Music and Vibroacoustic Stimulation in People with Rett Syndrome – A Neurophysiological Study

Märith Bergström-Isacsson

Thesis submitted for degree of Doctor of Philosophy

2011

Supervisors: Professor Tony Wigram,

Professor Christian Gold and Associate Professor Ulla Holck

Co-supervisor: Docent Bengt Lagerkvist MD

Consultant: Peter O.O. Julu MD PhD

Department of Communication and Psychology

Faculty of Humanities

Aalborg University

Denmark

English Summary

Background

Rett syndrome (RTT) is a neurodevelopmental disorder found all over the world. The disorder affects basic body functions including the central control of the autonomic nervous system in the brainstem. Music seems to be extremely important to almost every person with RTT and is used by parents and carers in different situations, e.g. to calm down, to activate, to motivate and in communication. The importance of music for people with RTT has been documented in the literature. Dr Andreas Rett (Rett, 1966), who first described the syndrome, wrote about it as early as 1966. No study has been undertaken to examine more closely why music is so important, and how music physiologically affects people with RTT. Generally people with RTT have very definite favourite pieces of music, and when they listen to a preferred tune, a clear reaction can be observed. The importance of favourites and preferred genre amongst the RTT group has been investigated in a Swedish and an American study (Houtaling, 2003; Merker, Bergström-Isacsson, & Witt Engerström, 2001). Both studies confirmed that music appeared to be significant for people with RTT, as revealed by their responsiveness to music and the fact that they had musical favourites reported by primary caregivers. Relatives described the use of music as a “drug” to calm down, helping to ameliorate anxiety, impatience and screaming, as well as something that could help in making contact, getting to sleep, and when anxiety was provoked, for example during visits to the doctor or dentist – usually when nothing else seemed to work (Bergström-Isacsson, 2001). People with RTT have tremendous communicative difficulties (Elefant, 2002; Trevarthen & Burford, 2001). The majority are without speech and explicit body language. Parents and other caregivers generally have to trust their own ability to interpret the individual’s communicative signals, such as facial expressions and eye-pointing. Earlier research has indicated that these signals might sometimes be misinterpreted (Bergström-Isacsson, Julu, & Witt Engerström, 2007). Music therapists and researchers have found that some songs seem to have a calming effect while other songs cause increased breathing, and that the different responses are difficult to interpret (Bergström-Isacsson, et al., 2007; Mount, Hastings, Reilly, Cass, & Charman, 2001). Research in the medical field has indicated that people with RTT generally have an immature brainstem and dysfunctions of the autonomic nervous system (Armstrong & Kinney, 2001; Julu, 2001). The brainstem controls much of the autonomic nervous system, which coordinates and controls the body’s basic functions. The autonomic nervous system responds very quickly to how we experience our surroundings and to our feelings, and it also controls some of our facial movements. The autonomic nervous system is divided into two parts: the parasympathetic system and the sympathetic system. The sympathetic part increases blood pressure and pulse in order to manage sudden changes. When the sympathetic part is stimulated we become excited, we blush, become alert and ready to defend or flee. When the parasympathetic part is activated the pulse slows down, the heart's pump volume decreases, blood pressure sinks, the pupils close, and salivation and intestinal movement increases. The parasympathetic part works as a natural brake so that the sympathetic part does not run amok. In this study the intention was to go "inside" the participants, with the help of a brainstem assessment, and measure physiological brainstem responses to their preferred music and also to music that was unknown to them. There was also an intention to go "outside", and identify facial expressions that were related to the music and to measured brainstem responses. Since music can have stimulating or calming effects, it is of interest to combine different musical stimuli with facial expressions and the autonomic responses disclosed by a brainstem assessment. Emotional responses observed in facial expressions, and elicited by music, might differ from those triggered by abnormal spontaneous brainstem activation (ASBA). However, it might also be possible that music elicits ASBAs. It is therefore important to combine findings from brainstem assessment with identification of facial expressions in order to differentiate, if possible, those that express true emotion from those that are elicited by abnormal nervous activity.

The review of the literature has identified previous research that forms the basis of the investigations performed in this present study. Based on clinical experience and parental reports, assumptions have been made about how music is experienced, psychologically and physically (e.g. stimulating or calming), by people with RTT, and the consequential benefits. In previous research differing opinions have been expressed on styles of music, and whether vibroacoustic stimuli can have an influence. The aim of this study was to examine what effect musical stimuli had on the control functions of the autonomic nervous system and on cortical emotional reactions in participants with RTT.

Hypotheses

The following six hypotheses are formulated regarding the expected autonomic responses within subjects when different types of musical stimuli are given.

1. *An unknown piece of music (Horn), especially chosen for this purpose,* causes only an arousal (a physiological arousal response) without a sympathetic or parasympathetic increase.
2. *Activating music (Activating), chosen by parents or carers,* causes a sympathetic response (an activating response).
3. *Calming music (Calming), chosen by parents or carers,* causes a parasympathetic response (a relaxing response).
4. *Vibroacoustic stimulation (VT)* causes a parasympathetic response (a relaxing response).
5. *VT combined with a specially chosen piece of music (VT+Mu)* causes a parasympathetic response (a relaxing response).
6. *The specially chosen music that was played in the combination with VT, but now played on its own, (Mu)* causes a parasympathetic (a relaxing response).

The responses are compared with a baseline period in which the most consistent measurements are found regarding normal breathing, blood gases within normal range, in the wakeful state and no epileptic activity. Responses from RTT and non-clinical participants (children aged between 1 and 5 years) are also compared.

Method

Design

This experimental study was designed as both a between-groups and a within-subject study (also called a repeated measures design). Participants in the RTT group were compared with participants in a non-clinical group, and the baseline scores for each individual in both groups were compared with the scores for the six musical stimuli used in the study. The repeated measures design was used to increase the sensitivity of the test, since participants served as their own controls, and thus cross-subject variation was not a problem. This type of design was possible because the reactions to the different stimuli were assumed to be relatively short. In addition, a non-clinical group of normally developed children was recruited to explore possible differences and similarities in responses. Physiological data were collected from a medical brainstem assessment. The group-level analyses were supplemented by case vignettes, where additional physiological parameters could be taken into account. Data were also collected from video analyses of facial expressions, using the Facial Action Coding

System (FACS). The aim of including FACS was to identify facial expressions (Action Units = AUs) elicited by possible pathological brainstem activities and, if possible, to separate those expressions from emotional expressions triggered from the cortex. These expressions were then categorised into positive-, negative- and ambiguous expressions, and correlated with results from brainstem assessment and the music used.

Participants

The participants of the study were 35 patients with RTT referred to the Rett Center for routine brainstem assessment over a period of two years (2006-2007). Six participants were excluded due to the exclusion criteria, so 29 participants with RTT remained in the study. To be part of the study a person, female or male, had to have been diagnosed with RTT before referral to the Rett Center and the brainstem examination. A genetic test was not necessary, as RTT is still considered to be a clinical diagnosis. Identical analyses, except EEG, were made of 11 children with a normal development, in this study called the non-clinical group. Of 13 children invited to the non-clinical group, 11 participated in the study. The non-clinical group, six girls and five boys, had a normal birth and a normal physical and cognitive development, reaching normal milestones as expected.

Technical equipment

The NeuroScope from MediFit Instruments Ltd, London, UK was used to record the beat-to-beat heart rate from ECG R-R intervals. Systolic and diastolic blood pressures were also recorded beat to beat by using the Portapres model 2. A photoplethysmographic finger cuff was used to obtain continuous digital arterial blood pressure in the Portapres. Breathing was registered with a piezoelectric plethysmographic belt round the lower part of the rib cage. All breathing movements were also integrated in a computer, together with partial pressure of oxygen and carbon dioxide levels in the blood, registered transcutaneously. The equipment for registering breathing movements, arterial blood pressure, and the transcutaneous measures of oxygen and carbon dioxide, was connected to the Medulla Lab via a computer, which calculated all data and made it possible to study cardiac function, heartbeat by heartbeat. An electro cap (ECI) with built-in electrodes was used to produce an electroencephalogram (EEG). All data were registered in a computer, and could be seen as graphs on the screen, providing the opportunity to discuss the developments minute by minute during the brainstem assessment. The whole process was synchronised and filmed with two digital video cameras, thus enabling later examination of the results in detail. The EEG camera was focused on the participants' faces, while another camera was used to record all other behaviour and movements during the assessment. The video recordings from the EEG camera and the EEG machine were also used for coding facial expressions, and for analysing relations between brainstem responses, music and facial expressions. During registration the participant sat on a beanbag with built-in loudspeakers. During *VT* as well as *VT+Mu*, the low-frequency tones came from the loudspeakers in the beanbag and were experienced as vibrations. A CD player connected to the beanbag produced the vibrations, and an additional CD player provided the music played during *VT+Mu* as well as the music selected by parents or carers.

Procedure

Each parent or carer was interviewed prior to the assessment. During that interview they were asked about the participants' favourite pieces of music used for activating and calming purposes. They were also asked questions about whether the person had previously had or was currently having music therapy, which method of music therapy was then used, and if and how they used music at home. Prior to brainstem assessment, the participants were given a medical examination; this was necessary as the RTT participants had come to the Rett Center for a medical examination, not primarily as research participants. The participant and the parents or carers were then introduced to the assessment room, the environment and the technical equipment. Just before the assessment started, the participant was placed on the beanbag. All the electrodes for ECG and oxygen and carbon dioxide, breathing belt, finger cuff and EEG cap were connected to the participant. The video cameras, the microcomputer and the EEG machine were synchronised to begin monitoring. At the beginning of the brainstem assessment a baseline for the brainstem autonomic function of the participants (recorded during a set period) was established. The baseline values were monitored and marked when the participant was breathing normally, with blood gases within the normal range, or as normal as possible, and was awake, with no signs or evidence of agitation and with no epileptic activity (Julu et al., 2001).

Data collection and analyses

The study data were collected during the investigation of brainstem control functions of the autonomic nervous system for approximately one hour. The control situation was the person's own baseline. After baseline was established, the participants were exposed to six different musical stimuli: *Horn*, *Activating*, *Calming*, *VT*, *VT+Mu* and *Mu* in randomised order. The continuous dependent variables measured were: Cardiac Vagal Tone (CVT), Cardiac Sensitivity to Baroreflex (CSB), Mean Arterial blood Pressure (MAP) and the Coefficient of Variation of Mean Arterial blood Pressure (MAP-CV). These parameters were used to categorise brainstem responses: parasympathetic-, sympathetic-, arousal- and unclear responses to the different musical stimuli. The categorical brainstem responses were the ones included in the hypotheses describing expected responses to the six different musical stimuli. The participants were taken back to baseline, or as close to baseline as possible, after the presentation of each stimulus through a wash-out period. After presentation of the last stimulus the monitoring was completed. Nothing else went on in the assessment room when the participant was exposed to the stimulus. Transcutaneous blood gases of oxygen and carbon dioxide and breathing were also measured during the assessment, as a way of observing the brainstem's ability to balance blood gases and categorising the participants' breathing phenotype. Blood gases were used in the case vignettes to obtain a more comprehensive understanding of the interpretations of individual responses.

A video analysis of facial expressions from the last minute of each stimulus was carried out simultaneously with the analysis of CVT, CSB and MAP. By using the video synchronised with the EEG machine it was possible to code and mark both frequency and duration for all facial expressions in the EEG machine, which was important for identifying both events of facial expressions and individual facial movement patterns. Combinations of AUs coded using FACS may be described with emotion labels if investigators choose to do so, but this inferential stage is a step outside FACS (Ekman & Rosenberg, 2005). In this current study the inferential stage was used to investigate whether FACS can be used as a method to identify and distinguish between expressions connected with emotions and expressions caused by abnormal brainstem activity. Each AU was identified and marked (start and stop of the AU) and transformed into facial events (a period where AUs related to each other appear).

In this present study, Tool for Music Analysis (TMA) was used to identify basic changes in the music which might be important for different emotional responses. TMA was developed by the researcher and musicologist Erik Christensen, based on Aare, Grønager & Rønnenfelt (2003), Grocke (1999) and Hooper (2003, 2010). TMA also made it possible to compare the parents' and carers' choice of the participants' favourite tunes.

Results

Continuous and categorical brainstem responses

The physiological baseline values differed within the RTT group and the non-clinical group, as well as between the groups. CVT and CSB were higher in the non-clinical group compared with the RTT group, and MAP was significantly lower. These higher values in the non-clinical group may indicate a more mature brainstem, and thereby a stronger ability to balance and control sudden changes in the autonomic nervous system. In the RTT group the expected categorical responses related to the hypotheses were observed in 7% for *Horn*, 36% for *Activating*, 39% for *Calming*, 52% for *VT*, 32% for *VT+Mu* and 28% for *Mu*. Comparing the two populations, the expected response was usually seen in a minority of cases, both in RTT and non-clinical children; expected responses for the three stimuli (*Activating*, *VT*, *VT+Mu*) occurred in over 30% of both RTT and non-clinical children; the expected calming response to *Calming* was more common in RTT (39%) than in non-clinical children (9%). An unclear response, meaning that there could be an activation of all parameters measured (CVT, CSB and MAP), was found in both the clinical and the non-clinical group among the youngest children. An unclear response could also be a brainstem shutdown, implying a decrease in all parameters. This response is connected with a brainstem that is unable to cope with too much input or stimuli. This is an abnormal behaviour which is mainly observed when the brainstem is very immature and easily becomes overwhelmed. Brainstem shutdown was observed only in RTT participants. The findings also disclosed the impact of blood gases and breathing patterns on RTT participants' physiological responses to the music and on their facial expressions.

Interpretation of facial expressions and emotional expressions

The results from analyses of facial expressions in the RTT group show that *Activating* evoked more smiles and similar reactions than any other stimulus. Conversely, the *Mu* stimulus evoked more negative responses such as anger or anxiety, and *Horn* also evoked several similar reactions. The overall chi-square test confirmed that the responses were not randomly distributed ($p < .001$), which might indicate that people with RTT indeed have intentionality and music preference. In the non-clinical group, smiles were most often seen in *VT+Mu* and *Calming*, but were also reasonably common in *Activating*. Negative reactions were seldom observed overall. False smiles during *Activating* were common in both populations.

Categorical brainstem responses in relation to music and facial expressions

From the analysis of facial expressions, it became clear that a majority of the individuals with RTT had a unique specific disorder-related movement pattern. These movement patterns seemed to be related to abnormal brainstem activity. Individual movement patterns were not observed among the non-clinical participants. Overall, the analysed categorical brainstem responses agree with the output from the participants' facial expressions, except in the case of *VT*. The analyses of facial expressions in connection with whole pieces of favourite music also show that all participants from both groups responded when the musical stimuli started, but there seemed to be differences in the way the groups responded to the stimuli over time. In the case vignettes, measured blood gases were used as an additional parameter to obtain a more comprehensive understanding of individual responses. When they were compared, it was clear that music had an obvious effect on all four of them, but that there were differences in their ability to control experienced responses, balance blood gases, and communicate experienced emotions.

Discussion

In the research underlying this thesis, both RTT participants, and non-clinical participants, responded to different kinds of music in various ways (parasympathetic-, sympathetic-, arousal- and unclear responses), but not necessarily with the expected responses. An immature brainstem, observed in RTT, is not capable of balancing autonomic nervous system functions. When the participants with RTT were exposed to music they could respond with e.g. genuine happiness to start with, but due to the poor control function of their brainstems, this happiness sometimes changed to a physiological condition of stress. To be able to identify this changeover, it is extremely important to be observant of changes in facial expressions. From a clinical perspective the findings indicate that it is possible, based on the correlation between results from brainstem assessment and FACS, to interpret facial expressions among RTT participants and thereby hopefully diminish the risk of misinterpretation. The detailed case vignettes indicate that it is good to observe continuous or categorical brainstem responses, but to be able to understand the participants' state of well-being, it is better to also include blood gases, breathing movements, facial activity and emotional changes in the analyses.

Limitations of the study

Sample size is one issue to be taken into account. A sample of 29 individuals, who were not randomly chosen, cannot be general and is not representative of the RTT population. The results therefore relate only to this sample.

Directions for further research

Further research should try to combine more neurophysiological procedures to investigate the influence of music on body and mind. Blood gases should then also be monitored and analysed as continuous variables. Different kinds of music gave diverse responses that might be of interest to investigate. FACS itself, and in combination with brainstem assessment in an RTT population, is a new and untried combination of methods. Further research in the area is essential to be able to draw general conclusions.

Conclusion

One of the main findings in this study was that most individuals with RTT had a unique specific disorder-related movement pattern in their facial expressions, which could easily be misinterpreted as expressions of emotions. These movement patterns appeared to be elicited by sudden abnormal brainstem activity (ASBAs); they occurred spontaneously, and did not necessarily directly indicate emotion. However, this abnormal brainstem activation might also *cause* emotions such as anxiety and fear. These findings were based on the correlation between results from brainstem assessment and FACS. The analyses also indicated that it seems possible to distinguish between these individual movement patterns and expressions of emotions, but that detailed observations are necessary.

The present study also showed that RTT participants respond to different kinds of music in various ways, similar to non-clinical participants with comparable brainstem maturity. This was confirmed both by assessment and analyses of brainstem responses, and by analyses of facial expressions. All participants from both groups responded when the music and vibrations started, but there seemed to be a difference in how they responded to the stimuli over time. Almost all participants in this study used music in one way or another. The importance of, and the response to, music indicated that the part of the brain which receives and processes music seems to be intact in RTT, which may explain why music is so important throughout the individual's life. Music might also be important for people with RTT because it seems to take over the role as the main tool for communicating, interacting with other people, and understanding contexts and situations. It was also commonly used as a very important tool by other people in their relation to the RTT participants.

This research study has highlighted that we misinterpret expressions of emotions in the RTT population due to lack of knowledge. The combination of brainstem assessment and FACS has been invaluable for this finding. It is most relevant to know about all problems and difficulties related to RTT, and it is important for clinicians to see the whole person, not only the problems, and to be sensitive to facial and emotional expressions.

Taken alone, neither the results from brainstem assessment nor those from FACS present "the truth", but the combination might lead us in the right direction. The only truth is that people with RTT have tremendous difficulties, which of course have to be taken care of, but we must never forget that they also need enrichment in life, for example in the form of music.

References

Aare, A., Grønager, J., & Rønnenfelt, P. (2003). *Rockmusik i tid og rum*. Århus: Systime.

Armstrong, D., & Kinney, H. (2001). The neuropathology of the Rett disorder. In A. Kerr & I. Witt Engerstrom (Eds.), *Rett disorder and the developing brain* (pp. 57-84). New York: Oxford University Press.

Bergström-Isacsson, M. (2001). *Musik och Rett syndrome - en musikterapeutisk tolkning.* Bachelor, Royal College of Music, Stockholm.

Bergström-Isacsson, M., Julu, P. O. O., & Witt Engerström, I. (2007). Autonomic responses to Music and Vibroacoustic Therapy in Rett Syndrome. *Nordic Journal of Music Therapy, 16(1)*, 42-59.

Ekman, P., & Rosenberg, E. L. (Eds.). (2005). *What the face reveals*. New York: Oxford University Press.

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

Grocke, D. E. (1999). *A phenomenological study of pivotal moments in guided imagery and music (GIM) therapy.* Ph.D., Unversity of Melbourne, Melbourne.

Hooper, J. (2003). *PFSM Predictable Factors in Sedative Music*. Paper presented at the National Association of Music Therapy Conference, USA.

Hooper, J. (2010). *The development of criteria for defining sedative music and its impact on adults with mild, moderate, and severe intellectual disability and challenging behaviour.* Ph.D., Aalborg University, Aalborg.

Houtaling, C. (2003). *Music and Rett Syndrome: A Survey from the Parental Perspective.*

Julu, P. (2001). The central autonomic disturbance in Rett syndrome. In A. Kerr & I. Witt Engerström (Eds.), *Rett disorder and the developoing brain* (pp. 131-182). New York: Oxford University Press.

Julu, P., Kerr, A., Apartopoulos, F., Al-Rawas, S., Witt Engerström, I., Engerström, L., et al. (2001). Characterisation of the breathing abnormality and associated central autonomic dysfunction in Rett disorder. *Archives of Diseases on Childhood, 85*, 29-37. Scandinavica 1990;suppl 1396.

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.

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

Rett, A. (1966). *Uber ein cerebral atropisches syndrome bei hyper-ammonmine*. Vienna: Bruder Hollinek.

Trevarthen, C., & Burford, B. (2001). Early infant intelligence and Rett syndrome. In A. Kerr & I. Witt Engerstrom (Eds.), *Rett disorder and the developing brain* (pp. 303-326). New York: Oxford University Press.