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The presence of coherence in sympathetic and phrenic activities in a developing mammal

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Abstract. To determine whether are development changes in the baroreceptor and central respiratory modulation of sympathetic activity, we used ordinary and partial coherence spectral analyses on cervical and splanchnic sympathetic activity in swine 1-36 days old. Removal of baroreceptor influences from cervical sympathetic and splanchnic spectra using partialization shows that 3-6 Hz peaks are due to baroreceptors since coherence decreased in > 19 days old while remaining unchanged in < 2 weeks old piglets. The 8-12 Hz band (present in normal coherence after 21 days) was revealed in piglets < 14 days old after removal of respiratory modulation by partialization; similarly increased coherence was also observed in the 16-18 Hz band through 3 weeks. Thus, use of partial power and coherency is a useful tool for unmasking the complex relationships found in developing SYMP outflows. These results suggest that there is a period of reorganization within the SYMP rhythm generating circuits, which may be essential for normal development.

Key words: neonate, coherence, spectral analysis, partialization, sympathetic activity, splanchnic, cervical sympathetic, respiratory rhythm generator, phrenic activity

INTRODUCTION

Sympathetic (SYMP) efferent discharge is characterized by the occurrence of synchronized activity manifested as slow waves in whole nerve recordings. Most of what is known about periodicities in SYMP nerve discharge (SND) has been obtained in adult mammals. SND usually shows three major types of periodicity: (1) a slow respiratory (RESP)-related rhythm, (2) a 2-6 Hz, often related to the cardiac cycle (Cohen and Gootman 1970, Gootman et al. 1987) and (3) a "10 Hz rhythm" (range 8-13 Hz) (Cohen and Gootman 1970, Gootman and Cohen 1970, 1971, 1973, 1980, 1981, Gootman et al. 1975, 1987). A still higher frequency was occasionally observed in cervical sympathetic discharge (Gootman and Cohen 1973, Gootman et al. 1987). Until recently, a controversy (Gebber and Barman 1980) existed as to the presence of the 10 Hz rhythm (Barman et al. 1992, Cohen and Gootman 1970, Gebber et al. 1995).

While there have been studies of SYMP activity in neonates, few studies have actually analysed SYMP activity from the viewpoint of monitors of the brain stem SYMP rhythm generating systems. In fact, most studies of the developing SYMP nervous system, including fetal and conscious animals, have obtained recordings of SYMP discharge so excessively filtered that well-known periodicities present in adult SYMP discharge (cf. Gootman and Sica 1994 for review) were effectively eliminated. To the best of our knowledge, periodic discharge in SYMP activity of neonates was first reported in the early 1980s (Gootman et al. 1981, 1984).

SYMP rhythmic activity was analysed in the earlier studies utilizing auto- and cross-correlation techniques. More recently, spectral analysis has been applied to SYMP discharge (Kocsis et al. 1990, Kenny et al. 1991, Barman et al. 1992). These studies reported a strong correlation in adult SYMP discharge, as revealed by high values of coherence between nerve pairs. Although we have shown an age-related delay in coherence between SYMP outflow from different spinal levels (Gootman et al. 1995), the possible roles of afferents, either baroreceptor or respiratory-related in the onset of or delay in coherence have not been examined.

Recently, partialization has been used to reveal commonality and differences in the neural circuitry underlying rhythmicity in SND (Kocsis 1994, Cohen et al. 1995, Gebber et al. 1995). Partialization refers to the ability to mathematically subtract a periodic input from oscillatory signals, thereby permitting evaluation of the importance of that input to different SYMP preganglionic pools. We have recently applied partialization to the power spectra of SYMP outflows, splanchnic and cervical sympathetic nerves, to determine the importance of periodic inputs, i.e., arterial pressure (AoP), circuits making up the RESP rhythm generator, on the periodicities found in SYMP outflows.

METHODS

Experiments were performed on 15 Yorkshire piglets of either sex 1-36 days old, initially anaesthetized with Saffan (12 mg/kg, im) (Gootman et al. 1990). The external jugular and femoral veins were cannulated for continuous infusion of Saffan (12-16 mg/kg/h) and 5% dextrose in water (4 ml/kg/h). A cannula was placed in the femoral artery for both continuous monitoring of arterial pressure (AoP) and intermittent determination of arterial blood gases and pH. Needle electrodes were placed for monitoring lead II of the electrocardiogram (ECG) and for determination of heart rate (HR). The animals were tracheotomized and artificially ventilated with 100% O_2. Normocapnia (arterial partial pressure of CO_2=35-45 Torr) was maintained by adjusting the tidal volume and/or ventilator rate as needed. End-tidal CO_2 was continuously monitored (Sensormedics LB-2 Infrared Analyzer) and kept between 4.5 and 5.0 %. Movement artifacts were avoided by immobilization with intermittent injection of decamethonium bromide (1-2 mg/kg). In some animals, bilateral thoracotomy were carried out in order to diminish movement artifacts, and an end-expiratory load of 1-2 cm H_2O was applied to minimize atelectasis. Rectal temperature was maintained at 39°C by a servo-controlled

heating blanket (Harvard) and by infrared heating lamp.

A C_5 or C_6 phrenic nerve root (PHR), a cervical sympathetic nerve (CS), and the left greater splanchnic nerve (SPL) were exposed, desheathed, and immersed in paraffin oil bath. Following the surgery, the rate of Saffan infusion was reduced to the recording level (2-6 mg/kg/h), and the animals were allowed to stabilize for 1 h. Further details of surgery are given in our previous papers (Gootman et al. 1984, 1990, 1991a,b, Cohen et al. 1991).

Monophasic recordings (0.3 Hz-3 kHz) were obtained from the cut central ends of the PHR, CS, and SPL nerves using bipolar platinum electrodes. All analog signals were stored on FM magnetic or VCR tape for off-line computer analyses which included (in various combinations) efferent SPL, efferent CS, efferent PHR, ECG, AoP, intratracheal pressure, end-tidal CO_2 and derived pulses marking times in the cardiac and RESP cycles. Further recording details can be obtained from earlier papers (e.g., Gootman et al. 1991a).

Signal analysis

Autopower and coherence spectral analyses of nerve activities were performed for all animals as follows: neural signals were low pass filtered (40 Hz) and sampled at 128 Hz. Marks were positioned at the onsets and offsets of PHR bursts; these marks were then used as triggers for a fast Fourier transform routine (FFT). The number of FFT points was set to equal the length of the shortest duration of PHR discharge and padded with zeroes to attain the next power of two (usually 128 or 256). The mean and any other trend was then subtracted from each data point; further smoothing of the data was accomplished with a Hamming function. Power spectral estimates were then calculated for each segment and the final power spectrum (1 Hz bin width) was obtained by ensemble averaging of all individual segments. Each average consisted of at least 25 inspiratory (I) or expiratory (E) phases. Relative power was calculated according to the following equation:

$$\frac{A(f) - Min(f)}{\Sigma A(f) - nMin(f)}$$

where:

A = amplitude

f = frequency

n = number of bins

Min = minimum value all (f)

and then plotted on a three dimensional plot of frequency vs. age vs. relative power. The resultant relative power then expressed the amount each frequency contributed to the total power.

Coherence

To detect correlated (coherent) frequency components in the activities of different nerves, it was first necessary to compute the average cross-power spectrum for the pair of signals. Next, the coherence spectrum was derived as the ratio of the squared magnitude of the averaged cross-power estimate to the product of the individual auto power spectra (Jenkens and Watts 1968). To determine whether coherence estimates were statistically significant, a test for significance of non-zero coherence (Jenkins and Watts 1968) was performed to estimate the minimum values in coherence spectra that would be considered significant (as described in earlier papers (Gootman et al. 1995, Sica et al. 1996).

Partial power and coherence analyses

Recently, to examine further the age-related changes revealed in the relative spectra, partial coherence analysis (Jenkins and Watts 1968, Koscis 1994, Cohen et al. 1995) was used to remove the influences of pulse-synchronous baroreceptor nerve activity (as reflected by the arterial pulse) on SYMP activity and on the coherence between two SYMP preganglionic nerves. With this method, it is possible to determine whether the coherence between two SYMP nerves is a function of a third signal entrained to the arterial pulse, i.e., baroreceptor afferent activity. In addition, to eliminate the possible role of the circuits gener-

ating I activity, partialization using PHR activity was carried out.

RESULTS

Spontaneous sympathetic activity in neonates has a number of periodicities due to synchronized activity resulting in an envelope of slow waves which are clearly evident in recordings with band-pass filtering in the 0.1 Hz to 3 kHz range. These slow waves appear to be entrained to the cardiac and central RESP cycles (cf. Figs. in Gootman et al. 1991a,b,c, Gootman and Sica 1994). Power spectra and coherence functions of SYMP and PHR discharge were obtained by a FFT routine and coherence was estimated. PHR discharge also defined the I and E epochs used for gating spectral estimates. The analysis revealed peaks in four regions (3-6 Hz, 8-12 Hz, 18-24 Hz, 30-38 Hz). Single average histograms, triggered from the peaks of AoP, showed cardiac locking of both SPL and CS activity (Gootman et al. 1984, 1987, 1991). As expected, activity during systole was at minimum amplitude. The 3-6 Hz peaks, presumably related to baroreceptor influences, varied from insignificant values of coherence (K^2<0.1) in swine < 2 wks old to significant values (K^2 > 0.30) in animals ≥ 19 days old (Gootman et al. 1995). Thus, age-related power spectra revealed that the slow waves were not coherent between SYMP outflows in young animals (cf. Figures in Gootman et al. 1995). The fact that these slow waves were unrelated to baroreceptor inputs until the animals were more than two weeks of age is illustrated in the CS-SPL coherence spectra of Fig. 1. The 3-6 Hz peaks (presumably due to baroreceptors) were present in ordinary coherence at all ages (Fig. 1, top graph). However, upon partialization coherence decreased in > 19 days old while remaining unchanged in ≤ 2 weeks old piglets (Fig. 1, compare top and bottom spectra).

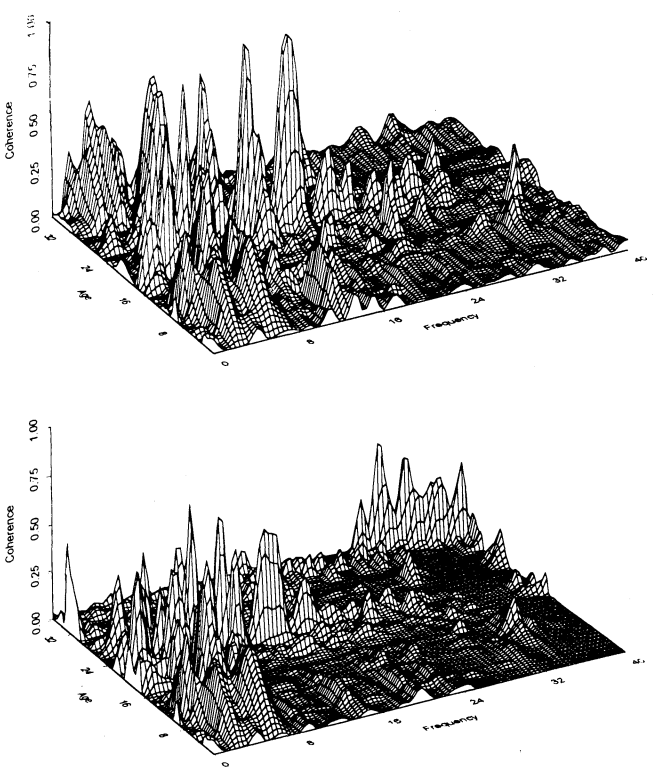

Fig. 1. Coherence between splanchnic and cervical sympathetic nerve activities *versus* age before (top) and after (bottom) partialization on the basis of the aortic pressure signal.

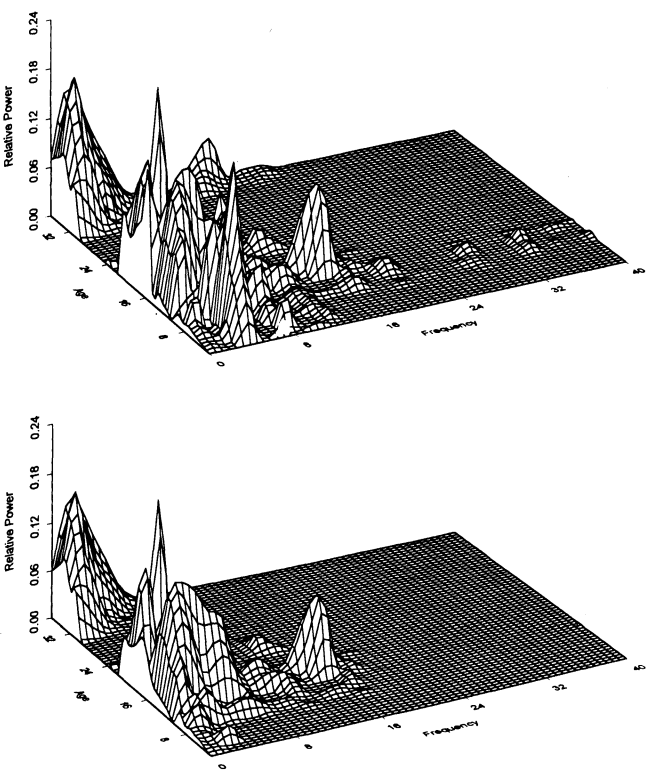

Fig. 2. Relative power of cervical sympathetic activity (gated in expiration) *versus* age before (top) and after (bottom) partialization on the basis of the aortic pressure signal.

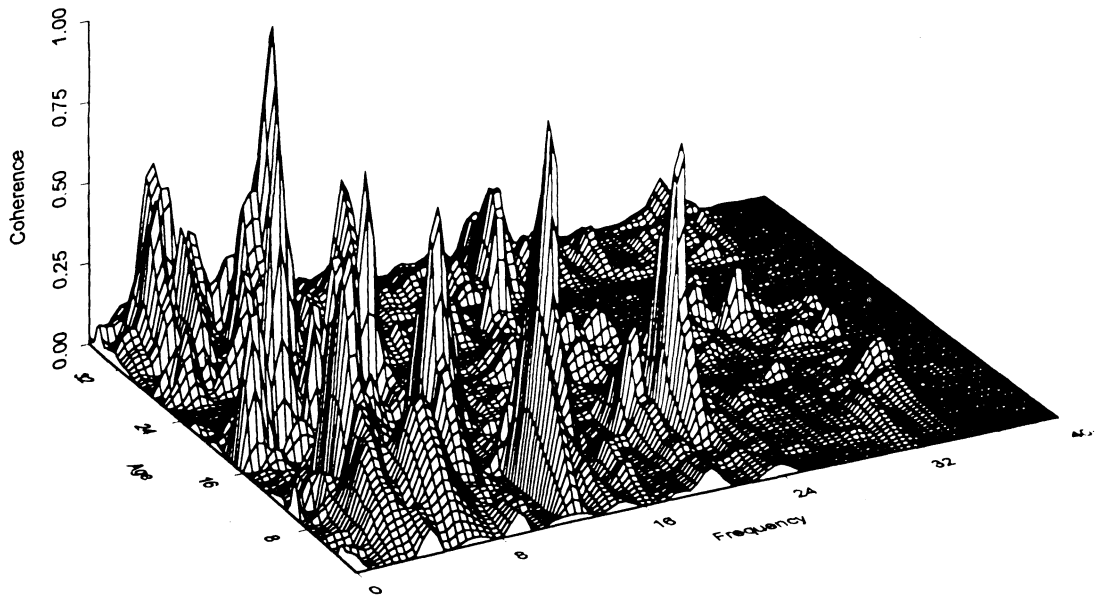

Fig. 3. Coherence between splanchnic and cervical sympathetic nerve activities *versus* age after partialization on the basis of the phrenic nerve signal.

In addition, relative spectra either continuous or gated (cf. Fig. 2) revealed a very low oscillation in SYMP activity (< 1.0 Hz). Furthermore, higher frequencies appeared and then disappeared with increasing postnatal age (see Fig. 1, top).

Partial coherence analysis was also used to remove the influences of the neural circuits generating the central I phase as indicated by PHR activity. The 8-12 Hz frequency band for the SPL-CS coherence increased followed partialization in younger animals, e.g., compare ordinary coherence spectrum of Fig. 1 (top) with the partial coherence spectrum of Fig. 3. This result implies that coherence between SYMP outflows was masked by these neural circuits, and suggests that I-related inputs in young piglets interfered with synchronizing influences emerging from central SYMP circuits, thereby decreasing coherence. In addition, there is evidence that the respiratory rhythm generating circuits may exert differential effects depending upon age as well as preganglionic pool of neurones. For example, in animals > 30 days the low frequency band (Hz) in CS activity is decreased after partialization of PHR activity (Fig. 4). In contrast, SPL activity over the same frequency band showed little

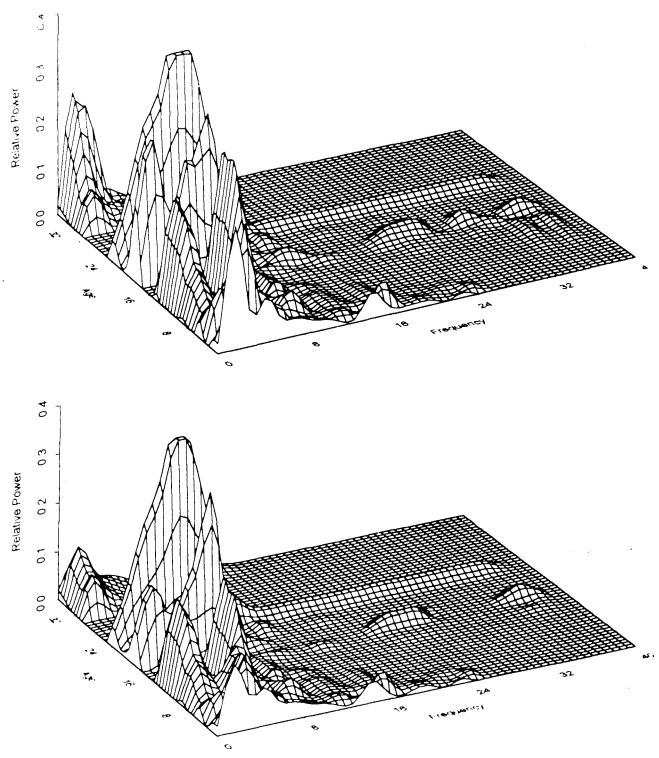

Fig. 4. Relative power of cervical sympathetic activity (gated in inspiration) *versus* age before (top) and after (bottom) partialization on the basis of the phrenic nerve signal.

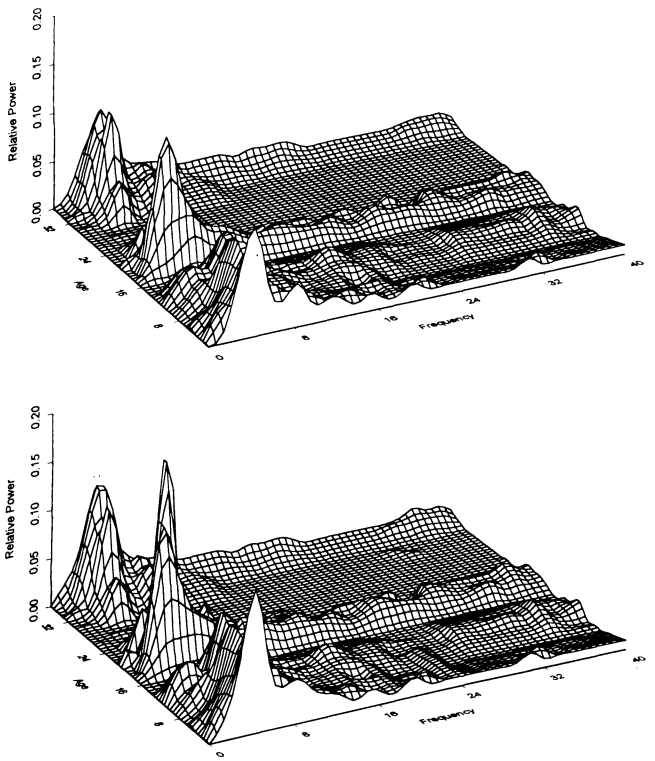

Fig. 5. Relative power of splanchnic activity (gated in inspiration) *versus* age before (bottom) and after (top) partialization on the basis of the phrenic nerve signal.

activity (cf. top and bottom spectra of Fig. 5); however, in the 3-6 Hz range, partialization revealed effects at > 2 wks of age, i.e., a small decrease in relative power (top).

Thus the 8-12 Hz frequency band was present in the normal coherence after 21 days but not in piglets < 14 days until the circuits driving PHR rhythmicity were mathematically eliminated (Fig. 3). This partialization also increased coherence in the 16-18 Hz frequency band through 3 weeks of age. After 23-25 days partial coherence analysis with AoP or PHR resulted in a decline of coherence values in the 3-6 Hz for AoP and 8-12 Hz and 16-18 Hz with PHR (these were all statistically significant: $P<0.05$).

DISCUSSION

There have been far fewer studies of periodicities in SND of neonates than of adults (Gootman and Sica 1994). Nevertheless, we have now documented that, while periodicities are present in spontaneous SND at birth (e.g., Gootman et al. 1981, 1984, 1990, 1991), these periodicities are not coherent in SYMP outflows from different segmental levels until about 19 days of age (Gootman et al. 1995). Such a finding indicates a significant degree of postnatal maturation of spontaneous SND occurring in our animal model of human development. This does not mean that responses to simple afferent stimulation are not present in young pigs. For example, we found that, in very young piglets (4 h old), baroreceptor stimulation evoked different responses in CS and SPL; a 44% decrease in SPL activity with an unexpected 55% increase in CS; the direction of heart rate change (decrease) was appropriate (Cohen et al. 1991).

While coherence in CS was reported in kittens (Sica et al. 1990, Gootman and Sica 1994; only our recent work has shown delay in onset of coherence in SND from different segmental levels (Gootman et al. 1995). Postnatal delays in onset of components of various cardiovascular reflexes have been reported by us (cf. Gootman 1991, Gootman and Gootman 1994); e.g., delays to about 25 days for onset of responses to complex visceral afferent inputs, i.e., Valsalva maneuver (Gootman et al. 1991a,b). Thus, the onset of coherence at about 19 days is close to the time for onset of responsivity to these more complex visceral afferent inputs suggesting that maturation of cardiovascular regulation is delayed until linkage of independent SYMP oscillators occurs. It is also of interest that this is the same time frame for weaning and the piglet's ability to survive away from the sow. In kittens, coherence between CS and PHR did not occur until 6 wks of age (Sica et al. 1990, Sica and Siddiqui 1993).

The present paper examined postnatal maturation of brain stem oscillators regulating SND by determining whether coherence is a function of postnatal maturation and whether the onset of coherence of SND is effected by afferent inputs from baroreceptors and/or respiratory rhythm generating circuits using partialization. Since such studies have not previously been carried out in neonates, determining the onset of coherence at different segmen-

tal levels is essential to our understanding of maturation of the systems generating, regulating and integrating SND, and thus of cardiovascular (CV) system regulation. The piglet is a particularly good model to use even though it matures more rapidly than its human counterpart; nevertheless the balance between pre- and postnatal brain maturation is relatively comparable between piglets and humans (Dobbing 1974, Martin et al. 1994). It appears that the vasomotor brain stem system is complex in neonates, with independent oscillators regulating SND not linked until later in postnatal life. The absence of a response to a complex afferent input, e.g., *Valsalva maneuver* (Gootman et al. 1991a,b), at an age when simpler reflex arcs are functional, suggests that complex CV integration of these afferent inputs could not be accomplished until brain stem systems mature, as indicated by coherence at the neuronal level (evidence of organization (integration) of the disparate parts of the SYMP rhythm generating system). Finally, the SYMP generator may be more complex than earlier thought since in piglets < 19 days of age, the periodicities present in SND were not coherent (Gootman et al. 1995). Thus multiple oscillators probably were functioning independently at first, which then become linked.

We found that the value of coherency in the 3-6 Hz band between SPL and CS was not appreciably altered by partialization with the arterial pulse in <3 wk old piglets; however, in older piglets (>20 days), it decreased markedly. The 8-12 Hz frequency band coherence increased followed partialization with PHR activity in the younger animals. These results imply that coherence between SYMP outflows was masked by afferent modulation. This is the first evidence suggesting that afferent inputs in the young animal might be creating interference patterns between the networks driving different SYMP outflows such that coherence decreases; yet, in older piglets, these afferents increase entrainment over these same frequency bands. In addition, PHR partialization increased the coherence value of a higher frequency band (16-18 Hz) in the CS - SPL coherence spectra in younger piglets; this was not observed in spectra from older animals.

Our results, to date, indicate that the 19-24 days period seems to be pivotal for neonatal swine. At this age coherence is suddenly very significant between SND from different segmental levels and responses to complex afferent inputs are now obtained. All these findings suggest maturation of integration within emergent networks that show coupling at this age. In addition, the central pattern generator for RESP activity shows significant linkage with the SYMP rhythm generator(s) within this time frame. Thus, we may be approaching an explanation for the end of the critical period in the life of the newborn (establishment of linkage). Recently, we raised the possibility that the 'window of occurrence' for Sudden Infant Death Syndrome is a reflection of a delay (or abnormalities) in the coherence between the RESP and SYMP pattern generators (Gootman et al. 1995). A delay might predispose failure of coordination of these systems such that cardiorespiratory dysrhythmia and death might ensue.

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