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Neonatal Skin-to-Skin Contact: Implications for Learning and Autonomic Nervous System Function in Infants With Congenital Heart Disease

Tondi M. Harrison, PhD, RN, FAAN[1], Chao-Ying Chen, PhD, MS, PT[2], Phyllis Stein, PhD[3], Roger Brown, PhD[4], and Jill C. Heathcock, MPT, PhD[5]

Abstract

Background: Infants with complex congenital heart disease (CCHD) often develop neurodevelopmental disabilities. Cognitive abilities are associated with vagally mediated autonomic function. Skin-to-skin contact (SSC) interventions enhance infant neurodevelopment and autonomic function in other high-risk populations. **Aim:** To examine the effects of a neonatal SSC intervention on learning and autonomic function in 3-month-old infants: infants with CCHD who received neonatal SSC ($n = 10$), typically developing (TD) infants ($n = 16$), and infants with CCHD without SSC ($n = 10$). **Methods:** This secondary data analysis measured cognitive function using the mobile paradigm (MP), a classic measure of learning based on operant conditioning. Autonomic function was assessed with heart rate (HR) and HR variability (HRV). Data were analyzed with repeated-measures general linear mixed modeling with $\alpha = .10$ for this exploratory study. **Results:** Learning rates were TD = 75%, cardiac-SSC = 70%, and cardiac-control = 40%. Learners demonstrated significant reductions in HRV during the MP; nonlearners exhibited no change. TD and cardiac-SSC groups exhibited increases in HR and reductions in HRV during the MP. No significant changes occurred in the cardiac-control group. Nonlinear HRV during the MP differed only in the TD group. **Conclusions:** Findings suggest improvements in cognitive and autonomic development in 3-month-old infants with CCHD who received neonatal SSC. Learning and autonomic function results in infants with CCHD who had not received SSC suggest reduced capacity to muster the physiologic resources to carry out this cognitive task. Findings provide preliminary evidence in support of implementation of SSC with infants with CCHD and support additional research.

Keywords

congenital heart disease, autonomic nervous system, skin-to-skin contact, heart rate variability, neurodevelopment

Worldwide, more than 400,000 infants are born each year with complex congenital heart disease (CCHD), requiring surgical intervention within the first weeks of life (van der Linde et al., 2011). About half of these infants experience neurodevelopmental disabilities including cognitive delays (Marino et al., 2012). These neurodevelopmental sequelae of CCHD result from biological and environmental factors that adversely affect brain development during a critical period of rapid brain growth (Andropoulos et al., 2014; Marino, 2013). Techniques to support and protect the infant brain before and after surgery and to assist in creating an environment supportive of brain development are urgently needed. These techniques may include supporting development of the autonomic nervous system (ANS) and fostering sensitive maternal caregiving (Harrison, 2009; Harrison & Ferree, 2014; Marino, 2013; McCusker et al., 2010), both of which are widely recognized critical factors in optimizing infant development, especially in the first months of life (Feldman, Rosenthal, & Eidelman, 2014; Perry, Blair, & Sullivan, 2017).

According to Schore's regulation theory, interactions between the mother and her infant directly influence the infant's brain development through highly complex interactions between maternal sensory stimuli and infant neurobiological responses (Schore, 1996). A major component of these

[1] The Ohio State University College of Nursing, Columbus, OH, USA
[2] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong
[3] Washington University in St. Louis, St. Louis, MO, USA
[4] Medical Research Consulting, Middleton, WI, USA
[5] The Ohio State University School of Health and Rehabilitation Sciences, Columbus, OH, USA

Corresponding Author:
Tondi M. Harrison, PhD, RN, FAAN, The College of Nursing, Martha S. Pitzer Center for Women, Children, and Youth, Newton 360, 1585 Neil Avenue, Columbus, OH 43210, USA.
Email: harrison.473@osu.edu

neurobiological responses occurs in the ANS. Schore demonstrated that sensitive maternal caregiving supports the development of coordinated responses of the sympathetic and parasympathetic divisions of the infant's ANS. Stimulating, positive maternal–infant interactions are associated with predominantly sympathetic activity, while maternally supported recovery from arousal (i.e., relaxation) is associated with predominantly parasympathetic (vagus nerve) activity. The highly technological intensive care unit (ICU) entails exposure to multiple stimulating stressors including noise, light, interrupted sleep, and pain (Daniels & Harrison, 2016), which result in prolonged sympathetic nervous system activation without access to a source of relaxation, potentially modifying the balanced development of the ANS (Daniels & Harrison, 2016; Schore, 1996).

Positive sensory experiences are the foundation for infant brain development (Chorna, Solomon, Slaughter, Stark, & Maitre, 2014). The physical presence of the mother, with the host of sensory stimulation contained in her presence, is the basic regulatory framework for development of the infant's autonomic, endocrine, and behavioral function (Feldman, 2007; Hofer, 1994; Schore, 1996). Interactions between mothers and their newborn infants occur primarily while the mothers are holding their infants (Feldman, 2007). Infants hospitalized with CCHD have little opportunity to experience critical neuroprotective maternal stimuli (Reynolds et al., 2013). Restricted mother–infant physical contact is associated with multiple adverse outcomes including fragmented sleep–wake states, impaired gross and fine motor skills, higher levels of arousal and excitability, and greater infant behavioral stress cues (Reynolds et al., 2013; Scher et al., 2009).

The act of holding an infant, undressed except for a diaper, next to the mother's skin provides a multisensory experience for both mother and infant, stimulating olfactory, tactile, auditory, visual, kinesthetic, vestibular, and thermoregulatory systems (Bloch-Salisbury, Zuzarte, Indic, Bednarek, & Paydarfar, 2014). Mother-provided skin-to-skin contact (SSC) interventions have neuroprotective effects in hospitalized premature infants, including improved autonomic function (Feldman & Eidelman, 2003), enhanced neurodevelopment (Feldman, Weller, Sirota, & Eidelman, 2002), and better cognitive skills (Feldman et al., 2014).

Cognitive abilities are associated with vagally mediated autonomic function (Hansen, Johnsen, & Thayer, 2003; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Prefrontal cortex activity during cognitive tasks results in inhibition of the vagus (i.e., vagal withdrawal), enabling suppression of irrelevant stimuli and selective attention to the task (Hansen et al., 2003; Thayer et al., 2009). Autonomic function can be measured using heart rate variability (HRV), a result of the precise regulation of the intervals between heart beats due to constant input from both the sympathetic and parasympathetic nervous systems (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Measurement of HRV can be performed using frequency domain methods that partition the total variance of heart rate (HR) into various underlying rhythms that can be linked to physiologic processes (e.g., thermoregulation or baroreceptor activity). Specifically, the variance in beat-to-beat intervals at the rhythm of respiration, known as high-frequency power HRV (HF HRV), is an accepted marker of vagal (parasympathetic nervous system) control of HR (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Thus, HF HRV provides a potential index of prefrontal activity during a task (i.e., lower HF HRV in association with a cognitive task would indicate cognitive engagement). Along with vagal withdrawal during cognitive tasks, sympathetic activity (indexed by HR) is increased. Research has demonstrated that higher HRs are associated with cognitive challenge in adults (Hansen et al., 2003), children (Wolfe & Bell, 2004), and infants (Lewis, Hitchcock, & Sullivan, 2004).

Nonlinear measurements of HRV, such as detrended fluctuation analysis (DFA), provide insights into the organization, rather than the magnitude, of the changes in HR signal. In healthy adults, short-term DFA decreases with challenging physical activity (Chen, Liaw, Chang, Chuang, & Chien, 2015). Similar decreases may be expected with focused attention to a cognitive task. Nonlinear measures have rarely been examined in infants with CCHD (Harrison & Brown, 2017; Smith et al., 2009) and may provide additional information about potential effects of unopposed sympathetic activity on HRV in this population.

The purpose of this reanalysis of existing data was to examine the effect of a neonatal SSC intervention on infant cognitive and autonomic function at 3 months. A learning task was presented, and concurrent autonomic activity was measured in 36 three-month-old infants: one group ($n = 10$) with CCHD who received a neonatal SSC intervention and two control groups including 10 infants with CCHD receiving routine care without SSC and 16 typically developing (TD) infants. Our research questions were as follows: (1) To what extent does cognitive function differ among the groups? (2) To what extent does autonomic function differ among the groups? and (3) To what extent is cognitive function associated with autonomic function in these infants?

Method

Design

This study was a secondary analysis combining data from two pilot studies. The first was conducted over 17 months and included 16 TD infants and 10 infants with CCHD (cardiac-SSC) who were recruited to refine and test a 14-day SSC intervention. The second pilot study was conducted over the subsequent 21 months and included 10 infants who had not received SSC (cardiac control) and who participated in a descriptive study of neurodevelopment in infants with CCHD. Because these were pilot studies conducted to refine study methods and determine effect sizes for future larger studies, we did not conduct power analyses (Fairchild & MacKinnon,

Table 1. Sample Characteristics.

Characteristic	TD ($n = 16$)	Cardiac-SSC ($n = 10$)	Cardiac-Control ($n = 10$)
Maternal age (years)	31.8 ± 5.2	29.0 ± 6.0	26.1 ± 5.0
Household income[a]			
<US$30,000	4 (25.0)	4 (40)	4 (40)
US$30,000–70,000	3 (18.8)	—	3 (30)
>US$70,000	9 (56.3)	6 (60)	2 (20)
Infant gender, male	6 (37.5)	7 (70)	6 (60)
Infant ethnicity/race[a]			
Non-Hispanic/Black	2 (12.5)	—	2 (20)
Non-Hispanic/White	13 (81.3)	9 (90)	7 (70)
Hispanic/multiracial	1 (6.3)	—	—
Non-Hispanic/American Indian	—	1 (10)	—
Cardiac disease[b,c]			
Single ventricle	—	4 (40)	6 (60)
Transposition	—	4 (40)	3 (30)
Interrupted aortic arch	—	1 (10)	0
Tetralogy of Fallot	—	1 (10)	0
Coarctation	—	0	1 (10)
Infant age at surgery (days)	—	7.10 ± 3.4	8.30 ± 5.2
ICU LOS (days)	—	3.70 ± 2.3	4.41 ± 3.3[d]
Hospital LOS (days)	—	13.50 ± 4.7	15.00 ± 3.6[d]

Note. Data are presented as mean ± *SD* or *n* (%). Cardiac-control = infants with complex congenital heart disease not receiving SSC; Cardiac-SSC = infants with complex congenital heart disease receiving skin-to-skin contact intervention; ICU = intensive care unit; LOS = length of stay; SSC = skin-to-skin contact; TD = typically developing infants.

[a]One family in the cardiac-control group did not share income or ethnicity/race information. [b]No significant differences in sample characteristics between cardiac groups (Kruskal–Wallis test). [c]One infant was intubated preoperatively. [d]One infant in the cardiac-control group had an ICU LOS of 50.3 days and hospital LOS of 96.0 days, and this outlier was excluded. Inclusion yielded a mean (*SD*) of ICU LOS of 9.0 (14.8) and hospital LOS of 23.1 (25.8).

2009). The Human Subjects Review Board approved both pilot studies and waived the need for approval for this analysis of existing data.

Setting and Sample

In the original pilot studies, we recruited convenience samples of newborn infants with CCHD at birth from a large Midwestern children's hospital heart center. Infant inclusion criteria for both studies were (1) born at ≥37 weeks gestation and (2) diagnosed with congenital heart disease requiring surgical intervention within the first month of life (cardiac groups) or reported by parent to be a TD infant (TD group: first pilot study). Eligible mothers were (1) English speaking, (2) ≥18 years of age, and (3) the infant's primary caregiver. Mothers in the SSC group needed to be able to participate in the SSC intervention for a minimum of 14 consecutive days following surgery. Exclusion criteria for the infants included presence of coexisting, noncardiac congenital defects or syndromes because of potential independent effects on cognitive and autonomic function. To contain costs for the studies involving in-home data collection, potential participants were limited to those living within an approximately 75-mile radius of the hospital.

All infants with CCHD had surgery within the first 30 days of life (mean = 7.1 days; *SD* = 3.3) for multiple types of cardiac disease. Type of CCHD, age at surgery, and length of stay in the ICU and hospital did not differ significantly between the cardiac groups (see Table 1). Infants in the cardiac-SSC group experienced a mean of 1,046 ± 459 min of SSC during their hospitalization, with a minimum/maximum of 469/1,728 min. Of the 10 infants who received SSC, 6 received it preoperatively (mean = 213 ± 219 min; minimum/maximum = 35/595 min) as well as postoperatively. A total of four infants in the cardiac-SSC group received SSC more than once a day (2× daily = 3; 3× daily = 1). Diaries of 8 of the 10 mothers documented SSC in the home, but 2 mothers left their diaries in the hospital at discharge and did not document home SSC. No infants in the cardiac-control group received SSC. We did not obtain data on neonatal SSC among TD infants.

SSC Intervention (Pilot Study 1)

The SSC intervention for the first pilot study was initiated as soon as possible after recruitment. According to Schore's regulation theory, the effect of the mother's behavior on patterns of ANS function is based on repeated experiences (Schore, 1996). Therefore, mothers provided SSC daily preoperatively, when possible, and for 14 consecutive days postoperatively beginning when the infant had been extubated and judged by the attending cardiologist to be physiologically stable for holding. For the intervention, the infant, dressed only in a diaper, was placed prone and tucked into a Kangaroo Zak® cloth holding device (Nurturedbydesign.com) worn by the mother around her bare torso. The mother sat in a recliner at an approximately 40° angle and held the infant in SSC until the infant fell asleep and awakened independently (i.e., approximately 60–90 min).

The bedside nurse supported infant transfer and positioning until the mother was comfortable doing so independently.

Mothers documented the actual time in minutes they spent holding the infant in SSC in a daily diary. To ensure intervention integrity, study staff directly observed the initiation of SSC for the first 4 days, giving the mother the opportunity to provide the intervention under varying environmental conditions and with different nursing staff support. Study staff worked with the nursing staff to reduce interruptions and distractions and to provide privacy. After these initial observations, study staff were present at SSC a minimum of every 2–3 days to monitor intervention delivery, while the infant was hospitalized and talked with the mother by telephone every 2–3 days if the infant was discharged home before the end of the 14-day intervention.

Routine Care (Pilot Study 2)

Infants with CCHD in the comparison group received the usual care provided in the cardiac units, which did not typically include SSC. The study protocol allowed bedside nursing staff to support mothers who independently sought to provide SSC to their infant. However, no nurses or mothers reported SSC among the comparison-group infants.

Measures

Cognitive function. Cognitive function was tested using the mobile paradigm (MP; Rovee & Rovee, 1969), a classic measure of learning based on operant conditioning in which the infant is observed for changes in kicking frequencies when the infant's leg is either connected (acquisition) or not connected (baseline and extinction) to a crib mobile. The MP procedure is described in detail elsewhere (Heathcock, Bhat, Lobo, & Galloway, 2004). Briefly, two identical white plastic mobile stands are attached to each side of a crib or Pack 'N Play® (see Figure 1). A soft satin ribbon is fastened around the infant's right ankle and attached to the right-side stand. A research-designed mobile consisting of five bells and five colorful wooden blocks is placed on the left-side stand. Timing for the 3-min baseline phase, during which kicking does not result in mobile movement, begins at that point. Then the mobile is moved to the right-side stand for the 9-min acquisition phase, during which kicking results in movement and sound. Finally, the mobile is moved again to the left-side stand for the 3-min extinction phase, during which kicking does not cause mobile movement. The MP has a long history in developmental research examining learning in full-term healthy infants (Rovee & Rovee, 1969) and can distinguish between high-risk and healthy infant populations (Haley, Grunau, Oberlander, & Weinberg, 2008; Heathcock et al., 2004).

Kicking was defined as simultaneous flexion and then extension (or vice versa) of the knee and hip of >15°. Consistent with published protocols, individual learning was defined as a kicking frequency during extinction of ≥1.5 times that observed during baseline (Adler, Gerhardstein, & Rovee-Collier, 1998; Heathcock et al., 2004; Rovee & Rovee, 1969). Two independent coders scored kicking from the videotaped MP task, and interrater Cronbach's α was >.85. Percentage of infants demonstrating learning was calculated for each TD and cardiac group. In addition, infants were classified into learner and nonlearner groups for separate analyses.

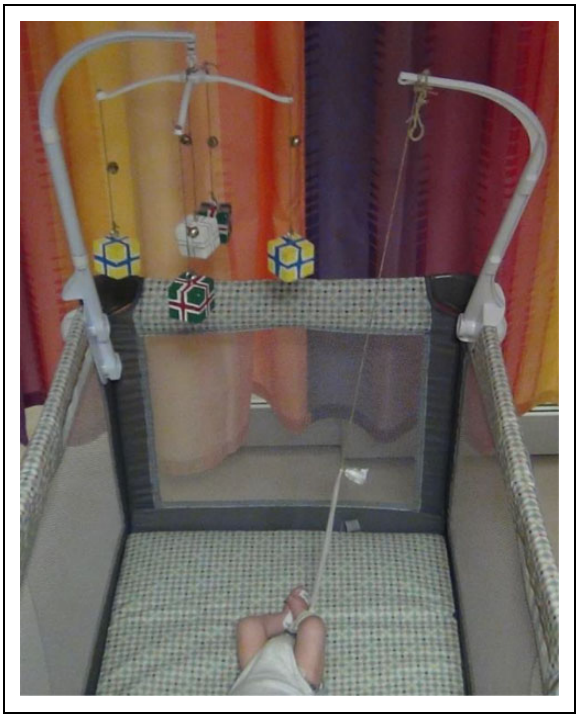

Figure 1. Setup for mobile paradigm task.

ANS function. ANS function was assessed with measures of HR and HRV using continuous electrocardiographic (ECG) recordings collected with a three-channel ambulatory Holter recorder (GE Healthcare, Inc., Wauwatosa, WI). The ECG data were initially sampled at 250 Hz and filtered to 125 Hz by the GE MARS 5000® Ambulatory ECG Analysis and Editing System for R-wave detection.

HR. HR was calculated continuously and recorded at 1-min intervals. Data analysis was based on averages for the 30-min pre-MP period, each of the three phases of the 15-min MP, and for 30 min post-MP.

HRV. Each ECG complex was labeled as a normal or abnormal beat by the computer software using a template pattern-matching method for detection of R waves, which is updated in real time. The peak of the R wave was the fiducial point for the measurement of interbeat intervals. The first author (T.M.H.) verified this preliminary automated analysis, ensuring both accurate beat labeling and accurate identification of the R-wave peak to assure proper labeling of normal heart beats and artifact. We excluded interbeat intervals associated with ectopic beats, nonsinoatrial node-initiated complexes, and artifact from analysis. When it was necessary to insert a missing

Table 2. Kicking Rates Across Phases of the Mobile Paradigm by Group.

	Baseline		Extinction	
Group	Mean	*SD*	Mean	*SD*
TD	4.38[a,b]	2.98	10.96	8.13
Cardiac-SSC	8.08[a]	3.90	18.27	11.17
Cardiac-control	16.93[b]	23.23	19.63	23.03

Note. Cardiac-control = infants with complex congenital heart disease who had not received SSC as neonates; cardiac-SSC = infants with complex congenital heart disease who had received a neonatal skin-to-skin contact intervention; SSC = skin-to-skin contact; TD = typically developing infants.
Significant between-group comparisons, as calculated by Mann–Whitney tests, are denoted with use of same superscript. [a]$U = 40.00$, $p = .036$; [b]$U = 41.00$, $p = .041$.

beat, we labeled it as unclassified to ensure that it was not included in the HRV calculation. Both linear and nonlinear HRV measures were obtained.

Linear HRV. Linear measures of HRV were calculated using frequency-domain methods. Power spectral analysis was performed using the Lomb-Scargle periodogram, which accurately produces estimates of underlying HRV parameters directly from the inherently unevenly spaced heartbeat data (Laguna, Moody, & Mark, 1998; Ruf, 1999).

The primary frequency-domain HRV parameter examined in this study was HF HRV using an infant bandwidth (0.24–1.04 Hz). Measures of HF HRV expressed as the natural log of milliseconds squared [ln (ms^2)] were calculated in 1-min epochs, averaged for the 30-min pre-MP period, for each of the three phases of the 15-min MP, and for the 30-min post-MP recovery period. HF HRV measures were compared within and between groups (TD, cardiac-SSC, and cardiac-control groups and learner, nonlearner groups).

Nonlinear HRV. Nonlinear measures of HRV were assessed using short-term DFA (DFA1). DFA is a measure of the fractal component of a time series of the intervals between normal beats (Peng, Havlin, Stanley, & Goldberger, 1995) and an index of the extent of correlation between successive beat-to-beat intervals. DFA1 measures the degree of correlation among 4–11 successive intervals (Stein, Domitrovich, Hui, Rautaharju, & Gottdiener, 2005). For the present study, we considered lower values of DFA1 during a cognitive task to be a marker of focused attention. Values range from 0.5 (*completely random*) to 1.5 (*completely correlated*), with normal values at around 1.0 (Peng et al., 1995). Because DFA1 calculations require at least 1,000 heartbeats, this measure was reported for the 30-min pre-MP period, the entire 15-min MP period, and the 30-min post-MP period.

Procedures

Demographic information was collected at the time of recruitment to the pilot studies: the newborn period for infants with CCHD and 3 months of age for TD infants. The SSC intervention was initiated during the infant's newborn hospitalization for care of CCHD, and the mother documented minutes in SSC daily. The MP was completed in the participants' homes when the infants were approximately 3 months old. Each session was videotaped for later coding. Before the start of the MP, seven ECG electrodes were attached to the infant's chest, and a 30-min pre-MP recording was obtained. The recording continued through the 15-min MP and for 30 min following its completion.

Data Analysis

Study variables were analyzed with descriptive statistics and nonparametric group comparisons. HR and HRV measures were analyzed with repeated-measures general linear mixed modeling. Standardized effect sizes and confidence intervals were calculated for within-group phase contrasts of the MP. Consistent with conduct of exploratory studies, especially with fixed samples (Fairchild & MacKinnon, 2009), Type 1 error rate was set at .1 in order to retain promising relationships for future examination in fully powered studies.

Results

Cognitive Function

Differences in kicking rates (see Table 2) between MP baseline and extinction were scored as learning in 64% of all infants ($n = 23$), including 75% of TD infants, 70% of cardiac-SSC infants, and 40% of cardiac-control infants. Differences in learning rates between groups were not significant ($\chi^2 = 2.528$, $df = 2$, $p = .294$).

Autonomic Nervous System Function

HR. The TD and cardiac-SSC groups both had significantly higher HR during the MP compared with the cardiac-control group. These two groups also had significant increases in HR during the MP with large effect sizes (see Table 3). In the cardiac-control group, no significant changes in HR occurred across the MP, although HR decreased post-MP (see Table 4 and Figure 2).

Linear HRV (HF HRV). HF HRV during phases of the MP differed by group only during extinction, where the TD group had significantly higher HF HRV compared with the cardiac-SSC group ($F = 3.357$, $p = .073$). Group trajectories across the MP differed. Reductions in HF HRV occurred during acquisition in TD infants ($F = 2.629$, $p = .107$, effect size = .27) and during extinction in cardiac-SSC infants ($F = 3.126$, $p = .079$, effect size = .38). No significant changes in HF HRV occurred across the MP in the cardiac-control group (see Tables 3 and 4; Figure 2).

When we split the sample into learners and nonlearners, HF HRV in learners ($n = 23$) was significantly lower during the 3-min extinction phase compared with the 3-min baseline phase (the comparison between these two phases determined the presence or absence of learning; $F = 2.895$, $p = .091$, effect

Table 3. Effect Sizes and Confidence Intervals for Within-Group Contrasts Across the Mobile Paradigm (MP).

	HR Effect Size [CI]		HF HRV Effect Size [CI]		DFA1 Effect Size [CI]	
Group	Base Versus Acq	Base Versus Ext	Base Versus Acq	Base Versus Ext	Pre Versus MP	MP Versus post
TD	−0.68 [−1.37, 0.05]	−0.82 [−1.52, −0.08]	0.27 [−0.43, 0.96]	0.24 [−0.46, 0.93]	0.82 [0.08, 1.51]	−1.69 [−2.45, −0.85]
Cardiac-SSC	−0.21 [−1.08, 0.67]	−0.61 [−1.48, 0.31]	0.08 [−0.80, −0.95]	0.38 [−0.52, 1.25]	0.35 [−0.60, 1.26]	−0.85 [−1.77, 0.15]
Cardiac-control	−0.01 [−0.89, 0.86]	−0.07 [−0.94, 0.81]	0.07 [−0.81, 0.94]	0.14 [−0.74, 1.01]	−0.01 [−0.88, 0.87]	−0.48 [−1.34, 0.43]
Learner	–	–	0.09 [−0.49, 0.66]	0.25 [−0.34, 0.83]	–	–
Nonlearner	–	–	0.28 [−0.50, 1.05]	0.27 [−0.51, 1.03]	–	–

Note. Acq = acquisition phase of MP; base = baseline phase of MP; cardiac-control = infants with complex congenital heart disease who had received routine care, not including a neonatal SSC intervention; cardiac-SSC = infants with complex congenital heart disease who had received a neonatal SSC intervention; CI = confidence interval; DFA1 = short-term detrended fluctuation analysis; Ext = extinction phase of MP; HF HRV = high-frequency heart rate variability; HR = heart rate; MP = mobile paradigm; pre = pre-MP; SSC = skin-to-skin contact; TD = typically developing infants.

Table 4. Descriptive Statistics for Heart Rate and Heart Rate Variability Across the Phases of the Mobile Paradigm.

	HR (bpm)					HF HRV (ln [ms^2])					DFA1		
Group	Pre	Base	Acq	Ext	Post	Pre	Base	Acq	Ext	Post	Pre	During	Post
TD													
Mean	146.40	141.35	148.61[a]	150.25[b]	145.03	3.98	4.18	3.92	3.95[c]	4.12	1.07	0.99[d]	1.12
SD	13.34	8.86	12.98	12.42	17.24	0.97	0.72	0.71	0.79	1.19	0.12	0.08	0.07
Min	118.00	122.67	122.67	129.67	97.67	2.07	2.94	2.17	2.23	1.76	0.89	0.85	1.01
Max	176.00	157.67	187.67	178.67	184.67	6.36	5.89	5.19	5.05	8.65	1.28	1.16	1.21
Cardiac-SSC													
Mean	144.43	146.80	149.41[e]	153.27[f]	147.05[g]	3.99	3.63	3.56	3.28[c]	3.83	1.11[h]	1.08[d]	1.14
SD	13.27	11.47	13.08	9.67	23.97	1.64	0.86	0.92	0.87	1.37	0.08	0.06	0.07
Min	106.00	127.00	122.00	138.33	88.33	1.54	2.31	1.89	2.12	1.64	1.01	0.99	1.03
Max	170.67	166.33	176.67	172.00	195.33	8.98	5.14	5.77	5.68	7.07	1.27	1.15	1.27
Cardiac-control													
Mean	139.07	138.10	138.36[ae]	139.20[bf]	135.78[g]	3.89	3.97	3.90	3.85	4.23	1.03[h]	1.03	1.08
SD	14.87	17.03	16.19	15.29	18.81	1.00	0.89	0.89	0.77	1.36	0.08	0.09	0.10
Min	109.00	108.67	112.67	117.67	101.33	1.65	2.11	2.25	2.36	1.79	0.91	0.90	0.82
Max	167.33	164.67	170.33	163.67	169.67	6.42	6.19	6.87	5.38	7.91	1.19	1.17	1.18

Note. Acq = acquisition phase of mobile paradigm; base = baseline phase of mobile paradigm; cardiac-cont = infants with complex congenital heart disease who received routine care, not including SSC; cardiac-SSC = infants with complex congenital heart disease who received SSC intervention; DFA1 = short-term detrended fluctuation analysis; during = during mobile paradigm; Ext = extinction phase of mobile paradigm; HF HRV = high-frequency heart rate variability; HR = heart rate; pre = pre mobile paradigm; post = post mobile paradigm; SSC = skin-to-skin contact; TD = typically developing infants.

Significant within-group comparisons: (1) HR TD: pre > base, $F = 3.379$, $p = .068$; base < Acq, $F = 6.764$, $p = .107$; base < Ext, $F = 10.164$, $p = .002$; Ext > post, $F = 3.500$, $p = .064$. (2) HR cardiac-SSC: base < Ext, $F = 3.357$, $p = .069$; Ext > post, $F = 2.991$, $p = .086$. (3) HF HRV TD: base > Acq, $F = 2.629$, $p = .107$. (4) HF HRV cardiac-SSC: pre > base, $F = 3.275$, $p = .073$; base > Ext, $F = 3.126$, $p = .079$; Ext < post, $F = 5.432$, $p = .021$. (5) HF HRV cardiac-control: Ext < post, $F = 3.513$, $p = .063$. (6) DFA1 TD: pre > during, $F = 8.021$, $p = .006$; during < post, $F = 20.433$, $p = .001$.

Significant between-group comparisons are denoted with use of same superscript. [a]$F = 3.455$, $p = .068$; [b]$F = 4.011$, $p = .050$; [c]$F = 3.357$, $p = .073$; [d]$F = 5.569$, $p = .020$; [e]$F = 3.262$, $p = .076$; [f]$F = 5.282$, $p = .025$; [g]$F = 3.402$, $p = .070$; [h]$F = 3.459$, $p = .066$.

size = .25). HF HRV was also significantly higher in learners during the post-MP recovery compared with the extinction phase of the MP ($F = 9.061$, $p = .003$). We observed no differences in HF HRV across the MP in nonlearners ($n = 13$), although effect sizes were similar to those of learners (see Table 3; Figure 2).

Nonlinear HRV (DFA1). In this analysis, we excluded data for one infant with insufficient normal beats during the MP to calculate DFA1. In the TD group, DFA1 was significantly lower during the MP compared to pre- and post-MP (pre-MP vs. MP: $F = 8.021$, $p = .006$, effect size = .82; MP vs. post-MP: $F = 20.433$, $p = .001$, effect size = −1.69). Although there were no significant differences in DFA1 within either of the cardiac groups, we observed a decrease with a small-to-moderate effect size during the MP compared to pre-MP in the cardiac-SSC group (see Table 3). Pre-MP DFA1 was significantly higher in the cardiac-SSC group compared with the cardiac-control group ($F = 3.459$, $p = .066$). DFA1 during the MP was significantly higher in the cardiac-SSC group compared with the TD group ($F = 5.569$, $p = .020$; see Table 4).

Discussion

In the present study, we examined effects of an SSC intervention during the first month of life on cognitive and ANS

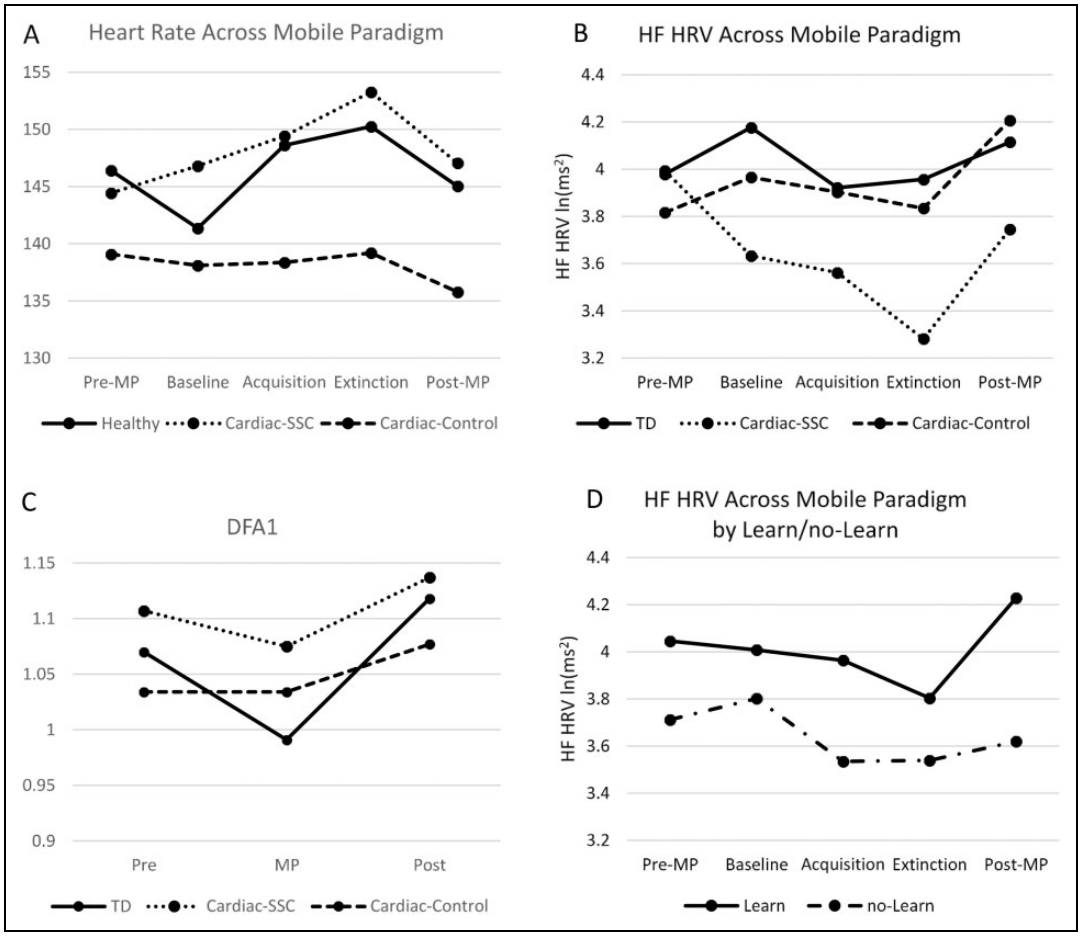

Figure 2. Trajectories of (A) heart rate, (B) high-frequency heart rate variability (HF HRV), and (C) short-term detrended fluctuation analysis (DFA1) across the mobile paradigm (MP) by health condition group, and HF HRV trajectories across the MP by (D) learn group. Because DFA1 is calculated with at least 1,000 beats, values are shown for the 30-min pre-MP, 15-min MP, and 30-min post-MP phases. Cardiac-control = infants with complex congenital heart disease who received routine care, not including skin-to-skin contact (SSC); cardiac-SSC = infants with complex congenital heart disease who received SSC intervention; TD = typically developing infants.

function at 3 months of age in infants who underwent surgery for CCHD shortly after birth. One group of infants with CCHD had SSC and the other had usual care. We compared these infants with a group of TD infants born healthy. Our results suggest that there was improvement in both cognitive and autonomic development in infants with CCHD who had received SSC as neonates compared with those who had received usual care. These findings provide preliminary evidence in support of the implementation of SSC during the neonatal period in these vulnerable infants.

Cognitive Function

Rates of learning, measured using the MP, were similar at 3 months of age between TD infants and infants with CCHD who had received SSC as newborns. In contrast, rates of learning tended to be lower in infants with CCHD who had not received SSC as newborns, but power was limited by the small sample size. Although one previous study demonstrated similar rates of learning with the MP in premature infants compared with healthy infants (Haley et al., 2008), others have found significantly lower rates of learning in premature infants (Gekoski, Fagen, & Pearlman, 1984; Heathcock et al., 2004). One factor that might impact cognitive development infants with CCHD is brain maturity. The brain maturity of more than half of full-term infants born with CCHD has been shown to be similar to that of premature infants born at 35–36 weeks' gestation (Licht et al., 2009). Immature brains are more susceptible to brain injury, and preoperative brain injury (stroke, white-matter injury) is common among infants with CCHD (Block et al., 2010). Post-birth brain injury is also common and is likely associated with perioperative procedures including anesthesia and cardiopulmonary bypass, which alter brain hemodynamics and are associated with changes in brain tissue and impaired neurodevelopment, including cognitive function (Andropoulos et al., 2014; Ing et al., 2012). Our preliminary findings about the potential beneficial effect of SSC, a known neuroprotective intervention (Feldman et al., 2014; Kaffashi, Scher, Ludington-Hoe, & Loparo, 2013), in a population at high risk for alterations in

cognitive development (Andropoulos et al., 2014; Marino et al., 2012) support further research in this area.

Autonomic Function

Decreased HF HRV is a marker for parasympathetic withdrawal during cognitive engagement (Hansen et al., 2003; Thayer et al., 2009). In the present study, learners demonstrated significant reductions in HF HRV during the MP and robust recovery (return to baseline) following the MP; nonlearners exhibited no such change. However, effect sizes calculated between the MP phases were similar between learners and nonlearners, necessitating additional research before drawing firm conclusions. These findings are similar to those of a study of autonomic activity of premature and healthy infants during the MP in which learners demonstrated greater parasympathetic withdrawal during the MP compared with nonlearners (Haley et al., 2008).

As expected, given their better learning performance, HF HRV trajectories of the TD and cardiac-SSC infants are closely aligned with those of learners. Both the TD and cardiac-SSC groups demonstrated reductions in parasympathetic activity during the MP, whereas the cardiac-control group did not. These findings suggest that TD infants and infants with CCHD who had received SSC experienced greater engagement in the task (increased HRs), greater recovery from the task (decreased HRs), and more capacity for regulating HR during and after the task (HF HRV reductions and increases, respectively). The much lower rates of learning for the cardiac-control group, lower HRs, and flattened HF HRV trajectories suggest reduced capacity of infants who had not received SSC to engage in and muster the physiologic resources needed to carry out this cognitive task.

These findings are consistent with those of our previous work. Infants with transposition of the great arteries who had received standard postoperative care that did not include SSC demonstrated impaired autonomic function during and after the challenge of feeding at 2 weeks and 2 months of age compared with an age- and sex-matched group of infants born healthy (Harrison & Brown, 2012). In contrast, we observed improvements in autonomic function over time in a single-group study of 10 infants with CCHD who received SSC postoperatively (Harrison & Brown, 2017). Although we cannot draw firm conclusions because of small sample sizes, these studies, along with the current study, provide evidence of the potential positive impact of SSC, a noninvasive and demonstrably safe intervention, on autonomic function in infants with CCHD.

Interestingly, the phase of the MP in which HF HRV decreased differed by group. TD infants tended to show reductions during the acquisition phase, while the cardiac-SSC infants showed significant reductions during the extinction phase. These differences in trajectory suggest that TD infants were able to make the connection between kicking and mobile movement earlier in the task. The infants with CCHD who had received SSC did not appear to demonstrate cognitive engagement physiologically until the link between kicking and mobile movement was removed (see Figure 2). In addition, parasympathetic withdrawal, reflected by marked reductions in HF HRV during the learning phase of the MP, was more pronounced in the infants with CCHD who had received SSC compared with the TD infants (see Figure 2). This qualitative difference in trajectory between the two groups with higher rates of learning is supported by the findings of Haley and colleagues (2008), where parasympathetic withdrawal of learners was significantly more prominent in infants with a serious health condition (premature infants) than in healthy infants. Further investigation of relationships between learning and HRV within groups in this study was not possible due to small sample sizes, but this is a rich area for future investigation.

We used DFA1, a nonlinear measure of HRV, to examine the organization of the HR signal. Previous research has linked decreased DFA1 with high sympathetic activity (Stein, Domitrovich, Huikuri, Kleiger, & Cast, 2005). TD infants in the present study demonstrated a significant reduction in DFA1 during the MP task, indicating focused attention, consistent with the increases in HR and reductions in HF HRV discussed above. Although decreases in DFA1 during the MP did not reach significance in infants with CCHD who had received SSC, the effect size was a small-to-moderate .35. In contrast, DFA1 during the MP showed little change in infants with CCHD who had not received SSC, suggesting lack of focused response to the challenge.

DFA1 has not previously been studied in infants with CCHD. Researchers have reported significant reductions in DFA1 in premature infants during conditions that would be expected to increase sympathetic responses, such as following delivery of loading doses of caffeine (Huvanandana, Thamrin, McEwan, Hinder, & Tracy, 2018) and rewarming following therapeutic hypothermia (Massaro et al., 2017). Findings of DFA1 trajectories in cardiac-SSC infants similar to TD infants support further studies with sufficient sample sizes.

Limitations

Because the TD infants were recruited at 3 months of age, we do not know the extent of SSC, if any, these infants experienced as neonates. The sample size in the present study was too small to support definitive conclusions about relationships between cognitive and autonomic function. Whether the decrements in autonomic function observed in infants who had not received SSC were due to the lack of SSC or to unmeasured group differences (type of feeding, number and types of complications, differences in infant state) requires additional, fully powered studies. However, we submit that infants starting life in an ICU are already at high risk for autonomic dysfunction and, thus, are likely to be physiologically responsive to interventions, such as SSC, designed to promote healthy autonomic regulation.

Conclusions

SSC is a parent-provided, primarily nurse-initiated, intervention known to improve outcomes in high-risk infant populations (Feldman et al., 2002, 2014; Morelius, Ortenstrand,

Theodorsson, & Frostell, 2015). In the present study, we reported initial evidence of relationships among SSC, autonomic function, and cognitive function that have not previously been described in infants with CCHD. Consistent with Schore's theory, 3-month-old infants with CCHD who had experienced the mother's presence through a neonatal SSC intervention during their initial hospitalization for surgery demonstrated rates of learning and responsive autonomic function comparable with TD infants and surpassing those of infants with CCHD who had not received SSC. This study thus provides preliminary support for examining changes in the regulation of HR and the relationships of these changes with learning that will allow us to indirectly measure higher level cognitive function at a young age using the MP. This approach has the potential for eventual use as a measure of the effectiveness of early interventions, such as SSC, on enhancing autonomic function.

SSC is a low-cost, low-risk, noninvasive intervention that is highly valued in families of infants with CCHD (Harrison & Brown, 2017), supported by developmental literature in other hospitalized neonates (Feldman & Eidelman, 2003), and standard policy for neonates in many, if not most, children's hospitals. Although additional research is needed on the effects of SSC in infants with CCHD, we recommend that nurses encourage and support parents in the implementation of this intervention whenever the infant's health status is stable enough for holding.

Author Note

The content is solely the responsibility of the authors and does not necessarily represent the official views of Nationwide Children's Hospital.

Author Contribution

Tondi M. Harrison contributed to conception and design and to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Chao-Ying Chen contributed to conception and design and to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Phyllis Stein contributed to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Roger Brown contributed to design and to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Jill C. Heathcock contributed to conception and design and to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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