals diagnosed with schizophrenia are disproportionally affected by cardiovascular and cerebrovascular diseases (Bresee et al., 2010; Carney et al., 2006; Crump et al., 2013; Fan et al., 2013; Hennekens et al., 2005; Lahti et al., 2012; Lin et al., 2008), and their elevated rates of these diseases cannot be fully explained by lifestyle factors, such as smoking or use of antipsychotic medication (Fan et al., 2013; Osborn et al., 2007). Mounting evidence suggests that individuals with schizophrenia may have an underlying liability to cardiovascular disease (Andreassen et al., 2013; Correll et al., 2014; Kohen, 2004; Ryan et al., 2003; Spelman et al., 2007), and a recent study suggested that this liability might be reflected in the retinal microvasculature (Meier et al., 2013).

The retinal microvasculature offers a unique opportunity to visualize the microcirculation in vivo. The condition of the retinal microvessels

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can used to gauge the condition of the microvessels in the heart and brain, because the microvasculatures of the retina, heart, and brain are similar (Cheung et al., 2012; Patton et al., 2005). Prior research has shown that the retinal microvessels are sensitive to a range of cardiovascular risks (Ikram et al., 2013; Sun et al., 2009b), and wider retinal venules (veins) predict risk of coronary heart disease (McGeechan et al., 2009a; Wong et al., 2006b), stroke (Cheung et al., 2013; McGeechan et al., 2009b; Wong et al., 2006b; Yatsuya et al., 2010), cognitive impairment (Shalev et al., 2013), and dementia (de Jong et al., 2011) independently of other cardiovascular risks.

In an initial study of a population-representative cohort from New Zealand (the Dunedin Study), adults diagnosed with schizophrenia were distinguished from other cohort members by wider retinal venules, even after accounting for other cardiovascular risks (high blood pressure, pre-diabetes/diabetes, persistent tobacco dependence) (Meier et al., 2013). Further, adults with symptoms of psychosis and cohort children who exhibited symptoms of psychosis but did not develop schizophrenia had wider venules as adults (Meier et al., 2013), suggesting that wide retinal venules may be related to vulnerability to schizophrenia rather than the disease process itself (Malaspina, 2013). Based on these initial findings, we hypothesized that 1) wide venules may be apparent among adolescents and young adults who experience symptoms of psychosis, and 2) wide venules may be apparent among the unaffected relatives of adolescents and young adults with symptoms of psychosis. We tested these hypotheses in a sample of adolescent and young adult twins.

2. Materials and methods

2.1. Participants

Participants were members of the Brisbane Longitudinal Twin Study, an ongoing study of adolescent and young-adult monozygotic (MZ) and dizygotic (DZ) twin pairs and their siblings (Gillespie et al., 2013; Wright and Martin, 2004). As described in detail elsewhere (Gillespie et al., 2013; Wright and Martin, 2004), twins were initially recruited to the study from primary and secondary schools in South East Queensland in 1992, with new twins added at various intervals. All schools in South East Queensland were approached, and all regions in South East Queensland were represented. Comparisons of this sample with other population-based samples suggest that this sample is representative with respect to a variety of traits, including, for example, personality (de Moor et al., 2012) and retinal vessel diameter (Ikram et al., 2010; Mitchell et al., 2007).

The twins have undergone a variety of phenotypic assessments, including, most recently (and ongoing), an assessment of psychosis symptoms. A subset of participants also completed an extensive eye examination as part of the Twins Eye Study in Tasmania (Mackey et al., 2009; Sun et al., 2009c). Here we report on 531 participants for whom both eye exam and psychosis symptom data were available. These 531 participants included n = 45 individuals with one or more symptoms of psychosis (probands), n = 24 unaffected co-twins of the probands, and n = 462 controls (participants with no symptoms of psychosis). Demographic information for these participants is presented in Table 1. The study was approved by the ethics committees of the Royal Victorian Eye and Ear Hospital, the Royal Hobart Hospital, and the QIMR Berghofer Medical Research Institute, as well as the Australian Twin Registry, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all of the participants or their legal guardians, with the participants' assent before examination.

2.2. Measures

2.2.1. Psychosis symptoms

Participants reported on six lifetime symptoms of psychosis during either a computer-assisted telephone interview or an online survey using the same items (Gillespie et al., 2013). Symptoms were taken from the modified Composite International Diagnostic Interview (CIDI) (Kessler et al., 2005). Several studies of community samples have shown that CIDI-assessed psychosis symptoms correlate with demographic factors and psychiatric symptoms in expected ways (Scott et al., 2006, 2008; van Os et al., 2001; Varghese et al., 2011). In our sample, CIDI-assessed psychosis symptoms were associated with mental health problems ($r = 0.19$, $p < .001$), assessed with the Somatic and Psychological Health Report (Hickie et al., 2001a,b), and smoking ($F = 4.19$, $p = .040$), similar to other measures of psychotic experiences given in community-based samples (Kelleher and Cannon, 2011; Kelleher et al., 2012). Table 2 shows the prevalence of each psychosis symptom, and the prevalence of each symptom matched the prevalence in the larger study from which participants were drawn. Because of the rarity of some of the symptoms, we collapsed the responses into a single categorical variable reflecting the presence versus the absence of symptoms.

Table 1
Means (standard deviations) on demographic variables and health risks for controls, unaffected co-twins, and probands.

	Controls	Unaffected co-twins	Probands
	N = 462	N = 24	N = 45
Sex (% female)	61	58	58
Age at eye exam	20.74 (3.56)	19.67 (3.00)	19.91 (3.09)
Age at psychosis symptom assessment	26.70 (3.53)	26.13 (3.59)	26.04 (3.27)
Smoker (%)	16	25	27
Body mass index	22.51 (3.63)	22.54 (4.06)	23.43 (4.55)

Note. All pairwise comparisons between groups were non-significant.

2.2.2. Retinal vessel diameter

As previously described (Sun et al., 2009a,c), all of the twins had 10° stereoscopic optic disc–centered photographs using a Nidek 3-Dx/F fundus camera (Nidek) after dilatation of the pupils with tropicamide 1% or cyclopentolate 1%. Photographs were digitalized, and retinal vascular diameter was measured with computer-assisted software (IVAN, University of Wisconsin, USA) according to a standardized protocol (Wong et al., 2004). Two trained graders, masked to participant characteristics, performed the vessel measurements on the optic disc–centered image for both eyes for all of the participants. The largest 6 arterioles and venules coursing through a zone between half to 1 disc diameter from the optic disc margin were measured. As in the Dunedin Study (Meier et al., 2013), estimates were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), representing the average diameter of arterioles and venules of the eye, respectively, using a revised Knudtson–Parr–Hubbard formula (Knudtson et al., 2003). Intragrader variation was assessed in 67 randomly selected retinal photographs. The intragrader intraclass correlation coefficient was 0.95 for CRAE and 0.99 for CRVE. Intergrader reliability was assessed in 52 randomly selected retinal images, and the interclass correlation coefficient was 0.93 for CRAE and 0.98 for CRVE. The correlation between CRVE and CRAE was 0.51 (Sun et al., 2009c).

Table 2
Prevalence of psychosis symptoms among adolescents and young adults (n = 531).

Symptom	N	%
Saw a vision that other people could not see.	26	5
Heard voices that other people could not hear.	19	4
Experienced mind control (thought insertion or extraction).	3	0.6
Felt that mind was being taken over by strange forces.	3	0.6
Experienced attempts at communication from strange forces.	5	1
Believed there was a plot to harm you.	5	1

Note. '0' symptoms: n = 486; '1' symptom: n = 33; 2+ symptoms: n = 12. The prevalence of each psychosis symptom matched the prevalence in the larger study from which participants were drawn.