Nordic Journal of Music Therapy, 16(1) 2007, pp. 42-59.

Autonomic Responses to Music and Vibroacoustic Therapy in Rett Syndrome

A Controlled Within-subject Study

Märith Bergström-Isacsson, Peter O.O. Julu & Ingegerd Witt-Engerström

Abstract

We investigated the influence of music and vibroacoustic therapy (VT) on the autonomic nervous system in persons with Rett syndrome (RTT) at the Swedish Rett Centre in Östersund because professionals and families alike often claim that music plays a very important role in the lives of these people. The families even claim that they sometimes use music as "medicine" to calm down the Rett persons when nothing else seems to help. We studied 21 persons with RTT in the years 2003 and 2004. These were patients coming to the Rett Centre for routine brainstem assessment. The control status was the subject's own baseline autonomic function during rest. Subjects were stimulated using horn music, calming and activating music, then VT and VT with calming music embedded in it. The results show that it was possible to measure responses to music and VT within this group. These responses were unique for different stimuli. The horn music caused physiological arousal, activating music caused sympathetic response, and calming music caused parasympathetic response in our subjects. We also learned that observation of behaviours alone might be misleading and may not represent the autonomic responses accurately. It was also impossible to predict responses to different kinds of music. For example, each patient had different and unique calming music.

We concluded that music and VT have measurable effects on brainstem autonomic functions in persons with RTT. The effects are diverse and difficult to detect by observation of behaviours alone therefore would require formal and clinical monitoring of brainstem autonomic functions. This presents a new area for further research. We particularly hope that a clear understanding of the diverse effects of music and VT on autonomic functions will be helpful when forming the bases of rational uses of music in clinical management of persons with RTT.

Keywords: *Autonomic nervous system, brainstem examination, influences of music and vibroacoustic therapy, controlled within-subject study.*

Introduction

Rett Syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder found all over the world. The incidence can be as high as 1:10 000 female births in the most thoroughly investigated areas of the world (Kerr & Witt-Engerstrom, 2001). Andreas Rett was the first person to discern this disorder and publish it (1966).

Rett syndrome disorder is seen mainly in females. Various mutations in the gene for the methyl-CpG-binding protein 2 (MECP2) on the X-chromosome have been reported as a possible cause of RTT (Amir et al., 1999). Mutations of this regulatory gene cause disruptions of normal growth of neurons in the central nervous system (Kerr & Witt-Engerstrom, 2001). Persons with RTT include females of all ages and very few males (Leonard et al., 2001). Young children with RTT have an apparently normal initial development in the early period of life. RTT occurs in four stages. Stage I occurs at around nine months, when, after an apparently normal initial development, a delay in development appears. Stage II (15 months to 2 years) is a period of clinical regression when the loss of acquired abilities, such as communication and purposeful hand function, are accompanied by agitation and sometimes even anguished screaming. Then the clinical picture changes without warning. The child may regain some of the earlier abilities and start to communicate in a simple way or may even develop new skills. This is referred to as stage III. However, the neurological imbalance can cause gross motor problems with difficulties in movements and contractures may develop. Loss of or inability to walk is referred to as stage IV (Kerr & Witt-Engerstrom, 2001; Witt-Engerstrom & Hagberg, 1990).

Breathing difficulties are frequent in RTT. After years of research one has to this date identified 13 different abnormal breathing patterns. These patterns are fundamental for categorizing RTT into three phenotypes: *Apneustic breathers*; breath holds, regular breath holds, and protracted inspiration, *Feeble breathers*; rapid shallow breathing, shallow breathing, and central apnoea and *Forceful breathers*; hyperventilation, tachypnoea, and deep breathing. One state that is a result of breathing abnormalities is Valsalva´s manoeuvre, which is achieved by raising intrathoracic pressure using breathing movements. This state causes a characteristic change in blood pressure and heart rate (Julu & Witt-Engerström, 2005).

Observed Influences of Music in Rett Syndrome

There is considerable need for music among Rett persons according to those most associated with them. Parents, carers, and therapists have reported how this influences the daily life of persons with RTT (Hill, 1997; Holdworth, 1999; Merker, Bergström-Isacsson, & Witt-Engerström, 2001; Merker & Wallin, 2001; Montague, 1988; Wigram, 1991). Re-training to gain the lost skills and the learning of new tasks is possible in RTT and has been reported (Jacobsen, Viken, & von Tetzchner, 2001; Larsson & Engerstrom, 2001). Earlier research also tells us that music and music therapy appears to enable Rett persons to perform many tasks including functional hand use, which reduces stereotyped movements. Music can encourage Rett persons to make choices of toys, to vocalize, or pay attention and make eye contact when they would have normally not done so. Quite a large amount of studies have been done about how music appears to elicit emotion and creates communicative channels in Rett persons with moments of relaxation and calm (Allan, 1991; Bergström-Isacsson, 2001; Coleman, 1987; Elefant & Lotan, 2004; Hadsell & Coleman, 1988; Hill, 1997; Wesecky, 1986; Wigram, 1991; Wigram, 1995). Music therapists use songs as

MÄRITH BERGSTRÖM-ISACSSON, Swedish National Rett Centre. Address: Box 601, 832 23 Frösön, Sweden. Email: marith.bergstrom-isacsson@jll.se

PETER O.O. JULU, Dr. med., Swedish National Rett Centre, Frösön, Sweden/Breakspear Hospital, Hemel Hempstead, London.

INGEGERD WITT-ENGERSTRÖM, Dr. med., Swedish National Rett Centre, Frösön, Sweden.

tools for enhancing non-verbal communication. Surveys from Sweden and USA confirm how families and carers of Rett persons sometimes use music as a kind of medicine in situations when nothing else seems to work.(Elefant, 2002; Houtaling, 2003; Merker, Bergström-Isacsson, & Witt-Engerström, 2001).

Although music plays an important role in the lives of Rett persons, and most of them have at least one favourite tune, they are not capable of describing their own reactions or feelings in response to music or vibroacoustic therapy (VT). Nevertheless, much is still said about the Rett person's favourite tunes and the interpretation of their reactions to such tunes (Elefant, 2002; Mount et al., 2001b). We can only try and interpret the external reactions of Rett persons to music and VT without knowledge of the internal responses. It is therefore legitimate and reasonable at this stage to ask what really happens inside the Rett person in response to music. Are there different internal responses to variable types of music in Rett persons? These are two specific questions to be addressed in this present study. We know that music plays an important role in the lives Rett persons and most of them have a favourite tune or tunes.

The Autonomic Nervous System and the Output of Emotion

The autonomic nervous system is part of the motor output of emotion (Best & Taylor, 1966; Guyenet et al., 1996b). It mediates the visceral component of emotional output (Best & Taylor, 1966; Jordan, 1990; Jordan, 1991). The autonomic nervous system is made up of the sympathetic and the parasympathetic systems. These two sub-divisions of the autonomic nervous system influence most basic functions of the body including among other things breathing, the heart rate, and blood pressure. The brainstem sympathetic activity has a very close relationship with the changes in the mean arterial blood pressure (Sun & Guyenet, 1986). Therefore, the changes in the mean arterial pressure can be used as a non-invasive index of the brainstem sympathetic activity. It is now possible to monitor the mean arterial pressure heartbeat-by-heartbeat continuously using non-invasive methods (Idema et al., 1989; Jellema et al., 1996). Moreover, it is also possible to monitor cardiac vagal tone (CVT) continuously in real-time by non-invasive methods (Julu et al., 2003) and CVT represents brainstem parasympathetic activity. It means that the present advance in medical technology can allow us to monitor both sympathetic and parasympathetic activities in the brainstem using non-invasive methods by monitoring changes in mean arterial pressure and levels of cardiac vagal tone. These variables can be monitored simultaneously and continuously in real-time. We have used this new advance in medical technology to monitor brainstem autonomic activity as an index of emotional output in response to music and vibroacoustic therapy in Rett persons.

Aims and Hypotheses of the Study

Our aim was to investigate the emotional output in response to music and vibroacoustic therapy in Rett persons referred to the Swedish National Rett Centre in a period of one year. All Rett persons referred to the centre for brainstem examinations within the selected period were potential subjects for the study. The hypotheses of this investigation were formulated on the bases that emotional output would influence the brainstem autonomic activity in the following manners. First hypothesis: Emotional excitement will increase brainstem sympathetic activity above the resting baseline level. Second hypothesis: Relaxing or calming emotional response will increase brainstem parasympathetic activity above the resting baseline level. Third hypothesis: Arousal response without evoking a relaxed or excitement states will only cause physiological arousal measurable in the brainstem autonomic activity. The definition of the brainstem activity that signifies physiological arousal is given below in the Methods.

Materials and Methods

Subjects

This is a controlled within-subject study, also described as an auto-control study. It means that the same person is both a control and a test subject. The subjects are allocated to the different stimuli in a controlled order; horn music, calming music, activating music, VT and VT embedded with music.

Research shows that RTT population has an immature brainstem all through life (Julu et al., 1997) and the subjects are therefore matched according to brainstem maturity and not to age. Our subjects were persons with RTT who were coming to the Swedish Rett Centre for the examination of brainstem autonomic function in the calendar years 2003-2004. Further information about the subjects is given in the Results section.

Equipment and Materials

A bean-sack called "Musik-Molly" with built-in loudspeakers was used for administering vibroacoustic therapy. The musical elements of the vibroacoustic therapy come from an external compact disc (CD) player. A proprietor CD plays a tune of frequency 40 Hz and a peak of 89.4 decibels delivered directly to the seat to provide the vibroacoustic stimulus. The NeuroScope system (MediFit Instruments, Ltd, London, UK) was used specifically to measure cardiac vagal tone (CVT) and breathing movements, but was also generally used to collate and synchronisedother vital signs like arterial blood pressure, pO_2, and pCO_2 from other equipment. The NeuroScope obtains the electrocardiogram (ECG) used for measuring CVT directly from the subject via pre-jelled electrodes attached to the chest. Breathing movements are measured using a pieuzo-electric plethysmographic belt placed at the xiphisternal level around the chest. By attaching gas-sensing electrodes immediately above the liver, blood levels of oxygen and carbon dioxide was measured transcutaneously using a TCM3 machine (Radiometer, Copenhagen, Denmark). A finger-cuff was used to measure systolic, diastolic, and mean arterial blood pressure for each and every pulse by photoplethysmographic method using the Finapres (Omheda, CO, USA). The equipment for breathing movements, arterial blood pressure, the transcutaneous oxygen and carbon dioxide were all connected to a Medulla Lab (MediFit Instruments, Ltd., London, UK), which is part of the NeuroScope system. The electroencephalogram (EEG) was measured via a head cap fitted with built-in electrodes and worn like a swimming head cap. This was connected to a paperless video EEG machine (Nervous, Copenhagen, Denmark). The camera for the video EEG machine was focused mainly in the face of the subject, while another digital video recorder was used to record all other behaviours and movements during the registration. The internal clocks in all equipment in this study were synchronised to the nearest one second.

Monitoring of Brainstem Autonomic Function

Continuous real-time measurement of brainstem autonomic activity was carried out in the manner described by Julu and Witt-Engerström (2005). Briefly it was done as follows: Cardiac vagal tone (CVT) believed to be regulated by nucleus ambiguous in the caudal part of the ventrolateral medulla oblongata (Guyenet et al., 1996a), Cardiac Sensitivity to Baroreflex (CSB) believed to be regulated by the commissural part of the nucleus of tractus solitarius in the lower part of the dorso-medial medulla oblongata (Kasparov & Paton, 1999), arterial blood pressure, especially the mean arterial blood pressure (MAP) known to be regulated in the rostral ventrolateral medulla oblongata (Guyenet, 1990) and the heart rate (HR) which is regulated by both the nucleus ambiguous in the lower part and the cardioaccelerators in the rostral part of ventrolateral medulla oblongata (Jordan, 1995) were measured in synchrony and in real-time and interpreted beat-by-beat for every heart beat. Breathing movements, both the rate and rhythm known to be regulated by the ventrolateral brainstem from as low down as the level of first vertebrate to as rostral as the parabrachial nuclei in the ponds and the dorsal respiratory group of neurones in the vicinity of the nucleus of tractus solitarius (Blessing, 1997) were also measured in synchrony with the rest of brainstem functions. The transcutaneous partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2) representing blood gases were also recorded in synchrony. Blood gases are believed to be regulated in the medulla oblongata in conjunction with inputs from the arterial chemoreceptors (Spyer, Dale, & Gourine, 2004). The NeuroScope's method therefore quantifies, monitors and records the cardiorespiratory functions of the brainstem in real-time thereby facilitating the study of both temporal and causal relationships of brainstem responses to external stimuli.

What was Actually Measured by the NeuroScope's Method

All the procedures are non-invasive and painless. Breathing movements, pO_2, pCO_2, arterial blood pressure (BP) waveforms for the calculation of systolic, and mean and diastolic BP beat-by-beat were all collated by the NeuroScope system. The NeuroScope™ also monitors continuously the brainstem's regulation of cardioinhibitory activity known as cardiac vagal tone (CVT). This is measured in the form of a non-invasive index defined as "pulse-synchronised phase shifts in consecutive R-R intervals", which quantifies the CVT (Little et al., 1997). It is a form of R-R intervals variability. Here, the machine calculates the CVT from ECG R-R intervals as previously described (Little et al., 1999) and displays it on the screen in arbitrary units of a linear vagal scale (LVS). This scale is fully validated for clinical measurement of CVT (Julu, 1992).

The VaguSoft software (MediFit Instruments, Ltd., London, UK) in the NeuroScope system synchronises the ECG, HR, CVT, systolic, mean and diastolic BP, levels of blood gases, and calculates the cardiac sensitivity to spontaneous arterial baroreflex (CSB). The CSB is defined as the change in pulse intervals per unit change in systolic blood pressure and this is calculated beat-by-beat for every heart beat (Julu et al., 1996). It is a measure of the negative effect of blood pressure on HR and its measurement is made possible by the synchronous records of both ECG and BP waveforms.

The electroencephalogram (EEG) was recorded by a 16-channel Paperless-EEG (Nervus, Copenhagen, Denmark) via a head-cap. This is a quicker method and is well tolerated by Rett patients. A continuous video record time-locked with the physiological measurements is kept for behavioural analysis.

The Stimuli We have Used

We have described our stimuli using terms such as: activating, calming, or favourite music based on the authors', parents,' and carers' descriptions of the subjects' behaviours towards their favourite tunes. We had a total of five stimuli applied consecutively to each subject in this study.

Activating music – chosen by parents or carers. This is usually music with an up-tempo beat, or songs with a catchy refrain. In each case, repeats and clear rhythms encourage smiling, body movement, increased rate of breathing, rising of body, and increased contact with the surrounding. An exemplary music with such effects on one of our subjects is "Maya Piraya" by Lasse Åberg/ Janne Schaffer.

Calming music – chosen by parents or carers. This is usually music with a slow beat that gives a sense of physical security. It can climb towards refrain (expectancy) with soft lyrics and a supportive basic rhythm. The music can provoke responses in the forms of calmness, mental concentration, and or poverty of body movements. "Candle in the Wind" by Elton John was the calming music for one of our subjects.

Horn music. Our initial concept of a very basic response to music stimulation was that we should be able to observe at least evidence of physiological arousal in our subjects. The most appropriate stimulus for arousal in humans would be a horn call. This is because, for example, in fox hunting we use the horn for calling the hunters, in the military we use a horn (the beagle) for calling the soldiers and in the early days of the motorcar, we used the horn to warn pedestrians on the road. Therefore, music with a horn call embedded in it would be an appropriate stimulus for provoking arousal in humans. The music we chose is an unknown piece of goat-horn music suggested by Björn Merker, our former colleague. His explanation was that this piece of music is short, simple, and distinct at the start, which makes the beginning very clear. It also includes a complete musical sequence, which is unknown to all our subjects.

Vibroacoustic Therapy (VT). We used a 40 Hz carrier signal that is amplitude modulated using a sinusoidal wave of 5 seconds period to allow a peak of 89.4 dB to be delivered at the point where the subjects sit. This complex signal was chosen from earlier studies and our experiences that it is usually the carrier frequencies under 60 Hz that are most effective for persons with RTT (Skille, 1991; Wigram & Dileo, 1997).

VT and Music. The same VT stimulation as above but we added music (track 4 and 5 from CD Keeper of Time by INDIGO, Theta) chosen by the music therapist. We took this opportunity to examine if music embedded within VT increased the parasympathetic responses more than VT alone. We also examined the brainstem's competence in processing responses evoked by dual stimulation. It would give us a good indication whether the Rett person would be better off with one stimulus at a time or whether the patient can cope with dual or even multiple stimulations for future treatment.

Experimental Protocol

The relatives or carers were asked about how they would normally use music and how they interpreted the Rett person's reactions to music. The Rett persons would then sit comfortably in a reclined position with the carer or relatives holding one of the hands in position for blood pressure monitoring for at least one hour during brainstem assessment. The one-hour procedure began by monitoring and recording the brainstem autonomic activity during baseline status. This was defined as a status where the subject was awake and was breathing normally with no signs or evidence of agitations. In this status, the blood gases must be at normal levels and there must be no epileptiform activity in the EEG. A minimum baseline recording lasting one minute is sufficient, but longer periods of up to five minutes can be recorded. The Rett persons were then subjected to the five different stimuli described above after the baseline recordings in the following order: Horn music, activating music, calming music, VT only then VT with music. The subjects were exposed to horn music, activating music, and calming music for two minutes. The VT and VT with music interventions were both ten minutes in duration. There was a time difference because we tried to simulate a normal situation of VT treatment as close as was practically possible. The usual VT session is approximately 25 minutes, but it was impossible for us to carry out 25-minute stimulations twice during the brainstem monitoring session, which lasted only 60 minutes. Therefore, we compromised at a 10-minute duration each for two VT stimulations.

Markers were placed live in the records at the exact time for the starts and stops of the different stimuli during the procedures. These were to be used afterwards during data analyses. Everything being monitored was displayed on the computer screen and the curves could be seen live enabling an immediate discussion of the responses in order to make adjustments of the procedures. This was particularly useful for making sure that the subject had recovered from the previous stimulus before administering the next one to avoid a run-on response. The entire brainstem monitoring was synchronised with a video recording of the subject's physical activity to facilitate detailed study of behaviours later on.

Analyses of Data

Table 1 illustrates the rules we used for our data analyses. These rules were set up according to our study hypotheses and guided by the physiological definitions of arousal, being part of the defence responses. This means that an increased brainstem parasympathetic activity is similar to what happens in drowsiness or the desire to go to sleep (Delamont, Julu, & Jamal, 1998) and indicates a calming response and the relevant indicators that are shown in Table 1. Increased brainstem sympathetic activity as in the preparation for a physical exercise (Jordan, 1991) requires increased arterial blood pressure facilitated by the reduction of parasympathetic activity and the relevant indicators are shown in Table 1. The initial phase required for increasing arterial BP is the reduction of CSB, which is the negative feedback control of arterial BP. Therefore, CSB is the index that reacts most quickly and if there was only mild physiological arousal, it may be the only measurable response as is suggested in Table 1. Increases in either

Responses	***CVT***	***CSB***	***MAP***	***MAP_CV***
Parasympathetic response	CVT and/or CSB must increase	CSB and/or CVT must increase	Decrease or no change	5%, less or more
Sympathetic response	Decrease or no change	Decrease or no change	Must increase	5% or more
Arousal	Decrease or no change	Must decrease	Increase or no change	5% or more

Table 1: *The criteria used in the analyses and the designations of the types of autonomic responses to five different music and vibroacoustic stimuli (see text for details of the stimuli). CVT = Cardiac vagal tone, CSB = Cardiac sensitivity to baroreflex, MAP = Mean arterial blood pressure and MAP_CV = Coefficient of variation of the mean arterial blood pressure. Increases, decreases or no changes at all were measured relative to the baseline levels of the respective cardiovascular indices. Arousal = Physiological arousal and this can progress into a sympathetic response.*

sympathetic or parasympathetic activity will increase the variability of the arterial BP. The average baseline coefficient of variation in MAP was 5% or less. A variability of MAP above 5% indicated changes in the autonomic tone above the baseline level is illustrated in Table 1.

All the responses to the music stimuli were measured during the last minute of stimulation. This is because the initial part of the stimulation mainly includes the readjustment to the new stimulus and the priming of the brainstem response. For the VT, the responses were measured during the last 100 heartbeats of the stimulation. Since the VT stimulations were for relatively longer periods, we took advantage of the facts that autonomic cycles are event based and not time based. Therefore the appropriate periods of stimulation can be measured in numbers of autonomic cycles, that is, heartbeats instead of time. Since the brainstem responses to the various stimuli were varying continuously, we measured the maximum and minimum changes in each brainstem activity separately and in addition calculated the average value of the given activity within the specified time period defined above. All values were then expressed and presented as percentages of the baseline values. These are therefore relative changes compared to baseline levels and the maximum, minimum, and averages changes are all presented in the Results in this manner. Since the patients' relatives or carers were the ones that chose the activating and calming music, we investigated whether the subjects responded appropriately to every stimulus according to our hypotheses. We counted and presented in the Results the number of subjects who responded appropriately and those who did not. We also investigated the type of stimulus that provoked predominantly sympathetic or predominantly parasympathetic responses or exclusively arousal responses by counting and presenting in the Results the number of the respective subjects. We quantified the intensities of the sympathetic responses using MAP as the quantifiable index of sympathetic activity and we measured the total intensities of the parasympathetic responses using CVT and CSB as quantifiable indices of parasympathetic activity. These were calculated by combining together all individual relative changes in CVT and CSB to get the overall average value in response to the respective stimuli. Baseline values of autonomic tone were presented as means ± one Standard Deviation (*SD*). All the values we have measured or calculated were stored into a database together with the baseline values for each person.

The results obtained from the autonomic monitoring were also interpreted in relation to the auxiliary observations of the external behaviours

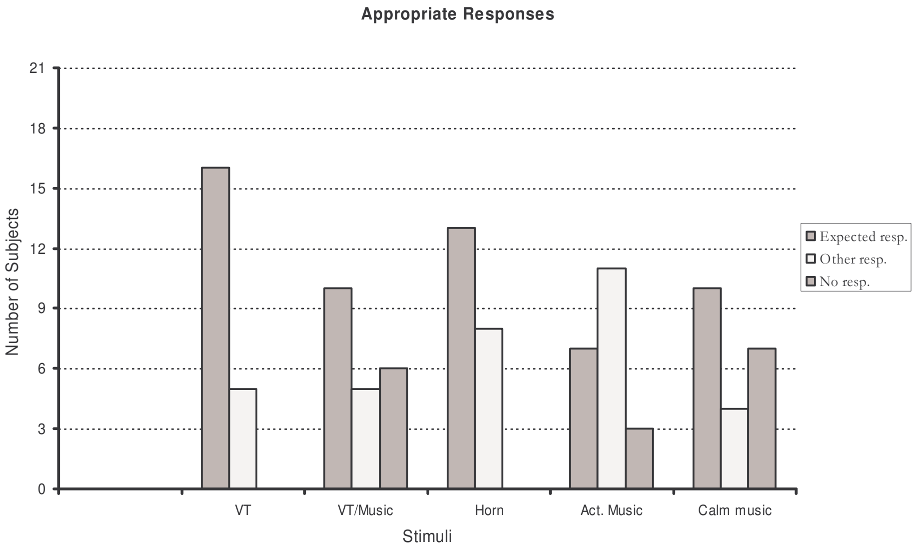

***Figure 1**: Appropriate Responses.*
Bar graphs showing the frequency, measured as number of subjects, and the nature of responses to five music and vibroacoustic stimuli. Expected resp. = Appropriate responses to the respective stimuli according to the prediction of the study hypotheses. Other resp. = Opposite or unexpected responses to the respective stimuli contrary to the prediction of the study hypotheses. No resp. = No significant change in any of the cardiovascular indices measured in response to the stimulus. There were appropriate responses to all the five stimuli. VT = Vibroacoustic therapy, VT/Music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Act. Music = Activating music, and Calm music = Calming music (see text for details of the nature of the five stimuli).

classified as normal or abnormal movements in the faces, arms, body, and breathing rhythms.

Results

Subjects

A total of 21 persons participated in the study, 20 girls and 1 boy. Out of possible 22 subjects, one was excluded due to the lack of sufficient baseline recording. The participating subjects were between 3-44 years old; their mean age was 20.9 ± 10.7 years. The baseline CVT in all these subjects was 4.6 ± 2.8 units in the LVS; CSB was 3.8 ± 2.9 ms/mmHg. The average baseline MAP was 65.8 ± 14.9 mmHg and HR was 92.2 ± 18.2 beats/min. Baseline breathing rate was 18.4 ± 4 breaths/min. There were 6 subjects (28.6%) classified as Forceful breathers, 8 (38%) were Feeble breathers, 6 (28.6%) were Apneustic breathers, and 10 (47.6%) had Valsalva's manoeuvre as a complication of breathing.

Appropriateness of Autonomic Responses

There were at least some appropriate responses to all five stimuli according to the study hypotheses (Figure 1). However, some subjects did not respond as defined in the hypotheses and some subjects did not respond at all to some stimuli. Notably the dual stimulation with VT and music, the activating or calming music chosen by the relatives or carers were the three stimuli that evoked no responses at all in some subjects (Figure 1). It was also notable that all the subjects responded in one way or the other to VT alone or to the horn music.

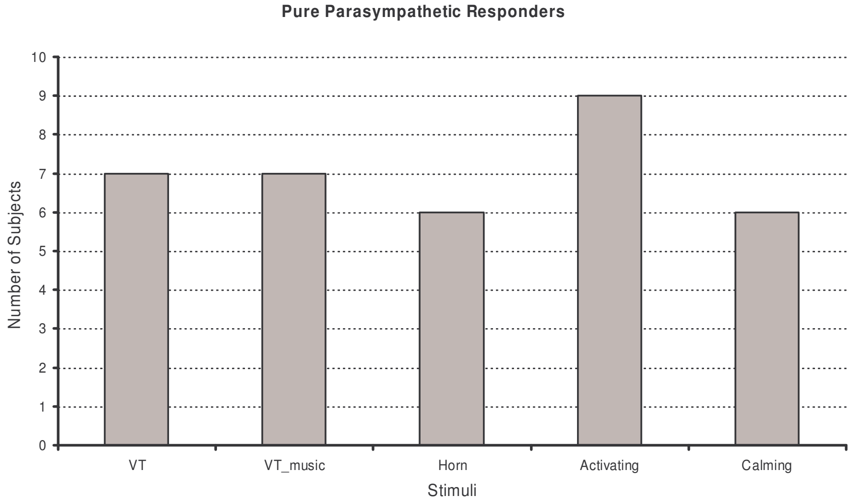

***Figure 2**: Pure Parasympathetic Responders.*
Bar graphs showing the frequency of pure parasympathetic responders to five music and vibroacoustic stimuli. VT = Vibroacoustic therapy, VT_music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Activating = Activating music, and Calming = Calming music (see text for details of the stimuli).

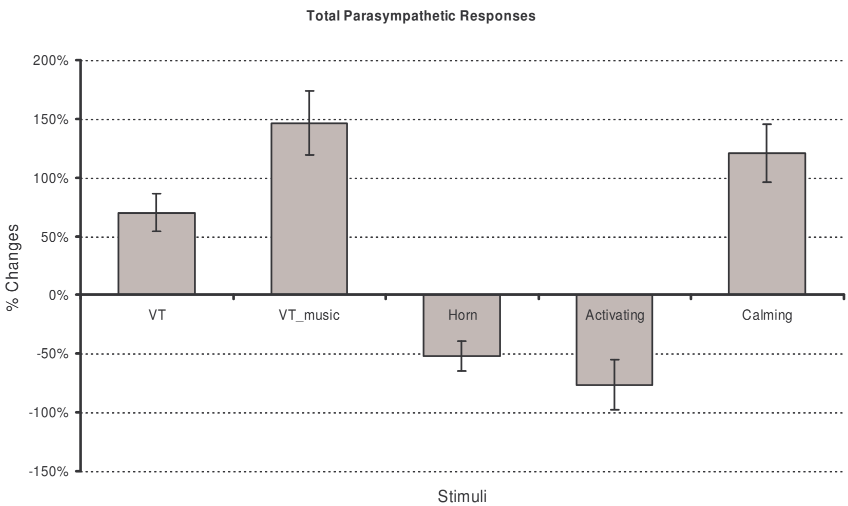

***Figure 3**: Total Parasympathetic Responses.*
Bar graphs showing the intensities of the parasympathetic responses to five music and vibroacoustic stimuli measured as the combined total percentage changes in levels of cardiac vagal tone and cardiac sensitivity to baroreflex. VT = Vibroacoustic therapy, VT_music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Activating = Activating music, and Calming = Calming music (see text for details of the stimuli). The horn music and the activating music caused net reductions of parasympathetic activity below the baseline levels while the other stimuli caused net increases in parasympathetic activity above the respective baseline levels. The error bars are standard errors of the respective means of the percentage changes among the responders.

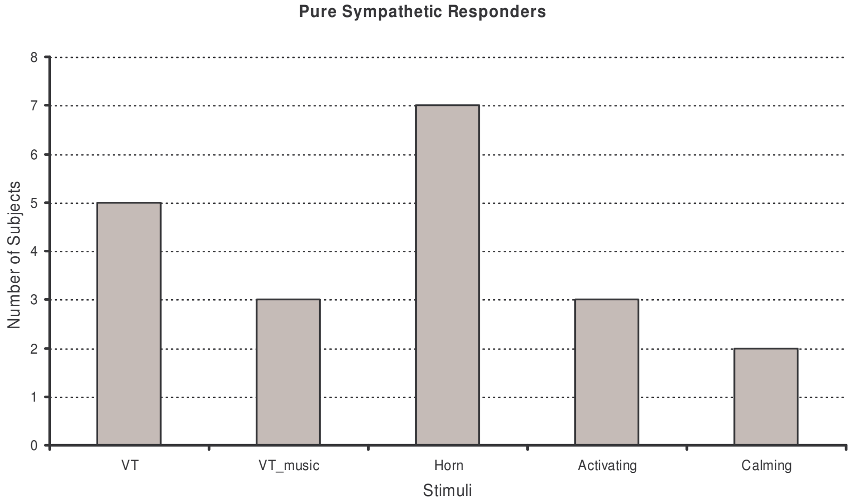

***Figure 4**: Pure Sympathetic Responders.*
Bar graphs showing the frequency of pure sympathetic responders to five music and vibroacoustic stimuli. VT = Vibroacoustic therapy, VT_music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Activating = Activating music, and Calming = Calming music (see text for details of the stimuli). It is notable that the horn music caused the most frequent pure sympathetic responses among our subjects.

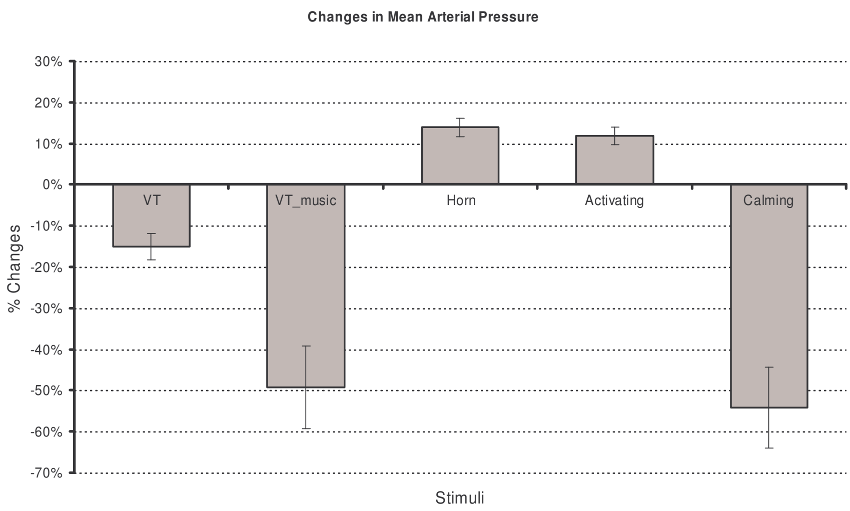

***Figure 5**: Changes in Mean Arterial Pressure.*
Bar graphs showing the percentage changes in the Mean Arterial Pressures in our subjects in response to five music and vibroacoustic stimuli. All the changes were measured relative to the baseline values of the means arterial pressures. VT = Vibroacoustic therapy, VT_music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Activating = Activating music, and Calming = Calming music (see text for details of the stimuli). The horn and activating music caused net increases in the mean arterial blood pressures in the responders while other stimuli caused net reductions compared with the respective baseline levels. It is notable that Vibroacoustic therapy accompanied by music and calming music were the most effective stimuli for the reduction of the mean arterial blood pressure in responders. The error bars are standard errors of the respective mean percentage changes among the responders.

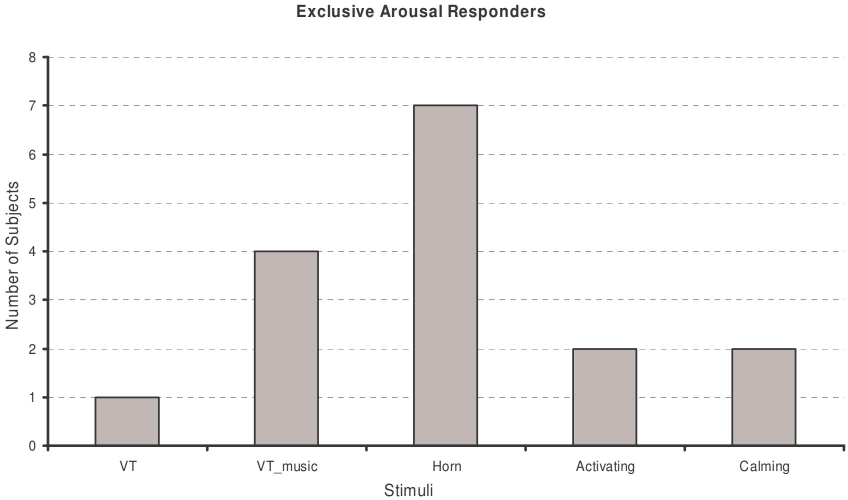

***Figure 6**: Exclusive Arousal Responders.*
Bar graphs showing the frequency of responders with exclusive physiological arousal responses to five music and vibroacoustic stumuli. VT = Vibroacoustic therapy, VT_music = Vibroacoustic therapy accompanied by a calming music, Horn = Horn music, Activating = Activating music, and Calming = Calming music (see text for details of the stimuli). It is notable that the horn music caused the most frequent arousal responses among our subjects.

Overall Parasympathetic Responses
We counted the number of patients with an exclusive parasympathetic response to each of the five stimuli and found that it was the "activating music" that caused the most frequent responses (Figure 2). A few of our subjects had exclusively parasympathetic responses to all of the five stimuli. Parasympathetic response was, however, the most common response in many of o our subjects to virtually all the stimuli.

In order to quantify the intensities of the parasympathetic responses within the responders, the percentage changes of CVT and CSB were added together to represent the total parasympathetic response of each subject and then the mean value within the group was used to represent the overall parasympathetic response in our subjects for each stimulus (Figure 3). The stimulus that evoked the most intensive parasympathetic response within the group was the dual stimulation with VT and music, while the horn and the activating music evoked an overall parasympathetic withdrawal within the responders (Figure 3).

Overall Sympathetic Responses
We counted the number of patients with exclusive sympathetic response to each of the five stimuli and found that the horn music caused the most frequent sympathetic responses (Figure 4). A total of 20 subjects had exclusively sympathetic responses to at least one of the five stimuli we used.

In order to quantify the intensities of the sympathetic responses, the average changes in MAP within the responders were used to indicate the intensities of the sympathetic responses to the stimuli (Figure 5). These may or may not be associated with decreases in either CVT or CSB (see Table 1 for definitions). Only the horn and activating music caused an overall increase in the average of MAP within the responders (Figure 5). Vibroacoustic stimulation with or without embedded calming music and the "calming music" all decreased the average MAP.

Exclusive Arousal Responses
Significant reductions of CVT and or CSB without any significant change in MAP represented a physiological arousal (Table 1). We counted the

number of patients with exclusive physiological arousal response to each of the five stimuli and found that the horn music caused the most of the arousal responses (Figure 6). A total of 16 subjects had exclusive arousal responses to at least one of the five stimuli.

Discussion

We investigated the influence of music and VT on the autonomic nervous system in persons with RTT using objective neurophysiological measurements that the Swedish National Rett Centre uses for routine diagnostics and clinical management of RTT (Julu & Witt-Engerström, 2005). We were able to quantify the brainstem autonomic responses to music as indicated by the changes in CVT, CSB, and MAP, but our inferences of the emotional reactions whether it was calming, activating or just arousing responses were based on physiological descriptions of the changes in these indices during the emotions in the defence responses. Our interpretation was facilitated by observations of the person's immediate physical response to the stimulus, which we have also recorded in video for repeated reviewing if need be. We can therefore say that the influences of music and VT on brainstem autonomic functions are quantifiable using these methods. To our knowledge, this is the first objective and quantitative physiological measurement of the emotional responses to music and vibroacoustic stimulation using this kind of technical equipment.

Our sample of Rett persons included all the cardiorespiratory phenotypes, namely Feeble, Apneustic, and Forceful Breathers in similar proportions to that previously described in the Rett population (Julu & Witt-Engerström, 2005). The proportion of subjects with the common complication of Valsalva's manoeuvres among our subjects is also similar to what was previously reported in the RTT population (Julu & Witt-Engerström, 2005). We may therefore assert that we have a reasonable representation of the RTT population in our study even if we are aware of the limited number of subjects.

Much has been written about the importance of music among patients with RTT, especially about drawing their attention, or for the purposes of communication and relaxation (Allan, 1991; Bergström-Isacsson, 2001; Coleman, 1987; Elefant, 2002; Hadsell & Coleman, 1988; Hill, 1997; Merker & Wallin, 2001; Montague, 1988; Wesecky, 1986; Wigram, 1991; Wigram & Cass, 1995). It has even been reported that relatives of Rett patients use music as a sort of medicine when nothing else works (Merker, Bergström-Isacsson, & Witt-Engerström, 2001). There are also reports of the use of VT in persons with RTT (Skille, 1991; Wigram & Dileo, 1997). However, all of these studies offer explanations that are based on behaviour analyses and external observations of the subjects. These observations have not been substantiated with objective physiological measurements of the responses of the Rett persons. There is therefore a justifiable need for quantitative physiological measurements of the effects of music and vibroacoustics in persons with RTT not only because of the popular use, but also to give us some insight into the interaction between emotion and music. The Rett persons have no ability to influence their own responses to music. Therefore, there is no bias or placebo effects in their responses. Nevertheless, Mount et al. (2001a) have noted difficulties in understanding how RTT persons responded to calming music in particular. They identified that music intended to provide a calming and relaxing effect sometimes produced a noticeable increase in the level of anxiety in some subjects. Woodyatt and Ozanne (1992; 1994) proposed that hyperventilation is a sign of such music-related anxiety, especially when the patient hears a familiar music. We have also observed in this present study some unexpected autonomic responses to our music and vibroacoustic stimuli. Interpretation of responses to music is not as straight forwards as we would wish in RTT and we hope that our hypotheses based on objective physiological measurements here in this present study will help in the understanding of some of the mechanisms driving the responses to music and vibroacoustics.

It is clear from our results that it is possible to influence both the parasympathetic and the sympathetic activities of the autonomic nervous system using music and or VT. We have also observed that the majority of responders to our five stimuli responded appropriately according to our study hypotheses, except the responses to the activating music chosen by the parents or carers where the majority of the responders had the opposite autonomic reactions to what the study hypothesis had predicted. It is also encouraging in this present study that the two carefully chosen stimuli, the horn music and vibroacoustic on its own, both evoked responses in one way or the other without fail. There were non-responders to dual stimulation with vibroacoustic with embedded music, but this could be due to inability of some Rett persons to respond to multiple stimulations. We have observed in the Swedish National Rett Centre that some Rett persons with higher degrees of immaturity of the brainstem seems to respond only to a single stimulus at a time and do not respond to dual or multiple concurrent stimuli. The high frequency of the reverse effect of the activating music and many non-responders to the calming music, both of which were chosen by parents or carers on the basis of observations of the external behaviours of the patients, actually highlights how difficult it is to interpret responses to music. We need more research before we can draw firm conclusions and the discussion below explores the role of the autonomic nervous system in human responses to music and to vibroacoustics.

Calming Music – Predominant Parasympathetic Responses were Expected

When the parasympathetic system is activated a person feels calm, safe, and relaxed. This is the status adopted during feeding or at meal times. The relatives or carers were asked to bring with them the music they thought had a calming effect for the patient and we used that music as a stimulus for that particular patient only in this study. It implies that there were many different types of music used for this purpose as explained in the Methods. We assumed that a calming music means the music that evokes the calming side of emotion, the music that may arouse good and pleasant memories. However, it can also be a kind of music that produces tears.

Of the three types of responses we investigated, the calming music evoked pure parasympathetic responses more frequently among the responders. It was the worst stimulus for evoking pure sympathetic responses based on counting the number of responders. The calming music was the second most efficient stimulus for evoking intense parasympathetic response judging from the combined magnitudes of CSB and CVT changes. It was also the best stimulus for lowering the mean arterial blood pressure. The parasympathetic responses and blood pressure changes are consistent with a calm and relaxed emotion evoked by this type of music in our subjects.

Persons with RTT cannot express in words or explain clearly what is happening to them. It is understandable that tears in their eyes can cause fear amongst the people around the patient and may make the carers think that the patient does not like the music. However, it is possible that such tears convey joy rather than sorrow, like rather than dislike, and when this is the case it may be very unfortunate if carers avoided playing calming music to boost low parasympathetic activity in RTT.

Activating Music – Predominantly Sympathetic Responses were Expected

The relatives and carers have described with strong convictions the kind of music that activated the Rett persons and made them happy and alert. This is the music that is most often used and the one the family and the carers rely on when the patient is upset, sad, or angry. Again there was a variety of music for the different subjects and we used only one type of music recommended by the parents or carers for the respective subjects. Despite the strong convictions of the parents about the effects of the activating music, the results of this study show that only 33% of the subjects reacted as we expected. This was rather a surprise to the relatives and the professional carers alike. They were convinced they had interpreted the persons´ reactions correctly and that the persons were indeed activated and felt well with the music.

Our results indicates that the music described by parents and carers as "activating music" was most efficient in evoking pure parasympathetic responses and quite poor in evoking pure sympathetic responses judging from the counts of the number of responders. We assumed that activation of a person involved stimulation of sympathetic activity in preparation for the impending increase in physical activity. Increased sympathetic activity would invariably be associated with increased arterial blood pressure since MAP is linearly related to the brainstem sympathetic activity (Sun & Guyenet, 1986). Our measurements of the intensities of the autonomic responses showed that the activating music caused an overall elevation of MAP, but it caused an overall reduction of the combined levels of CVT and CSB. This is consistent with sympathetic stimulation. The intensity of the autonomic responses in the appropriate responders has therefore confirmed sympathetic stimulation evoked by the "activating music". We know that patients with the RTT have low baseline CVT and CSB compared to age matched controls (Julu et al., 1997) and excite easily because they lack sympathetic inhibition. Consequently, further reducing an already low CSB and CVT by introducing activating music could cause serious autonomic imbalance. The relatives and the professional carers have no access to autonomic data when playing music, and therefore they would be unaware of the cardiovascular changes caused by activating music. Subsequently, it may be prudent to limit the use of activating music unless there is a way to monitor whether or not the patient is "over reacting" to the stimulus.

Horn music – Physiological Arousal Response was Expected at Least

The reasons for choosing the horn music were explained in the Methods. The earliest change in cardiovascular regulation in preparation for concurrent increases in both blood pressure and heart rate is the removal of the feedback control system mediated by baroreflex. The quantifiable index of this cardiovascular feedback system is the CSB. Concurrent increases in both heart rate and blood pressure are required in the defence mechanism that enables us to flee from or to fight external dangers. It is also the same mechanism engaged when we are afraid of something. It is therefore reasonable that an alerting call from outside should enact this very early stage of defence response.

Our study shows that the horn music was the best stimulus for exclusive arousal response among this group, where only the feedback control of the cardiovascular system was withdrawn judging from the counts of the number of responders. At least 62% of the subjects responded appropriately. However, still many of our subjects proceeded further than this early stage into full sympathetic responses, while a few others went in the opposite direction and had a pure parasympathetic response. When we examined the intensities of the autonomic responses, the horn music caused an overall elevation of MAP, but there was an overall reduction of the combined levels of CSB and CVT. This is consistent with an overall sympathetic stimulation among the responders. The horn music therefore caused an overall sympathetic stimulation among the responders according to the intensities of the responses. It is possible that not all of the patients reacted to the horn music as we expected because of the immature brainstem in RTT. Future study of this nature using a control group of children with normal development of the brainstem will be enlightening.

VT – Predominantly parasympathetic Response was Expected

The type of vibroacoustic stimulation and the reasons for including this stimulus in the study has been discussed above. Vibroacoustic on its own evoked either pure sympathetic or pure parasympathetic responses with nearly equal frequency among our subjects judging from the counts of the number of responders. This was rather surprising because most, but not all of our subjects, looked relaxed and got calmer, breathing normally with reduced stereotypic movements and some even fell asleep during the brief VT therapy. Our results show that about 76% of our subjects responded to VT as expected, but that still leaves 24% with other kinds of responses. When we examined the intensities of the autonomic responses to VT, there was an overall increase in the combined levels of CSB and CVT, but an overall reduction in the level of MAP among the responders. This is consistent with an overall parasympathetic stimulation by VT. The intensities of the autonomic responses confirm an overall parasympathetic stimulation by VT in RTT.

VT with Embedded Music – Predominant Parasympathetic Responses Expected

The main purpose of embedding music in the VT was to examine if the dual stimulation would boost parasympathetic stimulation even more than VT alone. However, the combination of VT with music proved to be inconsistent for stimulating parasympathetic responses. Only 48% of our subjects responded with increased parasympathetic tone compared to 76% when stimulated with VT on its own. There were up to 29% non-responders to VT with music compared to absolute no non-responders at all when VT was used on its own. However, when we investigated the intensities of the autonomic responses, VT with music had the strongest stimulation of parasympathetic responses. There was an overall increase of nearly 150% of the combined levels of CSB and CVT compared to baseline levels, the highest response of all the five stimuli used in this study. Vibroacoustic on its own evoked about 75% increase in the combined levels of CSB and CVT, half of the level evoked by VT with music.

Vibroacoustic with music and the "calming music" were the best stimuli for lowering arterial blood pressure. The music embedded in VT and the "calming music" was different. The present study did not include an investigation to determine the effect of music embedded in VT. Consequently, the synergism between this music and the VT cannot be fully understood, and requires further examination.

The reason for the inconsistency of VT with music in the stimulation of parasympathetic responses in our subjects could be due to the immature brainstem in persons with RTT as mentioned previously above. Persons with RTT find it difficult to handle more than one stimulus at the same time. In order to understand this phenomenon, it would be interesting to examine how children with normal brainstem respond to the combination of VT with music.

Practical Uses of Our Results by Parents and Carers

"Calming music" can be used to provide a parasympathetic boost in persons with RTT and to increase the brainstem's capacity to control the autonomic functions. In two unpublished cases, we have observed in the Swedish National Rett Centre a reduction in epileptic activity in the electroencephalogram when CVT and CSB were increased using "calming music". The interpretation of external behaviour might not be sufficient for deduction of the autonomic outcome and the parental choice of music has a high level of non-responders. Professional recommendation of music, and when possible in conjunction with monitoring the autonomic outcome will be ideal for this purpose.

What parents and carers describe as favourite music (activating music) is often chosen from the observation of the way a patient reacts to such music. Our results indicate that this may not reflect the physiological responses of the patients. While it is important that parents should be sensitive to the patient's external reactions and should provide the music the patient want, caution could be exercised regarding the use of "activating music". External observations such as changes in the breathing of the patient, the size of the pupils, the intensity of stereotypical movements, and the character of smiles would be helpful information in aid of assessment of the autonomic outcome of that music. For example, in exaggerated sympathetic stimulation caused by "activating music", the patient would look over-animated; the smile seems forced and the pupils would be large and dark. In this case, it may be advisable to turn the music off at that moment. Such music can of course be used, but maybe for a short period at a time and might be deployed less often in persons with RTT due to the very low parasympathetic activity in this disorder.

Conclusion

We have identified a group of physiological measures of the autonomic function and used them to quantify autonomic responses to music and vibroacoustic stimulations. Indices of brainstem regulation of the cardiac vagal tone and baroreflex sensitivity were used to quantify parasympathetic responses, while the mean arterial blood pressure was used as a non-invasive quantitative index of sympathetic activity. We investigated autonomic responses to a collection of music described by parents and carers as "calming music" and "activating music" and obtained a high rate of physiological non-responders and a mixed autonomic outcome. Overall, "calming music" evoked parasympathetic responses and "activating music" evoked sympathetic responses in the responders. We have also investigated autonomic responses to additional professional choices of vibroacoustic and music stimulations. Horn music and vibroacoustic were effective stimuli that evoked responses in all the subjects in this group without fail. When a calming music was introduced to patients together with the vibroacoustic stimulus for dual stimulation, the arrangement became less effective and failed to evoke autonomic responses in some of our subjects. However, the intensities of the autonomic responses evoked by the dual vibroacoustic and music stimulation were the highest in the responders compared to those evoked by any other stimuli. The overall responses were as follows. The horn music evoked physiological arousal that proceeded to sympathetic stimulation in some patients. Vibroacoustic stimulation with or without a calming music evoked parasympathetic responses. This study showed measurable synergism between vibroacoustic and calming music. The study verifies that this technique could be useful as a tool for investigating responses to music and VT. It is important to stress, however, that we at this point are unable to make any clinical suggestions because of the novelty of this kind of investigation in the area of music, due to the versatile responses of this population, and because of the limited group of subjects. Further research is necessary.

Acknowledgements

The authors gladly acknowledge the support of the families and people with Rett syndrome. This was the result of teamwork. We are particularly indebted to our colleagues and team members Stig Hansen and Flora Apartopoulos, Glasgow University Hospital and to Dr. Bengt Engerström, Östersund Hospital. We acknowledge the support from the Department of Physiology, Sundsvall Hospital, who supplied the Swedish Rett Center with their Finapres and from the Department of Paediatrics Östersund Hospital who supplied us with a TINA. We are grateful for the support from the Medical Research Foundations of the Northern University Region of Jamtland County Council and of Östersund Hospital.

References

Allan, I. (1991). *Rett syndrome: A view on care and management.* Washington, D.C.: The National Rett Syndrome Association.

Amir, R. E., Van, d. V., I, Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat.Genet.*, *23,* 185-188.

Bergström-Isacsson, M. (2001). *Musik och Rett syndrom - en musikterapeutist tolkning. [Music and Rett Syndrome - a music therapeutic intervention].* Stockholm: Kungliga Musikhögskolan.

Best, C. H. & Taylor, N. B. (1966). The basal ganglia, the thalamus and hypothalamus. In C. H. Best & N. B. Taylor (Eds.), *The Physiological Basis of Medical Practice* (pp. 144-161). Edinburgh, London: E. and S. Livingstone Limited.

Blessing, W. W. (1997). Breathing. In W. W. Blessing (Ed.), *The Lower Brainstem and Bodily Homeostasis* (pp. 101-164). Oxford, New York: Oxford University Press.

Coleman, K. (1987). *Music therapy in Rett Syndrome: Educational and therapeutic intervention in Rett syndrome.* Clinton, MD: IRSA.

Delamont, R. S., Julu, P. O., & Jamal, G. A. (1998). Sleep deprivation and its effect on an index of cardiac parasympathetic activity in early nonREM sleep in normal and epileptic subjects. *Sleep*, *21*(5), 493-498.

Elefant, C. (2002). *Enhancing communication in girls with Rett syndrome through songs in music therapy.* Aalborg: Aalborg University.

Elefant, C. & Lotan, M. (2004). Rett Syndrome - Dual Intervention - Music and Physical Therapy. *Nordic Journal of Music Therapy*, *13*(2), 172-182.

Guyenet, P. G. (1990). Role of the ventral medulla oblongata in blood pressure regulation. In A. D. Loewy & K. M. Spyer (Eds.), *Central Regulation of Autonomic Functions* (pp. 145-167). New York, Oxford: Oxford University Press.

Guyenet, P. G., Koshiya, N., Huangfu, D., Baraban, S. C., Stornetta, R. L., & Li, Y. W. (1996a). Role of medulla oblongata in generation of sympathetic and vagal outflows. *Prog.Brain Res.*, *107,* 127-144.

Guyenet, P. G., Koshiya, N., Huangfu, D., Baraban, S. C., Stornetta, R. L., & Li, Y. W. (1996b). Role of medulla oblongata in generation of sympathetic and vagal outflows. In G. Holstege, R. Bandler, & C. B. Saper (Eds.), *The Emotional Motor System* (pp. 127-144). Amsterdam, New York, Oxford: Elsevier.

Hadsell, N. & Coleman, K. (1988). Rett Syndrome: A Challenge for Music Therapists. *Music Therapy Perspectives* (pp. 52-56).

Hill, S. A. (1997). The relevance and value of music therapy for children with Rett syndrome. *British Journal of Special Education*, *24,* 124-128.

Holdworth, J. (1999). Responsiveness to music in 21 girls and women with Rett syndrome. Submitted in the Department of Psychology, University of Hull.

Houtaling, C. M. (2003). *Music and Rett Syndrome: A survey from the parental perspective.* East Lansing: Michigan State University.

Idema, R. N., van den Meiracker, A. H., Imholz, B. P., Man In ‘t Veld AJ, Settels, J. J., Ritsema van Eck, H. J., & Schalekamp, M. A. (1989). Comparison of Finapres non-invasive beat-to-beat finger blood pressure with intrabrachial artery pressure during and after bicycle ergometry. *J.Hypertens.Suppl.*, *7*(6), S58-S59.

Jacobsen, K., Viken, A., & von Tetzchner, S. (2001). Rett syndrome and ageing: a case study. *Disabil.Rehabil., 23,* 160-166.

Jellema, W. T., Imholz, B. P., van Goudoever, J., Wesseling, K. H., & Van Lieshout, J. J. (1996). Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. *Clin.Sci.*, *91*(2), 193-200.

Jordan, D. (1990). Autonomic changes in affective behaviour. In A. D. Loewy & K. M. Spyer (Eds.), *Central Regulation of Autonomic Functions* (pp. 349-366). Oxford: Oxford University Press.

Jordan, D. (1991). The autonomic nervous system and behaviour. *Acta Neurol.*, *13*(6), 539-548.

Jordan, D. (1995). Central nervous integration of cardiovascular regulation. In D. Jordan & J. Marshall (Eds.), *Cardiovascular Regulation* (pp. 1-14). Cambridge: University Press Cambridge.

Julu, P. O., Cooper, V. L., Hansen, S., & Hainsworth, R. (2003). Cardiovascular regulation in the period preceding vasovagal syncope in conscious humans. *J.Physiol*, *549*(Pt 1), 299-311.

Julu, P. O., Kerr, A. M., Hansen, S., Apartopoulos, F., & Jamal, G. A. (1997). Functional evidence of brain stem immaturity in Rett syndrome. *Eur. Child Adolesc.Psychiatry*, *6*(Suppl 1), 47-54.

Julu, P. O. & Witt-Engerström, I. (2005). Assessment of the maturity-related brainstem functions reveals the heterogeneous phenotypes and facilitates clinical management of Rett syndrome. *Brain Dev.*, *27*(Suppl 1),S43-S53.

Julu, P. O. O. (1992). A linear scale for measuring vagal tone in man. *J Auton Pharmacol*, *12,* 109-115.

Julu, P. O. O., Hansen, S., Barnes, A., & Jamal, G. A. (1996). Continuous measurement of the cardiac component of arterial baroreflex (ccbr) in real-time during isometric-exercise in human volunteers. *Journal of Physiology-London*, 497P P 7-P 8.

Kasparov, S. & Paton, J. F. (1999). Differential effects of angiotensin II in the nucleus tractus solitarii of the rat--plausible neuronal mechanism. *J.Physiol*, *521*(1), 227-238.

Kerr, A. & Witt-Engerstrom, I. (2001). The clinical background to the Rett disorder. In A. Kerr & I. Witt-Engerstrom (Eds.), *Rett Disorder and the Develping Brain* (pp. 1-26). Oxford, New York: Oxford University Press.

Larsson, G. & Engerstrom, I. W. (2001). Gross motor ability in Rett syndrome--the power of expectation, motivation and planning. *Brain Dev.* 23(Suppl 1), S77-S81.

Leonard, H., Silberstein, J., Falk, R., Houwink-Manville, I., Ellaway, C., Raffaele, L. S., Engerstrom, I. W., & Schanen, C. (2001). Occurrence of Rett syndrome in boys. *J.Child Neurol., 16,* 333-338.

Little, C. J., Julu, P. O., Hansen, S., & Reid, S. W. (1999). Real-time measurement of cardiac vagal tone in conscious dogs. *Am.J.Physiol*, *276*(2 Pt 2), H758-H765.

Merker, B., Bergström-Isacsson, M., & Witt-Engerström, I. (2001). Music and the Rett disorder: The swedish Rett Centre survey. *Nordic Journal of Music Therapy*, *10*(1), 42-53.

Merker, B. & Wallin, N. (2001). Musical responsiveness in the Rett disorder. In A. M. Kerr & I. Witt-Engerström (Eds.), *Rett Disorder and The Developing Brain* (pp. 327-339). Oxford: Oxford University Press.

Montague, J. (1988). *Music Therapy in the Treatment of Rett Syndrome.* Glasgow: Wm. Brown, Ltd.

Mount, R. H., Hastings, R. P., Reilly, S., Cass, H., & Charman, T. (2001b). Behavioural and emotional features in Rett syndrome. *Disability and Rehabilitation*, *23*(3/4), 129-138.

Mount, R. H., Hastings, R. P., Reilly, S., Cass, H., & Charman, T. (2001a). Behavioural and emotional features in Rett syndrome. *Disabil. Rehabil., 23*(3-4), 129-138.

Rett, A. (1966). Über ein eigenartiges hirnatrophisches Syndrome bei Hyperammonamie im Kindsalter. *Wiener Medizinische Wochenschrift*, *116,* 723-726.

Skille, O. (1991). *Music Therapy: Manual and Reports.* Levanger: ISVA Publications.

Spyer, K. M., Dale, N., & Gourine, A. V. (2004). ATP is a key mediator of central and peripheral chemosensory transduction. *Exp.Physiol*, *89*(1), 53-59.

Sun, M.-K. & Guyenet, P. G. (1986). Medulospinal sympathoexcitatory neurons in normotensive and spontaneously hypertensive rats. *Am.J.Physiol.*, *250,* R910-R917.

Wesecky, A. (1986). Music therapy for children with Rett syndrome. *Am.J.Med.Genet., 1*(Suppl.), 253-257.

Wigram, T. (1991). Music therapy for a girl with Rett syndrome: Balancing structure and freedom. In K. E. Bruscia (Ed.), *Case Studies in Music Therapy.* Phoenixville, PA: Barcelona Publishers.

Wigram, T. (1995). A model of assessment and differential diagnosis of handicap in children through the medium of music therapy. In T. Wigram, T. Saperston, & R. West (Eds.), *The Art and Science of Music Therapy: A Handbook* (pp. 181-193). Chur, Switzerland: Harwood Academic Publishers GmbH.

Wigram, T. & Cass, H. Music therapy within the assessment process of a therapy clinic for people with Rett syndrome. London: BSMT Publications.

Wigram, T. & Dileo, C. (1997). *Music Vibration.* Cherry Hill, NJ: Jeffrey Books.

Witt-Engerstrom, I. & Hagberg, B. (1990). The Rett syndrome: gross motor disability and neural impairment in adults. *Brain Dev.*, *12,* 23-26.

Woodyatt, G. & Ozanne, A. (1992). Communication abilities and Rett syndrome. *Journal of Autism and Development Disorders*, *22,* 155-173.

Woodyatt, G. & Ozanne, A. (1994). Internationality and communication in four children with Rett syndrome. *Australia New Zealand Journal of Developmental Disabilities*, *19,* 173-183.