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Paternal Age Related Schizophrenia and Cardiac Autonomic Regulation Profiles

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We have proposed that “paternal age related schizophrenia” (PARS) is a subtype of schizophrenia with distinct symptom and cognitive profiles, regional cerebral metabolism, and sex effects (Malaspina et al., 2001; 2002; 2005; Rosenfield et al., 2009). These neurobiological features may be associated with abnormal cardiac autonomic regulation, as increased paternal age has been linked to elevated risk for heart defects in non-schizophrenia populations (Olshan et al., 1994).

Cardiac autonomic abnormalities are commonly reported in schizophrenia (Chang et al., 2009), and reduced heart rate variability (HRV; the heart's beat-to-beat variability which is linked to the autonomic nervous system and a person's response to stressors) is associated with acute psychotic states in schizophrenia (Valkonen-Korhonen et al., 2003). Lower HRV is associated with an activation imbalance between frontal and limbic regions in healthy subjects (Mujica-Parodi et al., 2009); a pattern which is similar to the resting regional perfusion profile we demonstrated for sporadic schizophrenia cases with older fathers (Malaspina et al., 2004). However, the relation between HRV and paternal age in schizophrenia is unknown. To that end, we conducted a pilot investigation to examine if cases with PARS have distinct profiles of cardiac autonomic regulation.

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All work for this study was completed at New York State Psychiatric Institute.

Contributors: Drs. Malaspina, Harkavy-Friedman, and Ray Goetz were involved in the design and writing of the study protocol. Drs. Kimhy and Goetz managed literature reviews and statistical analyses pertaining to the study. Drs. Malaspina, Antonius, Kimhy, Goetz and Crystal were involved in the writing of various drafts and the final manuscript. All authors contributed to and have approved the final manuscript.

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We compared 24-hour HRV between 18 schizophrenia patients, 4 with PARS and 14 Non-PARS, and 24 healthy controls. Diagnoses were obtained using the Diagnostic Interview for Genetic Studies and psychopathology was assessed in patients with the Positive and Negative Syndrome Scale (PANSS). The study was approved by the New York State Psychiatric Institute.

PARS was defined as the absence of any family history of psychotic disorders among first- and second-degree relatives and a fathers' age at the birth of the proband being ≥ 34 years; all other cases were considered Non-PARS. All subjects were physically healthy as indicated by physical examinations and laboratory evaluations. There was no cardiovascular, respiratory or endocrine illness, or current substance abuse. 12 patients were taking antipsychotic medication (PARS: no antipsychotic medication = 2 patients, typical antipsychotic medication = 2; Non-PARS: no antipsychotic medication = 4, typical antipsychotic medication = 1, atypical antipsychotic medication = 9).

Cardiac autonomic regulation was assessed with 24-hour ambulatory ECG monitors, while participants carried out their normal activities. The data were digitized using a Marquette 8000 scanner, and normalized for heart rate using natural log (Ln) transformations of msec². HRV was measured in spectral powers integrated into: High Frequency (HF; 0.15-0.50 Hz), Low Frequency (LF; 0.04-0.15 Hz), Very Low Frequency (VLF; 0.0033-0.04 Hz), and Ultra Low Frequency (ULF; 0-0.0033 Hz). Awake and sleep periods were confirmed using hourly inspection of R-R intervals to detect sustained drops in heart rate.

There were no significant differences between the groups on age, sex, duration of illness, ethnicity, and PANSS positive and negative symptoms (supplementary data). A repeated-measures Analysis of Covariance (ANCOVA) with age, sex, and medication status as covariates, diagnosis (PARS, Non-PARS, and controls) as the grouping factor, and awake vs. sleep as the repeated measure revealed no significant group effects for any of the frequency bands (Table 1). However, there was a significant time effect for the HF band and a strong trend for the ULF band, and marginally significant interaction terms (group-by-time) for the HF ($p=.071$) and ULF ($p=.068$) bands. Due to the uniqueness of the data, we conducted pairwise posthoc comparisons which revealed that while the PARS and Non-PARS groups did not significantly differ from the healthy control group, they did differ from each other. The pairwise comparison of the PARS and Non-PARS groups revealed a significant group-by-time interaction for the HF ($F=6.21$, $df=1/13$, $p=.027$) and ULF ($F=5.06$, $df=1/13$, $p=.042$) bands (supplementary data).

These posthoc results suggest that in PARS patients, wake period ULF activity was similar to that observed in healthy controls, and both were higher than in Non-PARS patients. During sleep, however, ULF activity in PARS patients declined significantly compared to the Non-PARS group. Interestingly, the lower sleep ULF values in both PARS and Non-PARS are similar to previous findings of lower sleep ULF in panic disorder patients (Yeragani et al., 1998). The unique ULF pattern found among the PARS patients may be particularly critical and should be further examined in future prospective studies. Other research suggests that aberrant and reduced HRV is related to increased risk for cardiac events (Tsuji et al., 1996), and individuals with schizophrenia are in general at higher risk for coronary heart disease and sudden cardiovascular mortality (Goff et al., 2005). It is currently unknown what the contribution of PARS is to cardiac events in people with schizophrenia.

The posthoc results also indicate that the PARS patients exhibited significantly smaller sleep-related rise in HR power compared to the other two groups, who displayed typical

increases. Since HF is related to parasympathetic activity, these results may suggest that in the PARS patients, a distinct parasympathetic activity pattern is indexed by the HF band.

Our findings lend support to the growing literature that suggests PARS may be a distinct subtype of schizophrenia. However, our results should be interpreted with caution. Limitations include the small sample and lack of significant group differences or group and time interactions in our initial analyses. It should be noted that in a separate, less conservative ANCOVA test, in which we did not control for medication status, we found significant group differences for all frequency bands (all $p \leq .003$; supplementary data). Additionally, we did not control for menstrual cycle phases in our analyses; HRV has been found to vary between the follicular and luteal phases (Sata et al., 1995). Future research should examine in larger samples differences in cardiac autonomic regulation between PARS and Non-PARS patients, as well as effects of menstrual cycles and medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Means, standard deviations, and the results of the repeated measures Analyses of Covariance (ANCOVA) for group effects on frequency bands during awake and sleep periods, controlling for sex, age and medication status.

Frequency Band	Period	PARS (n=4)		Non-PARS (n=14)		Healthy Controls (n=24)		Group Effect	Time Effect	Group/Time Interaction
		M	SD	M	SD	M	SD			
HF	Awake	5.22	.98	3.26	1.39	5.26	.82	F= 1.58 P= .220	F= 5.31 P= .027 *	F= 2.84 P= .071
	Sleep	5.45	1.57	4.27	1.65	6.00	.72			
LF	Awake	5.95	.76	4.58	1.39	6.42	.51	F= 1.85 P= .172	F= 0.00 P= .966	F= 0.41 P= .669
	Sleep	6.04	1.13	4.96	1.21	6.64	.55			
VLF	Awake	6.69	.63	5.51	1.17	6.96	.55	F= 1.09 P= .347	F= 3.41 P= .073	F= 0.58 P= .565
	Sleep	7.01	1.10	5.89	1.14	7.38	.57			
ULF	Awake	8.17	1.16	7.01	.87	8.18	.73	F= 0.31 P= .732	F= 3.99 P= .053	F= 2.90 P= .068
	Sleep	6.94	.80	6.99	1.40	8.07	.84			

* indicates statistical significance

Spectral powers are in Ln (natural log) of msec²; PARS - Paternal Age Related Schizophrenia; HF - High Frequency; LF - Low Frequency; VLF - Very Low Frequency; ULF - Ultra Low Frequency.