

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



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Thesis submitted for degree of Doctor of Philosophy
Aalborg University, Denmark

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Declaration

I confirm that this thesis: *Music and Vibroacoustic Stimulation in People With Rett Syndrome – A Neurophysiological Study* and the research it contains, has not previously been submitted as a whole or in parts, or submitted for assessment for a prize at an institution of higher education in Denmark or abroad.

Märith Bergström-Isacsson

*“And whenever the tormenting spirit from God troubled Saul,
David would play the harp. Then Saul would feel better, and the
tormenting spirit would go away”*

1 Sam 16:23

Abstract

Background: Rett syndrome (RTT) is a neurodevelopmental disorder which affects basic body functions including the central control of the autonomic nervous system in the brainstem. Music is used by parents and carers in different situations, e.g. to calm down, to activate, to motivate and in communication. The aim of the 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.

Methods: The study included 35 participants with RTT who were referred to the Swedish Rett Center for routine brainstem assessment during the period 2006-2007, and 11 children with a normal development. A repeated measures design was used, and physiological data were collected from a neurophysiological brainstem assessment. To identify facial expressions elicited by possible pathological brainstem activities, data were also collected from video analyses of facial expressions using the Facial Action Coding System (FACS). The control situation was the physiological baseline of the participant's own autonomic function at rest. After establishing a baseline the participants were exposed to six musical stimuli. *Horn* was chosen to elicit an arousal response and *Activating* (parents' choice) a sympathetic response. *Calming* (parents' choice), *VT* (Vibroacoustic stimulation), *VT+Mu* (VT combined with calming music) and *Mu* (that same music without vibrations) were expected to elicit a parasympathetic response. 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 as parasympathetic (calming) response, sympathetic (activating) response, arousal (alerting) response and unclear response. The analyses were supplemented by case vignettes, where additional physiological parameters were also taken into account. Facial expressions were coded and categorised into positive emotions, negative emotions and ambiguous responses. These expressions were then related to results from brainstem assessment and the music used.

Results: Continuous responses showed that *Calming* and *VT* increased CVT significantly in the RTT group. *Horn* elicited a similar response in both groups (decrease in CSB, indicating an arousal). 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*. The FACS analyses indicated that a majority of the RTT participants had specific disorder-related movement patterns in their facial expressions. The findings from analysing the case vignettes also disclosed the impact of blood gases and breathing patterns on RTT participants' physiological responses to the music and on their facial expressions.

Conclusion: Musical stimuli have measurable effects on brainstem autonomic functions in RTT and non-clinical individuals, but it is not possible to foresee responses to different kinds of music. The disorder-related movement patterns in facial expressions found in RTT individuals occurred spontaneously and may not directly indicate emotion. Brainstem assessment is a new method to observe and analyse autonomic responses to music. In combination with brainstem assessment, FACS can be used for identifying and separating pure brainstem triggered facial responses from facial expressions of emotions elicited from the cortex. However, FACS is a new method related to both RTT and music therapy, and presents a new area for further research. The findings from this present study might help caregivers, teachers and therapists to be more observant of specific details, which would ultimately benefit people with RTT.

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List of Abbreviations

<i>Abbreviation</i>	<i>Meaning</i>	<i>First mentioned</i>
<i>Activating</i>	Activating music chosen by parents or carers	1.3.
ASBA	Abnormal Spontaneous Brainstem Activation	2.6.
AU	Action Unit	2.4.3.
<i>Calming</i>	Calming music chosen by parents or carers	1.3.
CDKL5	Mutations of the CDKL5 gene	2.1.3.
CSB	Cardiac Sensitivity to Baroreflex	2.3.3.
CVT	Cardiac Vagal Tone	2.3.4.
DBP	Diastolic Blood Pressure	3.6.1.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – fourth edition	2.1.
ECG	Electrocardiogram	2.3.3.
EEG	Electroencephalogram	1.3.
FACS	Facial Action Coding System	2.4.3.
FMT	Functionally oriented Music Therapy	4.1.2.
FOXG1	Mutations of the FOXG1 gene	2.1.3.
<i>Horn</i>	Specially chosen music	1.3.
HR	Heart Rate	3.6.1.
LVS	Linear Vagal Scale	3.6.1.
MAP	Mean Arterial blood pPressure	2.3.4.
MAP-CV	Coefficient of Variations of blood pressure measured in percentages	2.3.4.
MeCP2	Methyl-CpG-binding protein 2	2.1.3.
MECP2	Mutations of the MECP2 gene	1.1.
mmHg	Millimetres of mercury, a measure of pressure	3.6.1.
ms/mmHg	Milliseconds per unit change in millimetres of mercury	3.6.1.
<i>Mu</i>	Music (the same as in <i>VT+Mu</i>) without <i>VT</i>	1.3.
NCCPC-R	Non-Communicating Children’s Pain Checklist - Revised	2.4.4.
NeuroScope™	NeuroScope, Medifit Instruments LDT	2.3.5.
pCO ₂	Carbon dioxide, partial pressure	2.3.4.

PDD	Pervasive Developmental Disorder	2.1.
PFSM	Predictable Factors in Sedative Music	2.5.2.
pO ₂	Oxygen, partial pressure	2.3.4.
PSSM	Potentials in Stimulatory and Sedative Music	2.5.2.
RPMF	Record of Predictable Musical Factors	2.5.2.
R-R interval	Intervals between 2 consecutive electrocardiographic R-waves	2.3.3.
RS	Rett Syndrome	2.1.
RTT	Rett Syndrome	1.1.
SBP	Systolic Blood Pressure	3.6.1.
SMMA	Structural Model for Music Analysis	2.5.2.
TMA	Tool for Music Analysis	2.5.2.
VNS	Vagal Nerve Stimulator	3.4.1.
VT	Vibroacoustic Therapy, stimulation, 40Hz	1.2.
VT+Mu	VT combined with music chosen by the researcher	1.3.

CHAPTER ONE

1. Introduction

1.1. Background for the study

This study has its origin in my clinical work as a music therapist at a national centre in Sweden focusing on one specific diagnosis: Rett syndrome (RTT).

RTT is a neurodevelopmental disorder recognised in the diagnostic manuals as belonging to the autistic spectrum and identified as having approximately the same prevalence in several populations all over the world. The syndrome affects basic human functions such as communication, praxis¹ movement and intellectual abilities. Nutritional² difficulties, autonomic dysfunction³ with breathing and peripheral circulation disturbances, epilepsy, body tension and severe scoliosis⁴ are all often observed. A child will remain totally dependent on other people for the rest of her life. RTT affects mainly girls, and mutations of a regulatory gene (MECP2) cause disruptions of the normal growth of neurons in the central nervous system (Amir et al., 1999; Clarke, Schanen, & Anvret, 2001). Even though RTT is the most common syndrome among girls after Down syndrome, it is still less known among some professionals, and almost completely unknown among lay people. Children with RTT have an apparently normal development through the first period of life. Around the age of 9 months a delay in development becomes apparent and by the end of the first year of infancy a child developing RTT is clearly falling behind (Trevvarthen & Burford, 2001).

Twenty years of clinical and neurological research in Sweden and Great Britain have shown disturbances in brainstem autonomic function among all patients diagnosed with RTT who have undergone an assessment of brainstem autonomic function (Glaze & Schulz, 2001; Trevvarthen & Burford, 2001). This extraordinarily serious and unusual disorder permeates the complexity of problems related to RTT, and may also be responsible for some cases of unexpected and sudden death.

¹ Praxis – accepted practice

² Nutritional – concerned with supplying or receiving nourishment

³ Autonomic dysfunction – weakened ability of the brainstem to control the autonomic nervous system

⁴ Scoliosis – lateral curvature of spine

People with RTT have tremendous communicative difficulties. The majority are without speech and explicit body language, which means a difficult life situation for both individuals with RTT and their parents and carers. In addition they generally have stereotyped hand movements and dyspraxia, which makes it even more difficult to communicate.

Over the years I have, as a clinician, observed an extreme response to musical stimuli amongst this group of clients, and I am not alone. There are many therapists, teachers, doctors and parents who have reported the same phenomena (2.2.4). As early as 1966, Andreas Rett (Rett, 1966) wrote about the importance of music but no study has been undertaken to more closely examine how music physiologically affects patients with RTT. Music has been reported to attract significant interest and provoke responses in this population, which has resulted in the utilisation of a variety of musical activities and interventions by parents, teachers and therapists. Music seems to play a very important role in the lives of people with RTT (Merker & Wallin, 2001; Montague, 1988; Wesecky, 1986). A majority have very definite favourite pieces, and when they listen to a preferred tune, a clear reaction can be observed (Elefant, 2002; Houtaling, 2003; Merker, Bergström-Isacsson, & Witt Engerström, 2001). Relatives describe the use of music as a “drug” to calm the girls down, helping to ameliorate anxiety, impatience and screaming, as well as something that can help them in making contact, getting to sleep, and when anxiety is provoked, for example during visits to the doctor or dentist – usually when nothing else seems to work. Parents may eventually use music as an alternative after they have tried calming down the child with words, hugs or other sensory input (Bergström-Isacsson, 2001). There is no earlier research that illuminates the underlying mechanisms but during my work with RTT patients I have been fascinated by the potential of music to wake, entice and calm. Considering the seemingly normal early period in RTT, one can speculate about a normal musical development (Merker & Wallin, 2001).

This current study will therefore focus on the effects of different musical stimuli on brainstem responses in a sample of participants with RTT, compared with children whose development is normal.

Another reason for the importance of music in an RTT population might be that they have lost almost all other ways to communicate. These questions are not the main research

questions in the current study, but they have been raised during clinical work and are therefore important to discuss.

1.2. Clinical and personal motivation for the study

Music, and primarily receptive music (cd, mp3, parents' singing, dvd), is used in many different ways in relation to RTT but *music therapy* is not very common according to parents, carers and therapists (Bergström-Isacsson, Julu, & Witt Engerström, 2007). In my work with RTT I use improvisational music therapy inspired by both early development theory and analytically oriented music therapy methods. This is a way to investigate patients' musical preferences (songs and instruments), communication in and through music, level of cognition, patients' ability to take an active part in playing instruments, and how they can develop in and through music therapy.

In addition to the active methods I also use vibroacoustic therapy (VT⁵ see section 2.2.5.) as a music therapy method. During my clinical work I have observed how anxiety is subdued and body tension decreases when VT is practised. Hand stereotypies are calmed down, breathing becomes deeper and normalises. Previous research has shown a relaxing effect on the body (Wigram & Dileo-Maranto, 1997a) and calmer breathing, but there is no research that sheds light on any possible physiological background mechanisms.

People with RTT have enormous communicative difficulties, and therefore parents and other caregivers generally have to trust their own ability to interpret the patient's communicative signals, such as body movements, vocalisation, facial expressions and eye-pointing. Earlier research has indicated that these signals might sometimes be misinterpreted (Bergström-Isacsson, et al., 2007; Sigafos et al., 2010).

From my clinical work I discovered one clear misunderstanding in how to interpret facial expressions. During brainstem assessment, one girl was agitated and angry. I started to play her favourite tune and she immediately smiled and laughed. To begin with her physiological response to the music was fine and her smile was genuine. She really liked the music. Based on that reaction it was easy to understand why her parents concluded that music was something good that could influence her emotional state. However, what the monitoring system showed after one minute of music was something completely different. There was tremendous variability in mean blood pressure, uncontrolled

⁵ VT is used as the abbreviation for Vibroacoustic Therapy in this doctoral study. That is because the more common abbreviation, VAT might be confused with other abbreviations as for example Value Added Tax.

breathing, dilated pupils, and a decreased brainstem control function. She was in a state of stress and her immature brainstem was not able to control the situation. When I analysed her facial expressions in detail it was obvious that she enjoyed and liked the music to start with, which was confirmed by the technical equipment, but when her brainstem control functions failed there were also changes in her “smile”. One way to express what happened is that the girl became “too happy”. There was no doubt about the fact that she liked the music, but because of her immature brainstem her physiological system ran amok. The recommendations to her parents were of course that they should play the music she liked but maybe pay more attention to her facial expressions, her breathing pattern and her pupils.

Another girl had constant epileptic activity, variability in heart rate and blood pressure, breathing disturbances, and many involuntary movements in her body. When I played her favourite tune she became absolutely still and her face was blank. It was not possible to interpret any facial activity, and it was difficult to understand that she enjoyed the music. The monitoring system illustrated a considerably improved brainstem control function, stabilised blood pressure, stabilised breathing and reduced epileptic activity. This girl was focusing, listening and she also responded to changes in the music.

In both cases the parents gave their girls the music they thought the girls liked and was good for them; and for both girls the music was certainly connected with emotions. However, the way in which the brain coped with the emotions and how the girls communicated their experience of their emotions was different. With this in mind, I do not find it easy to distinguish between different emotional expressions in the group with RTT.

The problems of misinterpreting facial expressions indicate the importance of combining brainstem assessment with analyses of facial expressions in addition to the influence of music and VT⁶.

⁶ I would like to clarify that in Sweden the term vibroacoustic is used in other areas and disciplines outside the clinical field. Apart from referring to the therapeutic aspect of music, the expression is used within companies engaged in vibration measurement, analysis and change, in areas such as vehicle and machine vibrations, industrial noise, building acoustics and sound environment in public places.

1.3. Research context and content

The Swedish Rett Center in Östersund, Sweden, where I work, was created by child neurologist Ingegerd Witt Engerström, PhD. It is a national centre dedicated to RTT as a rare neurological disorder, bringing multi-professional competence to bear on the complicated, specific, and multiple needs of patients with RTT. The Rett Center comprises specialist care, research and development and is thus a competence centre. As a specialist care unit, the Rett Center constitutes an additional service to local and regional hospitals, on commission from the Department of Social Services. There are other centres in the world (in Australia, Denmark, and the USA) and also other Rett syndrome specialist teams (in England, France, Israel, Italy, Scotland, and Japan, just to mention a few) but so far the Swedish Rett Center is the first and only centre with a transdisciplinary team working *only* with an RTT population. This makes the position of music therapy unique, as it is an integral part of clinical work, research and the spread of knowledge.

Since 1998, the Swedish Rett Center has been able to study the control of the autonomic nervous system in the brainstem using the technique invented by Julu (Julu, 2001). This means that it is possible to make brainstem assessment including musical stimuli.

If the use of music and/or vibroacoustic therapy (VT) can somehow help or strengthen the brainstem control function, this would be of great importance for the individual. Music or VT could then be used to complement or replace pharmacological treatment with the aim of reducing anxiety, screaming, sleeping problems, or other severe difficulties. It would be beneficial for the patient and have an impact on both medical care and personal care. Based on my own observations and the descriptions of parents or carers, I have been increasingly interested in different responses to music and vibration. In my Bachelor's thesis, based on my work at the Rett Center, I investigated a psychological comprehension model and interpretation that dealt with similar issues (Bergström-Isacsson, 2001). In my Master's thesis I explained the potential for measuring the effects of receptive music and VT on the brainstem (Bergström-Isacsson, 2005; Merker, et al., 2001), and it was confirmed that the technique used made it possible to measure brainstem responses when participants were exposed to musical stimuli. In this doctoral study, I wanted to take this research to a new level and compare possible differences between an immature and a normal brainstem. In this experimental neurophysiological study, the participants are exposed to receptive music and vibroacoustic stimuli. There are

no interactions with the therapist; the participants only listen to or experience the music and the vibroacoustic stimulus.

Exposing the patients to music during a brainstem assessment is one way to observe whether calming music chosen by parents or carers (*Calming*) gives the expected sedative physiological response, and whether activating music chosen by parents or carers (*Activating*) gives the expected activating physiological brainstem response. The study also includes physiological brainstem responses to specific kinds of music such as *Horn*, *VT*, *VT* added to calming music chosen for this purpose (*VT+Mu*) and the calming music alone (*Mu*).

The technique currently used for brainstem assessments at the Rett Center, making this investigation possible, has already been tested (Bergström-Isacsson, 2005). The team performing the brainstem assessments at the Rett Center consists of a neurophysiologist, a physicist, a paediatric neurologist, an EEG technician and a music therapist.

As assessment of brainstem responses is only *one* indicator, and not possible to carry out on a daily basis, the study included the relation between brainstem responses and facial expressions, as well as a brief analysis and overview of the music generally used for people with RTT. This will be done by studying the functions of the central nervous system during a simultaneous⁷ brainstem examination on participants with RTT referred to the Rett Center and compared with a specially recruited non-clinical group consisting of young children with normal development.

1.4. Research questions

The main research questions are:

1. What effects do different musical stimuli have on autonomic functions and cortical emotional reactions in participants with RTT?
2. What effects do different musical stimuli have on autonomic functions and cortical emotional reactions in non-clinical participants, children between 1 and 5 years old with a normally developed brainstem?
3. Is it possible to observe any differences in responses between the two groups?

The hypotheses are presented in section 2.6.

⁷ All variables monitored are time-synchronised

1.5. Thesis guide

The RTT population or people with RTT in this thesis represent the RTT population in general. This general group will be referred to as patients, since they come to the Rett Center as clinical patients. The individuals taking part in the study will be referred to as participants.

I have organised the thesis into five chapters in a format typical of experimental studies.

Chapter two provides a review of relevant literature and provides a theoretical framework upon which this current study is based, including music and music therapy, epidemiology and genetics, as well as relevant parts of the brain, and measurable autonomic parameters. Chapter two also introduces how facial and emotional expressions can be interpreted in general, which is important for later analysis of the results, and gives an account of current clinical thinking and research findings in the areas in focus. On the basis of the research questions and the literature review, chapter two finally presents the hypotheses generated for this study.

Chapter three provides a detailed description of the aim of the study, a flow chart giving an overview of the different steps, the study design, parameters measured, materials and equipment, monitoring equipment, chosen clinical methods, criteria for the recruitment of participants, and the procedure of the trials.

Chapter four presents the results from the analyses of continuous dependent variables in participants with RTT, compared with a sample of non-clinical participants. The chapter continues with results of analyses of categorical brainstem responses in the two participant groups. Chapter four presents the results from testing hypotheses, applying statistical analyses on the data drawn from brainstem responses. These results are followed by results from video analyses of the effect of the different musical stimuli on facial expressions, analysis of the music and finally the relationship between measured data.

Chapter five discusses the main findings and the methodology of this current study in relation to the theoretical framework and findings from previous studies that were presented in chapter two. The research questions and hypotheses are discussed, as well as the weaknesses and limitations of this study, and the implications of the findings for clinical practice. Final conclusions are put forward, together with ideas for further research.

An extended version of the abstract can be found in the English and Swedish summaries.

The references mentioned throughout the text are listed, and appendices which provide all relevant and necessary information regarding tools and records used in the study are enclosed.

CHAPTER TWO

2. Literature Review and a Theoretical Foundation

The main issue of this thesis concerning the effect of music on people with RTT is to address the first research question, i.e. what effects do different musical stimuli have on autonomic functions and cortical emotional reactions in participants with RTT. The study is a neurophysiological experiment based on brainstem assessments and the origins of autonomic responses from the brainstem. In order to contextualise the subject, chapter two is divided into parts to clarify terms in the research questions: the background and the development of RTT, RTT and music, the background for understanding relevant brainstem functions including the autonomic nervous system, cortical emotional reactions including facial expressions and analysis, and finally how to categorise different musical stimuli into activating and sedative music.

2.1. Rett syndrome

In the DSM-IV (AmericanPsychiatricAssociation, 1994), Rett syndrome (RTT) is classified, together with autism, as a pervasive developmental disorder (PDD), characterised by delays in the development of multiple basic functions including socialisation and communication⁸. Clear clinical criteria have been agreed upon for diagnosing RTT and it is currently also possible to perform a genetic test to gain evidence in support of the diagnosis, but RTT is still a clinical diagnosis (Hagberg, Hanefeld, Percy, & Skjeldal, 2002; Hagberg & Witt Engerström, 1986). According to DSM-IV, people with RTT do not have the capacity to learn new skills, but this contradicts observations in clinical work as well as in research, which will be presented in 2.2.4. (Bergström-Isacsson, 2001; Elefant, 2002; Elefant & Wigram, 2005; Montague, 1988; Wesecky, 1986; Wigram, 1991). DSM-IV states that children with PDD vary widely in abilities, intelligence, and behaviour. Some children do not speak at all, others speak in limited phrases or conversations, and some (not those with RTT) have relatively normal language development. Repetitive play behaviour and limited social skills are also generally evident. Unusual responses to sensory information such as loud noises, strong lights, and pain are also frequent (AmericanPsychiatricAssociation, 1994).

⁸ However, arguments have been put forward in the workgroup for DSM-V (AmericanPsychiatricAssociation, 2010) implying that RTT might be classified otherwise in the next issue.

The abbreviations for Rett syndrome have varied. Today people with Rett syndrome *with mutations* in a gene of the X-chromosome called MECP2 are described as RTT (Roende et al., 2010). RS was previously used as the *clinical abbreviation* for the clinical syndrome but can be confused with RS1 (Retinoschisis1). Therefore the *recommendation* during the European Rett Syndrome Conference in Edinburgh, Scotland in 2010 was to use only RTT as the abbreviation for Rett syndrome. RTT is the preferred abbreviation in the medical database: Online Mendelian Inheritance in Man[®] (OMIM[®]) (McKusick-NatansInstitute, 2011), and will also be used in this doctoral thesis.

2.1.1. *Background and development*

RTT is a neurodevelopmental disorder that is found all over the world. It has most probably existed amongst humans throughout history, but might have been hidden behind other diagnoses such as intellectual disabilities, cerebral palsy and autism. Almost all of the RTT population are female, and very few males have been identified (Leonard et al., 2001).

Andreas Rett from Austria was the doctor who first recognised RTT in 1954. He described a constellation of characteristic symptoms, but that knowledge remained unrecognised by the medical community for more than a decade, as it was published in a relatively minor Austrian journal (Rett, 1966). However, other neurologists throughout the world had noticed similar symptoms (Ishikawa et al., 1978). Bengt Hagberg, a neuropaediatrician from Sweden, presented the first report in English in 1983. He had recorded 16 girls under the eponym “Morbus Vesslan” and presented them in a survey to members of the European Federation of the Child Neurology Societies in 1980 (Witt Engerström, 1990), which then led to a publication of a collaborative study on 35 girls (Hagberg, Aicardi, Dias, & Wilson, 1983). This publication opened clinicians’ eyes to the syndrome and rapid recognition occurred all over the world. Parental support groups started, the first one in the USA, and today there are parental groups and associations in many countries. These associations play an important role in supporting parents and encouraging clinicians and researchers all over the world to seek for the keys to solving the Rett disorder, if possible, and in the future, also curing it.

RTT was earlier believed to be a degenerative and progressive disorder, and it took many years to prove, and for it to be fully accepted, that this was not the case (Kerr & Witt Engerström, 2001). There is no doubt that RTT is a diagnosis that includes severe

intellectual disability and slow psychological (motor and cognitive) growth (a developmental slowing-down at around 25 weeks of infancy), but there is no continuing deterioration in serial clinical examinations, no progressive alteration in magnetic resonance imaging (MRI), and no evidence of progressive deterioration in an electroencephalogram (EEG) (Armstrong & Kinney, 2001). Furthermore, in the central nervous system there is no recognisable malformation, degeneration or inflammatory process, nor any consistent evidence of cellular disorder involving cytoskeleton⁹, lysosomes¹⁰ or myelin¹¹ (Armstrong & Kinney, 2001). In fact, the developmental potential of people with RTT has been noticed in clinical observations and surveys all over the world (Cass et al., 2003; Trevarthen & Burford, 2001; Witt Engerström et al., 2005).

Classical RTT is defined according to an international agreement (Diagnostic Criteria Working Group 1988) developed from earlier proposals (Hagberg, Goutieres, Hanefeld, Rett, & Wilson, 1985; Hagberg, et al., 2002; Kerr & Witt Engerström, 2001):

Criteria connected with classical RTT:

- Apparently normal prenatal and perinatal period
- Psychomotor development largely normal through the first 6 months or maybe delayed from birth
- Normal head circumference at birth
- Postnatal periodic deceleration of head growth after a few months of age
- Loss of achieved purposeful hand skills between the age of 6 months and 2½ years
- Stereotyped hand movements — wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
- Emerging social withdrawal, communication dysfunction, loss of words, and cognitive impairment
- Impaired (dyspraxic) or failing locomotion

⁹ The cytoskeleton is cellular “scaffolding” or “skeleton” contained within the cytoplasm and is made out of protein.

¹⁰ Lysosomes are cellular organelles which contain acid hydrolase enzymes to break up waste materials and cellular debris.

¹¹ Myelin is a dielectric (electrically insulating) material that forms a layer, the myelin sheath, usually around only the axon of a neuron.

The following are findings or signs called supportive criteria. They are not required for the diagnosis but may be seen as secondary symptoms in some RTT patients. They might not be seen from the beginning but may evolve with age:

- Disturbance of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing) during the waking state
- Bruxism (teeth grinding)
- Impaired sleep pattern from early infancy
- Abnormal muscle tone subsequently associated with muscle wasting and dystonia
- Peripheral vasomotor disturbances
- Scoliosis/kyphosis progressing through childhood
- Growth retardation
- Hypotrophic small and cold feet; small, thin hands

These findings may vary in severity and not all RTT patients present all these signs.

There are also exclusion criteria to be taken into consideration:

- Organomegaly or other signs of storage disease
- Retinopathy, optic atrophy, or cataract
- Evidence of perinatal or postnatal brain damage
- Existence of identifiable metabolic or other progressive neurological disorder
- Acquired neurological disorders resulting from severe infections or head trauma

2.1.2. *Stages in Rett syndrome*

The development of RTT may be divided into four stages. Stage I is the early period before going into stage II: regression. Stage III is a more stable, pseudo-stationary period. Finally, *when or if* the person has been able to walk and loses gait, he or she goes into stage IV: the non-ambulant stage (Hagberg, 1993; Hagberg & Witt Engerström, 1986; Witt Engerström, 1990).

Stage I. Early onset stagnation (Pre-regression¹²)

- Duration: weeks to months
- Onset age: 6 months - 1½ years
- Developmental progress delayed, with early postural delay

¹² A British survey used pre-regression, regression, early and later post-regression to describe the development (Kerr & Witt Engerström, 2001).

- Developmental pattern still not significantly abnormal but dissociated
- “Bottom-shufflers”

Stage II. Rapid developmental regression (Regression)

- Duration: weeks to months
- Onset stage: 1 – 4 years sometimes acute “pseudotoxic”
- Loss of acquired skills: fine finger, babble/words, active playing
- Mental deficiency, eye contact preserved, occasionally “in another world”
- Moderate breathing problems
- Seizures in only 15% of cases

Stage III. Pseudo-stationary period (Early post-regression)

- Duration: years to decades
- Onset: after passing stage II
- Apparently preserved walking ability with prominent hand apraxia¹³/dyspraxia¹⁴
- In apparent slow neuromotor regression
- “Wake up” period
- Stage III/IV non-ambulant patients

Stage IV. Late motor deterioration (Later post-regression)

- Duration: decades
- Onset: when stage III ambulation ceases
- Stage IVA: previous walkers, now non-ambulant
- Stage IVB: never ambulant
- Complete wheelchair dependency
- Severe disability: muscle wasting and distortions

There are people with RTT who do not fit into the definition of classical RTT. In British literature they are called “atypical” and according to Swedish tradition they are called “variants”: congenital (recognised from birth), early seizure/Hanefeld (early onset before regression), form fruste (regression after age 4), preserved speech/Zapella variant (words used after regression) and male variant (Kerr & Witt Engerström, 2001).

¹³ Apraxia – loss of the ability to execute or carry out learned purposeful movements.

¹⁴ Dyspraxia – an impairment or immaturity of the organisation of movements. It is an immaturity in the way the brain processes information which results in messages not being properly or fully transmitted.

The clinical stages and the diagnostic criteria are important and helpful in identifying patients with RTT. The diagnosis is however still fairly new and uncommon, and doctors might overlook the RTT-specific clinical symptoms and therefore give some patients an inappropriate diagnosis. This may also happen to trained specialists (Leonard, Bower, & English, 1997). The clinical signs of RTT are often indistinct in small children and it is not an easy task to identify the syndrome.

2.1.3. Occurrence and genetics

The classical form of RTT has a general incidence of no less than 1:10,000 new-born girls (Kerr & Witt Engerström, 2001). Other estimates exist both above and below this figure, experienced clinicians having generally searched most assiduously and found the highest. The Rett disorder affects mainly females but a few males have received the diagnosis (Leonard, et al., 2001). It is considered to be a genetic disorder but not hereditary (less than 1%). Most cases of RTT occur sporadically, but 4% of those reported in Britain had a relative with RTT (Kerr & Witt Engerström, 2001). Classical forms and variants of RTT, in both girls and boys, have been reported in the same family.

Intensive research into the cause of RTT is going on all over the world. There was a breakthrough in September 1999 when two research teams in the USA identified mutations in the MECP2 gene on the outermost part of the X-chromosome Xq28 that could be related to RTT. 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 to the normal growth of neurons in the central nervous system (Armstrong & Kinney, 2001). These findings have led to a more precise diagnostic procedure and to a better understanding of the biological background of the syndrome. Mutations often arise in the sperm, more rarely in the egg, and very seldom in the embryo (Kerr & Engerström, 2001).

Later, in 2004, two separate research centres discovered mutations in the CDKL5 gene, also on the X-chromosome, in patients with RTT. This locus seems to relate to severe seizure disorders and intellectual disability, and causes several clinical symptoms found in RTT. There was speculation in 2004 that both CDKL5 and MECP2 are part of the pathogenesis behind both RTT and Angelman syndrome¹⁵ (Tao et al., 2004; Weaving et

¹⁵ Angelman syndrome is a genetic disorder that primarily affects the nervous system. Characteristic features include developmental delay, severe speech impairment, intellectual disability, epilepsy and a small head size.

al., 2004). Since these findings are important for a better understanding of RTT, doctors ask for DNA tests on as many RTT patients as possible, for a probable confirmation of the clinical diagnosis, and also for research. MECP2 mutations have been found amongst 95% of patients with classical RTT, demonstrating that they are a relatively homogeneous group (Percy, 2008). So far, more than 250 different MECP2 mutations have been identified in individuals with RTT. Related to this genetic research, mutations on CDKL5- and FOXP1 genes have been found primarily among RTT patients diagnosed as variants (Gonzales & LaSalle, 2010); so, all in all, mutations in the CDKL5 and FOXP1 genes are rare compared with MECP2 mutations, and the findings regarding CDKL5 and FOXP1 mutations are still not fully understood. Research has identified mutations in the MECP2 gene in people with different types of developmental retardation (Samaco, Hogart, & LaSalle, 2005). In summary, RTT is still primarily a clinical diagnosis that is strongly supported by a mutation in the MECP2 gene.

A new breakthrough in the area of genetics was made in 2007 when Alan Bird and his colleagues at the Wellcome Trust Centre for Cell Biology, Edinburgh University, observed neurological improvement in *a mouse model with RTT*¹⁶ (Guy, Gan, Selfridge, Cobb, & Bird, 2007). The aim of their study was to find out if clinical symptoms of RTT might improve. The specific question was: can living, but transformed, nerve cells be repaired, or is the damage during development without a normal MeCP2 protein irreversible? According to Bird's study, it is likely that RTT-like neurological changes caused by absence of the mouse MECP2 gene, *can* be corrected by restoring the gene. However, this is true for mice; we are still a long way from treatment of humans, and we do not yet know if it is possible to transfer the results from a mouse model to humans. The researchers state that there are no immediate plans to start treating humans but that the results clearly illustrate the principle of regaining normalisation and provide new perspectives for possible future treatments. A current focus of investigation is the extent to which the clinical phenotype in RTT depends on the nature of mutation that causes the disorder. The first studies from initial genotype–phenotype research were somewhat inconsistent due to a small sample size and the use of different measures (Christodoulou & Weaving, 2003). Over the years, a more consistent picture has emerged and recent studies, undertaken on bigger samples sizes, have examined the severity of the phenotype in patients with common single individual mutations: p.R133C is associated with a milder

¹⁶ Mouse model = MECP2 mutant mice. Mice with RTT.

phenotype, whereas p.R255X and p.R270X are associated with a more severe phenotype, but there is still inconsistency across studies. Several genetic factors (e.g. skewing of X chromosome inactivation, genetic background) and clinical factors (typicality of the RTT presentation and selection criteria for cases, age at sampling, the items included in any phenotypic ‘severity score’) will affect any genotype–phenotype found, and there is variability in the phenotype even for groups of individuals with the same mutation. Research teams all over the world are working very hard on solving the questions around RTT (Charman et al., 2005; Kerr, Archer, Evans, Prescott, & Gibbon, 2006).

2.1.4. Communicative abilities and difficulties in Rett syndrome

The RTT population have severe communication impairments, which is one of the criteria connected with the syndrome (Hagberg, et al., 1985; Hagberg, et al., 2002; Hagberg & Witt Engerström, 1986; Kerr & Witt Engerström, 2001). The severe communication impairment in RTT includes loss of words, and thereby a limited ability to use *expressive* language (Didden et al., 2010; Sigafos, et al., 2010), even though *passive* language is preserved in varying degrees (Bartolotta, Zipp, Simpkins, & Glazewski, 2011; Wine, 2009). Involuntary stereotyped hand movements and dyspraxia make purposeful use of the hands difficult. This affects their ability to actively communicate using pictures, computer, sign language and speech synthesiser. Because of these severe problems it is difficult to assess their cognitive ability, and it is almost impossible to use standardised tests as these tests require expressed language or functional hands. People with RTT develop neither of these abilities, or only to a minor degree (Trevarthen & Burford, 2001). They are therefore extremely dependent on the ability of caregivers to observe and interpret their poor communicative signals – including their emotional expressions.

Up to now, there are mainly three ways to improve communication related below. Eye gaze or eye-tracking (“eye-pointing”) are almost always mentioned in connection with communication and people with RTT. In an RTT study on communication (Baptista, Mercadante, Macedo, & Schwartzman, 2006) an Eyegaze® device was used to record the participants’ visual scanning response to visual computer screen stimulation. The result showed that people with RTT can respond to simple commands in a consistent way, but as this is only a pilot study testing a new technique, further research is needed, according to the authors. Similar equipment is used at the Swedish Rett Center by the speech and language therapist during assessment procedures. She finds it interesting and well adapted

to some people with RTT (personal communication with Helena Wandin, the Swedish Rett Center).

Hadsell & Coleman (1988) highlighted the importance of promoting appropriate hand use, because the typical RTT hand stereotypies interfere with all learning tasks, including communication. In their opinion, appropriate hand usage should be promoted in structured activities, and they used two major techniques. First, the therapist may hold one hand, leaving the other free to touch or explore items. Second, the therapist may choose to transfer the stereotypical hand movement to the object to be manipulated and then gradually encourage separation of the hands.

The third possibility is to focus on changes in facial expressions to interpret a person's choice (Hadsell & Coleman, 1988), but is difficult to know if the interpretation is right. Reliable interpretation of facial expressions requires adequate knowledge about what facial movements to look for, as well as time and timing (Ekman & Rosenberg, 2005).

2.1.5. Short summary related to the research questions

RTT is a neurodevelopmental disorder that affects mainly females. People with RTT develop multiple disabilities and, in the same way as other children with severe intellectual disabilities, they will always suffer from tremendous difficulties throughout life. Major communication dysfunctions make people with RTT dependent on the ability of caregivers to observe and interpret their communicative and emotional signals. People with RTT are therefore open to misinterpretations. As seen in 2.3. and 2.4., the RTT population generally have an immature brainstem, which, among other things, can generate abnormal facial activity. In combination with the difficulty in reading their facial expression, this abnormal facial activity can create even more problems. Before this is explained further, the next section will focus on music and music therapy, since there are several ways in which music plays an important role for many people with RTT.

2.2. Rett syndrome and music therapy

It is well known that music can be a path to communication and understanding among children in general, but especially those with intellectual disabilities (Gold, Wigram, & Elefant, 2006; Savarimuthu & Bunnell, 2002; Wheeler, Williams, Seida, & Ospina, 2008). This is even more striking in people with RTT, since music and music therapy here are commonly used as medium, method and medicine (Lindberg, 2006; Merker & Wallin, 2001; Sigafoos et al., 2009; Wigram & Lawrence, 2005). There are several

examples of music being used intentionally, as most people with RTT have clear musical preferences (Elefant, 2002; Houtaling, 2003; Merker, et al., 2001)

In this part of the review there will be an overview of the literature on musical preferences, the use of music for different purposes, and music therapy with people with RTT. Music seems to play an important role in life for people with RTT and is therefore used in situations other than music therapy, e.g. medical assessment (Wigram & Lawrence, 2005) and as a window to reach their cognitive capacity (Merker & Wallin, 2001).

2.2.1. Rett syndrome and musical preferences

In London in 1999 there was a “MacKeith meeting”, a research symposium, focusing specifically on RTT. During this meeting there were discussions about how motor and autonomous shortcomings prevent an examination that could demonstrate maximum musical understanding among the RTT population. The need for closer studies of music and RTT, especially regarding the effect of music used to calm or activate the person, favourite tunes, interaction, etc. was raised. The meeting resulted in a survey which was sent out to all RTT families in Sweden (Merker, et al., 2001). The results from this survey support the assertion that music is of considerable importance, and in particular that the individual’s favourite tunes have a notable effect. In certain cases these favourite tunes can be seen or used as “medicine” when pharmacological remedies are not effective enough. Parents described in the survey how they used music as “first aid” to alleviate anxiety and anger, and as a “sedative drug”, e.g. when they went to the supermarket, the dentist or the doctor. In an essay based on the above-mentioned survey and clinical observations, Bergström-Isacsson (2001) also described the importance of music for people with RTT.

The results of the survey show that all people with RTT prefer children’s songs, irrespective of age, but that despite this finding they are more frequently given pop music as a listening option. The authors speculated regarding this finding and came to the conclusion that parents and carers gave the person the music they thought they themselves would prefer according to the person’s age. This study also states that the RTT population have clear favourites, but that the favourites can change if they are presented with new songs. Of the participants investigated (all of them girls), 67% aged 3-12 years, 69% between 13 and 19 years, 54% aged 20-28 years and 15% in the group aged 29-53 changed favourites. Nine respondents (out of a total of 70) commented that

the change was in the form of adding new favourites rather than replacing one favourite by another (Merker, et al., 2001). Music therapist Houtaling, USA, carried out a study based on the Swedish investigation which showed similar results (Houtaling, 2003).

From the results of a survey, the British music therapist Holdworth (1999) describes how music seems to influence the moods of people with RTT, where a recognised piece of music has a positive effect and where a non-recognised piece has a negative effect. Holdworth states that people with RTT favour simple, light and energetic music. She refers to other cases that have been reported and describes how the girls indicate that they prefer a certain song to another and show a higher level of self-expression when the song is sung (Holdworth, 1999).

In a doctoral thesis described further in 2.2.4., Elefant (2002) investigates the RTT participants' favourites and their ability to choose for themselves what they want to hear. Elefant states that a person has a musical preference when she or he can demonstrate clear choices between different music examples (Elefant, 2002). The choice can be proved by overtly showing when the person is able, through changed behaviour, to show happiness, interest or aversion as a definite and reliable response. These kinds of preferences are interesting from a cognitive perspective, since preferences signify the ability to distinguish, to remember and to recognise. This means that the person is capable of choosing a special song from a number of alternatives (Elefant, 2002). The recognition of a musical favourite can be shown by emotional expressions such as smiling and laughing, an increased level of activity and hyperventilation (Bergström-Isacsson, 2005; Merker, et al., 2001). Parents and carers apprehend the girls' favourites by interpreting their facial expressions and their breathing, but it is not always easy to interpret and to anticipate the response to music, amongst other things. Mount et al. (2001) have described behavioural and emotional features in RTT.

The episodes of anxiety, more so than the episodes of low mood, were reported to be precipitated by external events. Events leading to anxiety were reported to include sudden noises, some types of music, strange people and places, change of routine and expressive activity in proximity of the child. Events reported to calm the anxiety and self-injury were slow music, singing, holding, cuddling, massage, water play, and access to

favourite toys.

(Mount, et al., p. 132)

Calm music can be observed to have a calming and relaxing effect, but in people with RTT it may also provoke a higher level of anxiety (Mount, Hastings, Reilly, Cass, & Charman, 2001).

Summing up, there is no doubt that people with RTT have a clear interest and clear responses to music (Elefant, 2002; Hill, 1997; Merker, et al., 2001; Merker & Wallin, 2001; Rett, 1982; Trevarthen, 1997; Trevarthen & Burford, 2001; Yasuhara & Sugiyama, 2001). According to the above-mentioned survey conducted by the Swedish Rett Centre in 1998, 96% of the participants showed a clear interest in music (Merker, et al., 2001).

2.2.2. The use of music for different purposes

In general, music is a large part of every child's cultural environment. A foetus at 25 weeks gestation has a developed auditory function (Taylor, 2002; Trevarthen & Burford, 2001). Cochlea function, basilar membrane response, and development of both inner and outer rows of hair cells, all appear by the fifth to the seventh month of pregnancy, permitting transmission of encoded acoustic information to the eighth cranial nerve, which is the first cranial nerve to develop in the brain of the foetus. Research into auditory evoked responses in the foetus' brain shows that the stimulus is transmitted to the brain where it can be perceived and stored (Taylor, 2002). There is of course no research carried out to investigate foetus with RTT, but research on auditory evoked potentials in RTT infants demonstrates intactness of peripheral auditory and visual pathways (Glaze, 2005).

Infants are exposed to the music culture in their home and the surroundings, and they prove this by having favourite songs and a distinct musical preference (Houtaling, 2003; Merker, et al., 2001). Musical influence is present all the time, and music changes a person's behaviour – for instance by being calmer or more active, by being focused and concentrated, by showing emotions or by physical reactions. Nothing indicates that people with RTT will react in any other way (Trevarthen & Burford, 2001). They are musically sensitive; they show that they have musical preference in the form of favourites, artists and genre (as seen in 2.2.1.).

In a comparative study of healthy babies and children with Rett syndrome, Trevarthen concluded that they find intentional movements difficult and therefore it is difficult for

them to learn, but they answer very well to the stimulation of rhythm and melody. Musical and poetic forms of vocalisation for babies create emotional “stories” that the child can perceive, enjoy and take part in, long before the he or she can understand the spoken language. This pre-verbal level seems to be intact in girls with RTT (Trevvarthen, 1997).

In “Rett disorder and the developing brain” (Merker & Wallin, 2001), one of the chapters is concerned with how to see music as a window to the individual’s cognitive capacity in their inability to speak (Merker & Wallin, 2001). The conclusion is that people with RTT show a greater understanding and interest in music than one could really expect of them considering their linguistic shortcomings.

Music ranks second only to human language and language-based activities in its potential cognitive complexity. Structurally music is characterized by syntactic structure which, as in the case of language, exhibits hierarchical organization, but which, unlike language, is not a vehicle for the communication of referential meaning. This makes music a close to ideal medium by which to explore the cognitive capacities of patient populations lacking language, or exhibiting extreme language impairment, as is the case in the Rett disorder. It is therefore possible that the study of musical responsiveness and preferences on the part of Rett patients could provide a “window” on their cognitive capacities in absence of language. (Merker & Wallin, 2001, p. 328)

Parents and carers describe how people with RTT seem to connect music with people, places and situations and thus find help in understanding and interpreting their surroundings; and researchers state that it is primarily through music that people with RTT have contacts with the world around them (Houtaling, 2003; Merker, et al., 2001; Merker & Wallin, 2001; Trevvarthen & Burford, 2001). On the surface, the normal start in life for people with RTT has many parts, within which music plays an important role in the development of self and of relations with other people (Bergström-Isacsson, 2001). Most remain at a level of development with the feeling of the subjective self, up to the feeling of the verbal self (Stern, 1991)¹⁷. On this level of development, a large part of communication takes place in a very “musical way” also in RTT (Trevvarthen & Burford,

¹⁷ Stern did not write about RTT but his way to describe levels of development can very well be used as a model to understand RTT.

2001). This way to communicate can evoke vocal emotional expressions and body movements, even rhythmical movements, which indicate that the early communication and intention to communicate remain intact. The way one communicates at this level might therefore play a very important role for the rest of one's life (Stern, 1991)¹³.

Music can be seen as the main link to the social culture of people with RTT, and through research and clinical experience it has become clear that music is central and often the only working tool when they need help to be stimulated, to relax and to concentrate (Bergström-Isacsson, 2001, 2005; Mount, et al., 2001). Music is played frequently by parents and carers in order to make the person feel good in one way or another. As mentioned earlier (2.2.1.), parents and carers describe how music is used as a “drug” in situations when nothing else works (Merker, et al., 2001).

Even if people with RTT have clear preferences, they have a very small chance of influencing what music is played to them. It is left to people around them to interpret their reactions and emotional expressions to the music played. Music that is interpreted as calming by parents and carers *may* have an observable calming effect, but when it comes to people with RTT it is necessary to pay attention to details (Bergström-Isacsson, et al., 2007). It is common to see hyperventilation and an increased level of activity when the calming favourites are played (Woodyatt & Ozanne, 1992, 1994), which could very well indicate an activating response or an increased anxiety level instead of a calming response (Bergström-Isacsson, et al., 2007).

To identify more clearly the physiological and neurological responses in relation to affects caused by music, there are still many potential areas to be explored. However, an accumulating body of general knowledge shows that there is a recognised relation between emotional qualities experienced in music (Juslin & Sloboda, 2001). We can experience emotions of calmness, alertness, happiness or sadness when we are exposed to certain musical stimuli. This is also documented in Bonde (2009), and in the updated edition of Juslin and Sloboda (2010). Both of these references were published after I began my research study.

2.2.3. The use of music and music therapy in teamwork

Music can be used to advantage in different situations with people in general. Physiotherapists, occupational therapists, speech- and language therapists and doctors use music as a tool in assessment and treatment, both individually but also in team work (Witt

Engerström, et al., 2005). A Swedish survey (Lindberg & Oresten, 2003) investigated how physiotherapists in general use music in the habilitation process of children and adolescents with intellectual disabilities. The result revealed widespread use of music, both in treatment of children individually and in group settings. All participants agreed that the use of music during treatment was suitable for all children, regardless of age or diagnosis. The only limiting factor reported was what the individual child favoured or rejected. Reasons for incorporating music in physiotherapeutic treatment were: to make the treatment fun, to motivate, to soothe, to divert and entice, to simplify communication and interplay, and to enhance concentration and clarity. The most common interdisciplinary¹⁸ and transdisciplinary¹⁹ collaboration was between physiotherapists and pedagogues (Lindberg & Oresten, 2003). No collaboration between physiotherapists and music therapists was reported in their study, possibly suggesting that the participants were not aware of the availability of music therapy as an intervention, or they did not know any music therapists with whom they could establish collaboration (Lindberg & Oresten, 2003).

In my clinical work in a transdisciplinary team at the Swedish Rett Center, questions about music are regularly discussed. Music is used in almost every session, irrespective of profession. The physiotherapist uses songs in her clinical work to create an inspiring atmosphere, both in the assessment room and in the pool, and to support rhythmical movements. We, the physiotherapist and I, have worked very closely together and developed a music and movement programme. The songs and movements are intended for young children with or without disabilities. Working purposefully with body movements, beginning when children are small, can help to prevent future problems (Bergström-Isacsson & Larsson, 2008; Wigram & Weekes, 1985b; Witt Engerström, et al., 2005). A similar method with dual intervention has also been developed by Israeli music therapists and physiotherapists (Elefant & Lotan, 2004).

In the area of physical and multiple handicaps (cerebral palsy), Wigram developed a transdisciplinary approach with physiotherapists and other disciplines, including nurses, teachers and creative therapists. The approach included a music and movement

¹⁸ Interdisciplinary model – music therapists work more closely with other team members to determine certain goals and implementation plans collectively. Each professional delivers their section of the lane separately and no professional boundaries are crossed (Wheatley, 1985; Wheeler, 2003).

¹⁹ Transdisciplinary model – music therapists combine their work with other team members and take equal responsibility to implement plans and achieve goals. This model requires fluid boundaries between the professional roles of those involved (Wheatley, 1985; Wheeler, 2003)

programme, where music was adapted to a series of movements. The objectives for this work were to maintain maximum range of movement in a population where increasing flexor spasm leads to fixed flexion deformities and contractions (Grocke & Wigram, 2007; Wigram & Weekes, 1985a; Wigram & Weekes, 1985b).

2.2.4. Music therapy with Rett syndrome patients

From the very first recognition of RTT in 1966, Dr Andreas Rett mentioned the necessity of music in relation to people with RTT (Rett, 1966). He had realised the potential of music and music therapy in breaking through the barrier of difficulties, and at the same time provided information about the “hidden” abilities of people with RTT. Dr Rett worked together, and published together, with the Austrian music therapist Albertine Wesecky (Grasemann, Wesecky, & Rett, 1981). They did not publish anything about music therapy and RTT research together, but they separately stated the importance of music in relation to RTT (Rett, 1982; Wesecky, 1986).

In line with this, Trevarthen & Burford (2001) write about the powerful motivational factors that music provides, and how cooperation often takes place in conjunction with the musical dialogue (Trevarthen & Burford, 1995). They continue by describing RTT and early infant intelligence:

Near normal development in the earliest months indicates that core functions of motivation and socio-emotional response may be more intact than normally appears, and that more organized behaviour may be evoked by contingent and appropriately supportive stimulation. People with RTT respond by orienting and expressing pleasure to “emotional narratives” of nursery rhymes, musical games and songs. Therapies that incorporate rhythms of body movement, speech prosody and music, seek to support retained motives for purposeful action and communication. They may help counteract dysregulations of autonomic state, attention, motor co-ordination and emotion.

(Trevarthen & Burford, 2001, pp. 305-306)

From the time when the RTT disorder was recognised in 1966, little was known about the populations’ communicative abilities, or potential communicative abilities, and, it would seem from DSM-IV that RTT individuals lack learning abilities.

Back in the 1980s, Wesecky and the British music therapist Janette Montague described music as being important to people with RTT, and observed that they were receptive and discriminating towards sounds (Montague, 1988; Wesecky, 1986). They therefore describe music in terms of effective motivation and as providing a means by which communication can be established. Wesecky found that people with RTT have difficulty in learning new skills but that “some kind of learning” seems possible by emotional means, and therefore musical therapy lends itself particularly well to initiating a learning process.

Using case study material Sarah Hill (1997), a music therapist in England, describes the case of a girl with RTT. The study explains how music therapy can help the girl to develop non-verbal expressions which aid interaction, as this allows the free expression of the girls’s feelings. In this way music can be a tool of communication, but Hill expresses some hesitation about the ability of a person with RTT to develop new skills. However, she states that music may stimulate cognitive development, and emphasises the importance of further research (Hill, 1997).

Music therapist and Professor Tony Wigram, who was previously part of the English Rett Syndrome team, has carried out both clinical work and research in music therapy with RTT patients. Wigram has developed a model of assessment through the medium of music therapy to be used in situations where music therapy is part of a multidisciplinary evaluation requiring a diagnostic opinion (Wigram, 1995). It includes a close look at the way children respond under the following headings: general interaction and response, abnormal communication and behaviour, musical behaviour, transference of behaviours or features of pathology into musical behaviour interaction, and physical activity and behaviour. The model can be used for children with RTT but also for children with other diagnoses (Wigram, 1995).

In a single case study, Wigram writes about how one young girl shows her main areas of difficulty during music therapy assessment (Wigram, 1991). It was obvious that she enjoyed music, but had difficulty in making music and understanding what could be done with the instruments. Despite these difficulties and after twenty-two months of music therapy she developed her awareness of music and how to use music as a vehicle for expression, feeling and interaction; she also improved her hand use considerably, and understood the effect and the benefit of working with the music therapist. Music therapy had shown to be a facilitating process of learning.

In a case report, Wigram and physiotherapist Lawrence described how music therapy and physiotherapy can work together as a tool for assessing hand use and communicative ability in children with RTT (Wigram & Lawrence, 2005). By seating the child on the knee of the physiotherapist it was possible to evaluate physical skills, including fine and gross motor abilities, parallel to musical, emotional and communicative expressions.

In the first doctoral thesis in the area of music therapy with people with Rett syndrome, Cochavit Elefant (2002), an Israeli music therapist and part of the Israeli Rett Syndrome team, carried out a single case study. She investigated song favourites and enhancing communicative ability in music therapy in participants with RTT. She found evidence that the participants in her study revealed strong motivation for choosing songs from pictures, and were also able to confirm their choices. A single-case, multiple-probe design was used to evaluate individual choice of, and response to, familiar and unfamiliar songs. Seven girls, ranging in age from 4 to 10, participated in the study. The girls' cognitive abilities were not evaluated, due to the fact that it was impossible to use standardised tools for the assessment of intelligence levels on such severely disabled individuals. All sessions in the study were videotaped with two cameras continuously throughout each session. The girls in the study were familiar with song intervention and also with some of the songs used in the trials.

In order to better understand the participants' musical choices, Elefant made a musical analysis of the style of the most preferred songs, as well as the least preferred songs. These analyses indicated that the preferred songs were fast, lively, and had exciting word play in them which seemed to make the songs stimulating and interesting. The least preferred songs were all slower, more like lullabies, and parents reported that they had used these types of songs with their children when they were younger. As an informal "follow-up" to her study, two small experiments were carried out with non-clinical populations. One group of doctoral students and one group of music therapy students were asked to choose between the same songs as the RTT girls. The result showed that the preferred songs chosen by the RTT participants were also found to be the favoured songs of both groups.

The RTT participants in this study demonstrated that they were able to learn, and that they made impressive progress in learning between the sets.

Participants in this study have been found to be very responsive to song singing, a technique used in music therapy that involves the use of composed songs. The capacity to choose, demonstrated in the study, needs to be taken into consideration in assessment and evaluation of this population when determining their everyday needs and learning potential. If the girls with RS²⁰ included in this study are able to demonstrate a capacity for learning choice making and the expression of preferences, this warrants further generalisation to providing them with the opportunities to express their needs and wishes. Choice making is prerequisite for improving quality of life, and gain/sustaining control over one's immediate environment.

As a result of this study the participants expanded their communication skills into other areas of daily living. These included: picture symbols during interactive storytelling, during mealtime, computer games in the classrooms as well as with their caregivers at home. When working with this population of learning disabilities to enhance the use of spontaneous communication, one should arrange for plenty of opportunities set up throughout the day within different situations.

(Elefant, 2002, p. 274)

Elefant highlights the necessity for continuity in their ability to choose so they do not forget, but that re-learning takes less time than learning from scratch.

Music therapists, except Hill (1997) who hesitates slightly, agree that individuals with RTT have the capacity to learn new skills if they are given the right opportunity (Bergström-Isacsson, 2001; Elefant, 2002; Elefant & Wigram, 2005; Montague, 1988; Wesecky, 1986; Wigram, 1991), which is contradictory to what is written in DSM-IV definitions. They may achieve educational and social development if their intellectual capacity and learning ability is exposed.

Summing up, Elefant and Wigram state that in clinical work with people with RTT one needs to find the person's hidden potentials and skills, and the musical engagement and interactions achieved through individual and group music therapy constitute a medium that provides strong motivation. By using these attractive aspects of music in a

²⁰ The abbreviation RTT was not commonly used at this time.

therapeutic approach, Elefant & Wigram (2005) propose that the learnt process can be retained for months after the intervention has been terminated. They widen their conclusions and state that music therapy makes it possible to see the whole person with RTT. They also believe that the development of any child's activity is fundamentally a musical process and that the experience of being active in music can be an effective therapeutic tool. The authors (Wigram & Elefant, 2009) are pleasantly surprised at the amount of communication, engagement, functional physical activity, lack of resistance, prosocial behaviour, and lively emotional expression that can be seen in musical experiences with severely disabled children, RTT included.

Music therapy can open channels that make it possible for the RTT population to express mood, express emotions and communicate, as well as developing their ability to learn (Bergström-Isacsson, 2001; Elefant, 2002; Elefant & Wigram, 2005; Montague, 1988; Wesecky, 1986; Wigram, 1991). As mentioned earlier, music seems to be a window opener, not only into their cognitive capacity but also into their ability to communicate and their emotions (Merker & Wallin, 2001).

2.2.5. Receptive music therapy – vibroacoustic therapy

The above-mentioned literature on music therapy is based on active and improvisational music therapy. As this research study includes vibroacoustic therapy (VT), which is a receptive method, combined with music, this form of music therapy will be presented as follows.

Receptive music therapy is an approach when the person is a recipient of the music instead of being a musically active participant. One receptive method that is sometimes used in therapy with people with RTT, is VT (low frequency sound) (Bergström-Isacsson, et al., 2007; Hooper, 2002; Skille, 1991; Wigram, 1996; Wigram & Dileo-Maranto, 1997a). As in any other method, the choice of music is important. Music with a sedative character is generally preferred, but for some individuals it is more important to choose music from a familiar genre (Wigram, 1996).

The first VT prototype was put together in 1980 by a Norwegian music educator and therapist, Olav Skille, using a pair of ordinary loudspeakers, a home-made beanbag, a sound source, and an LP record. His patent claim for the first VT equipment had the following heading:

"Method for transfer of low frequency sound vibrations to the human body via air"

To clarify further, he continued: "Low frequency sound massage from a) music, b) pure sinusoidal tones, c) combination of music and sinusoidal tones" (Skille, 1980).

In his work as an educator amongst disabled children his interest made him investigate whether vibrations could relax children with severe handicaps by reducing the muscle tone, and this was his background knowledge when he first put together the VT prototype. The first time I met him, Skille said to me:

I started to think about how the music that came into the ear and was processed in the brain and then went out into the body, maybe could also work from the outside and into the body and the brain. I tried it and it worked.

(Skille, 1996, personal communication)

VT is used in clinical treatment with a periodic low frequent tone between 20Hz – 70Hz. There are, according to Skille, fundamental principles regarding which frequencies are most suitable in different conditions. Wigram (1996) considers that VT as a music therapeutic intervention is clearly useful in clinical treatment; that it also has an effect on healthy people; and that low frequency sound together with music has a significantly greater effect compared with music alone (Wigram, 1996).

VT has been tested as a therapeutic method amongst people with RTT. Wigram reported details from his work at the Harper House Children's Service, where each RTT client who came to Harper House had a VT session. The session started with the person in supine position on the bed. During the VT the therapist observed if hand-wringing or stereotyped movements decreased, if the person on the bed seemed to relax and if she was able to stretch out her legs. After a while the therapist turned the person over to a prone position. The therapist informed the patient in a reassuring way before every change. Every session was video-recorded and notes were taken. When this clinical study was done there were limited reports supporting the effect, but clear clinical observations could be made (Wigram & Dileo-Maranto, 1997b).

Since 1996, VT has also been used at the Swedish Rett Center. Clinical observations from VT sessions state that VT combined with relaxing music generally makes people with RTT achieve a relaxed status (Bergström-Isacsson, 2001; Bergström-Isacsson, et al., 2007). Other physical responses such as reduced abnormal breathing (for example hyperventilation and bloating), a decrease in stereotyped movements and relaxation in the whole body can be observed in a VT session (Wigram & Dileo-Maranto, 1997b). The VT

sessions in clinical work are video-recorded, notes are taken and the results are then discussed in the transdisciplinary team.

There are other similar methods and equipment (Hooper, 2002) such as: physioacoustic method, somatron system and music vibration table, but these methods have not been presented in this present study (Boyd-Brewer & McCaffrey, 2004; Ruutel, 2002; Ruutel, Ratnik, Tamm, & Zilensk, 2004).

2.2.6. Methods of video-based microanalyses in music therapy

All the literature mentioned is based on observations, either in clinical work or in research in clinical work, and different clinical techniques have been used. Over the last few years a large number of research studies have involved detailed analysis (Wosch & Wigram, 2007). The aim of this current study is to look closely at physiological responses, and carry out a reliable analysis of emotional behaviour. Therefore a brief overview of the focus for microanalyses used in music therapy research is presented here.

Video microanalysis has its history in pedagogical disciplines, psychotherapy, psychology and infant research, where it is part of the basic training to make systematic and detailed observations. The observed action or moment is strongly limited and every minimal change or changes in interaction between individuals, changes in behaviour, changes in facial expressions or changes in the music and dynamics, are scrutinised.

The book “Microanalysis in Music Therapy: Methods, Techniques, and Applications for Clinicians, Researchers, Educators and Students” (Wosch & Wigram, 2007) is a comprehensive guide of several microanalysis methods. Each chapter present a usable technique with the stages or steps required to undertake the analysis, as well as a description of how microanalysis helps us to understand more about what is occurring in the music therapy process. The methods are grounded in the authors’ research and in their clinical work.

Video analysis is used in music therapy to collect data regarding musical behaviour (Schultz, 2007; Schumacher & Calvert, 2007; Wigram, 2007), and also non-musical behaviour such as facial expressions and body language (Kim, Wigram, & Gold, 2009; Plahl, 2007). Video is a strong medium as it is possible to obtain rich information about details, even in very short clips (Ridder, 2007). It is also very useful in recognising small indicators of communication and social interaction in music therapy with all clients, but in particular those with severe communicative limitations (Holck, 2007). When using

video microanalysis it is possible to focus on every small moment and analyse what is functioning and also understand how an intervention succeeds or fails.

2.2.7. *Short summary related to the research questions*

The importance of favourites and preferred music genre amongst the RTT group is investigated in a Swedish and an American study (Houtaling, 2003; Merker, et al., 2001). Both studies confirmed that music appears to be significant for people with RTT, as revealed by their responsiveness to music and the fact that they have musical favourites reported by primary caregivers. Music was used for different reasons.

After reviewing current literature it is clear that since 1996, music therapy has developed further, as a result of the growing knowledge about RTT. Music therapy, music as an activity, and receptive music provide considerable motivational power for people with RTT, regardless of which approach is chosen. Musical intervention seems to be used for different reasons in therapy (not only by music therapists) and also in assessment and treatment situations to improve communication, learning skills, increased hand use, motivation for physical activity, and to increase focus and concentration.

Music therapists and researchers have found that people with RTT certainly can improve their learning skills. As music seems to be such a strong motivator for the RTT population, it is a medium worth using – not only by music therapists. Knowledge about the RTT populations' ability to learn and develop has changed their life situation dramatically over the years. Parents, carers, teachers and therapists nowadays *expect* people with RTT to improve and to continue developing new skills, and *this expectation* in itself is an important factor.

In spite of the fact that music in daily life, in treatment situations and in therapy, makes such a difference for people with RTT, some problems remain. Some songs seem to have a calming effect, while other “calming” songs cause increased breathing patterns and other responses which can be difficult to interpret, e.g. when a person responds to the music with a big smile and at the same time has large eyes with widened pupils, and increased breathing. This might very well be a smile of happiness to begin with, but the happiness then turns into something else, which could be a state of stress and anxiety. Responses of this kind are controlled by the brainstem, and by autonomic control functions which are immature and do not function very well in people with RTT (Julu,

2001). This is an issue that has not been considered in previous music therapy literature, so the next section will focus on the updated knowledge in this field.

2.3. Rett syndrome, the brain and the brainstem

Research in the medical field has indicated that the RTT population generally have an immature brainstem and dysfunctions of the autonomic nervous system. Observations made by parents, carers and clinicians may be related to this neurological dysfunction. The next section will present general information about the brain and the brainstem, followed by specific problems for the RTT population. Specific aspects of the pathology of RTT should be considered in relation to clinical findings and underlying neurological deficits. Therefore a short review of neuroanatomy and physiology (Berthold, 2009) as well as the arousal theory (Hart, 2008; Pfaff, 2006; Stern, 2010) is appropriate at this stage of the thesis.

2.3.1. General information about the brain and the brainstem

The brain, also known as the encephalon, is both part of and controls the central nervous system. It controls body functions such as heartbeat, blood pressure, body temperature, fluid balance, mental functions such as cognition, emotions, memory and learning ability. Electrical activity, consumption of glucose and oxygen are always ongoing in the living brain. The brain includes the two hemispheres with the temporal lobes, the diencephalon, the cerebellum, the midbrain and the brainstem²¹. The diencephalons sit underneath the cerebral hemispheres (Berthold, 2009). This part of the brain performs most of the vegetative functions of the body. The diencephalon includes the thalamus and hypothalamus. The amygdala is part of the limbic system and situated in the temporal lobes. The thalamus is the “relay station” and it receives signals from the viscera and somatic sensory inputs relaying information about temperature, pain and other sensory modalities at both conscious and unconscious levels. It relays these signals to different parts of the cerebral cortex for further processing and eventual perception by the person. The cerebral cortex determines actual responses to signals relayed from the thalamus.

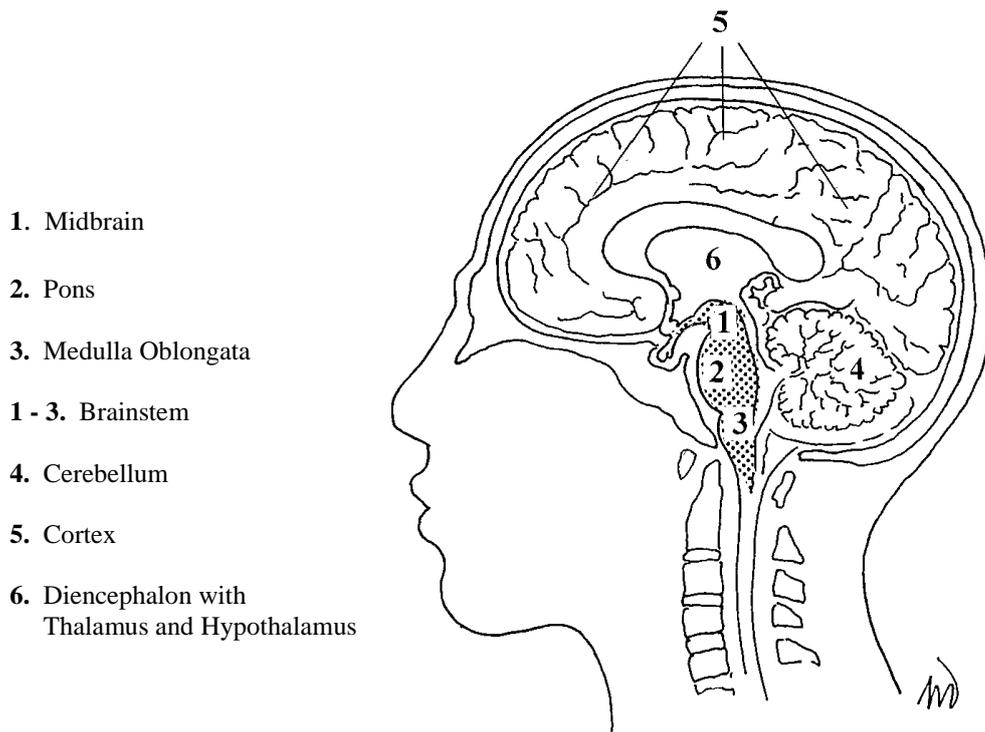
The autonomic nervous system *is part of the motor output* of emotions (Bergström-Isacsson, et al., 2007). It will therefore respond to those signals relayed by the thalamus that affect emotions (Berthold, 2009; Guyenet et al., 1996; Vetenskapsrådet & Forskning.se, 2005). The limbic system consists of most structures in the diencephalons,

²¹ For anatomy see Figure 1.

including the basal cortical structures such as the cingulate gyrus and the lower frontal lobe. It contains all the essential autonomic centres. The limbic system influences the autonomic motor neurones in the brainstem and uses these to *express the visceral aspects* of emotion (Guyenet, et al., 1996).

The autonomic nervous system is made up of the sympathetic and the parasympathetic nervous systems, which are influenced but not fully controlled by consciousness (Julu, 2001). These two sub-divisions of the autonomic nervous system control all the automatic functions of the body.

The brainstem is the lower extension of the brain where it connects to the spinal cord. Neurological functions located in the brainstem include those necessary for survival (breathing, digestion, control of heartbeat, blood pressure) and for arousal (being awake and alert). Most of the twelve cranial nerves emerge from the brainstem. The brainstem is also the pathway for all neurological communication between the brain and the rest of the body.



1. Midbrain
2. Pons
3. Medulla Oblongata
- 1 - 3. Brainstem
4. Cerebellum
5. Cortex
6. Diencephalon with Thalamus and Hypothalamus

Figure 1 The anatomy of the brain and the brainstem

Note 1. Sagittal section of the nervous system showing location of the major structures mentioned in the text. The diencephalon is a part of the forebrain containing the thalamus and the hypothalamus. The amygdala nuclei are located in the temporal lobes and are part of the limbic system. The latter is connected with the autonomic nervous system and expresses visceral aspects of emotions.

Note 2. The picture was created by the Swedish art therapist Åsa-Sara Sernheim.

The brainstem (important for a better understanding of RTT) consists of the *Medulla Oblongata*, which functions as a relay station for the crossing of motor tracts between the spinal cord and the brain (Berthold, 2009). It also contains the respiratory, vasomotor and cardiac centres, as well as many mechanisms for controlling reflex activities such as coughing, gagging, swallowing and vomiting. The *Midbrain* (mesencephalon) serves as the nerve pathway of the cerebral hemispheres and contains auditory and visual reflex centres. The *Pons* is a bridge-like structure, which links different parts of the brain and serves as a relay station from the medulla to the higher cortical structures of the brain; it also contains respiratory neurones (Berthold, 2009).

Emotions are experienced in the grey matter of the brain mediated through networks in the limbic system, including the amygdala, and the brainstem. Since, as mentioned

earlier, the latter controls our heart, blood pressure, heart rate and breathing, these bodily reactions are components that are involved in how we experience our surroundings, including music. In general, bodily reactions are expected to be the same for all humans. What differs is how the brain and the brainstem manage to control the various networks, and this depends on the maturity of the brainstem. A mature brainstem can control heart rate and blood pressure without problems, but an immature brainstem cannot. As mentioned above, the obvious responses to music given by people with RTT are well known among parents, carers and clinicians, but why and how is not yet fully understood.

2.3.2. *The brain, the brainstem and Rett syndrome*

The neocortex is considered to be the centre where all the higher levels of intellectual functions develop after birth (Trevorthen & Burford, 2001). There is evidence to suggest that the formation of the human embryonic neocortex depends on sub-cortical neurones. In the brain of a person with RTT, this seems to work almost normally during the earlier months of pregnancy²². At the end of the first year of life, it is clear that the general development in a person with RTT is slower than normal, as described in 2.1.

Clinical and neurological research over the last 20 years shows that much of the symptomatology in RTT is largely attributable to brainstem dysfunction (Julu, 2001). The brainstem control functions mentioned in 2.3.1., such as breathing, parasympathetic activity, blood pressure regulation, but also the tongue and pharyngeal movements particularly during swallowing, are all dysfunctional in RTT. The brainstem is immature in RTT, sometimes functioning at the same level as that of a baby (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), and may stay immature throughout life (Kerr & Witt Engerström, 2001).

As mentioned earlier, an immature brainstem regulates breathing very poorly. Therefore, most people with RTT suffer from severe breathing abnormalities (Julu et al., 2001; Julu & Witt Engerström, 2005). Three different cardiorespiratory phenotypes are identified. *Feeble breathers* have rapid shallow breathing, shallow breathing and frequent central apnoeas. *Apneustic breathers* have predominant and long breath-holding, regular short breath-holding and protracted inspiration. *Forceful breathers* have predominant hyperventilation, tachypnoea and deep breathing. Valsalva's manoeuvre, which involves raising intra-thoracic pressure using secondary breathing muscles against a closed glottis,

²² It is impossible to distinguish a newborn baby who later has RTT from a baby who develops normally.

is a common complication of breathing abnormalities in RTT. Valsalva's manoeuvre causes changes in blood pressure, blood gases and heart rate (Julu, et al., 2001). Research is going on worldwide, and even if correction of breathing difficulties does not solve all the problems in RTT, it is a step in the right direction.

To be able to identify brainstem responses, including breathing difficulties and for example responses to music, it is necessary to *monitor brainstem functions*. This has been difficult because of the lack of appropriate technological and physiological methods. It is possible to invasively reach the brainstem with electrodes through the nose, but this is too risky, and may not give access to all parts of the brainstem.

Research into physiological responses to music has been carried out, and some general examples will be presented before returning to brainstem assessment in RTT.

2.3.3. *Assessment of brainstem functions*

Over the years researchers have monitored physical responses (not in RTT) to music and musical events in different ways in different areas of scientific work (Bengtsson et al., 2005; Grape, Sandgren, Hansson, Ericson, & Theorell, 2002; Kreutz et al., 2003). With regard to assessment of brainstem functions related to music, various parameters have been used, but breathing rhythm, blood pressure and heart rate are most often utilised. Some other studies have included parameters such as changes in cardiac sensitivity to baroreflex (CSB, see 2.3.4. and 3.6.1.) and physiological arousal in relation to different genres of music, e.g. calming music.

One example is an Italian research team (Bernardi et al., 2001) who reported that rhythmic formulas such as rosary and yoga mantras could synchronise and reinforce inherent cardiovascular rhythms and modify baroreflex sensitivity. The quantity "baroreflex sensitivity" (see section 2.3.4. and 3.6.1.) can be interpreted as how sensitive the heart is to the pressure it generates. They compared the effects of an "Ave Maria" recitation and a mantra recitation on breathing rate and spontaneous oscillations in intervals between electrocardiographic (ECG) R-waves (R-R intervals²³) and on blood pressure and cerebral circulation. They found significant results during both spontaneous and metronome-controlled breathing, and they concluded that rhythm formulas, which

²³ The R-R intervals are the time intervals between two consecutive electrocardiographic R-waves. These are sharp positive waves in the QRS complexes that represent ventricular electrical cycle in the ECG registration. Heart rate increases during inhalation and decreases during exhalation cycles of breathing known as respiratory arrhythmia.

involve breathing at six breaths per minute, induce favourable psychological and physiological effects.

Bernardi, Porta & Sleight (2006) carried out another study of cardiovascular²⁴, cerebrovascular²⁵, and respiratory²⁶ changes induced by different types of music in musicians and non-musicians, including the importance of pauses. The results showed that ventilation (breaths per minute), blood pressure and heart rate increased, and mid-cerebral artery flow velocity and baroreflex decreased with faster tempi and simpler rhythmic structures compared with baseline (mid-cerebral artery blood flow are for assessment of regional cardiovascular control, in this case the cerebral blood flow). No habituation effect was seen. The participants were randomly exposed to the different music styles and a pause. The pause reduced heart rate, blood pressure, and minute ventilation, even below baseline. Musicians had greater respiratory sensitivity to the tempo than non-musicians. Bernardi et al. concluded that music induces an arousal effect, predominantly related to the tempo of the music. Relaxing or slow music can induce a calming effect and the relaxation is particularly evident during a pause. Music may first concentrate attention during a fast rhythm, and then induce relaxation during pauses or slower rhythms (Bernardi, Porta, & Sleight, 2006).

The technique for brainstem assessment and monitored parameters used in this current study has been used once before (Bergström-Isacsson, et al., 2007). The different studies that monitor physical responses have one thing in common: they measure autonomic functions – in other words, brainstem functions. Research involving brainstem assessments and RTT is being conducted in Sweden, Great Britain, the Netherlands, and Italy (Julu et al., 2008; Rohdin et al., 2007; Smeets et al., 2006). These experiments are just a few examples of ongoing research to find medical treatment for breathing difficulties in RTT. Since this is such an important issue for people with RTT, a short example is given in 2.3.5.

2.3.4. The autonomic nervous system in general and in relation to Rett syndrome

The autonomic nervous system is the underlying physiological basis and part of the output of emotion (Best & Taylor, 1966; Guyenet, et al., 1996). It is therefore important to describe the autonomic nervous system, and how some properties can be measured. The autonomic nervous system cannot be steered by will (even though some parts, e.g.

²⁴ The cardiovascular system is the organ system which distributes blood in the body.

²⁵ The cerebrovascular system is a system pertaining to the blood vessels of the brain.

²⁶ The respiratory system includes airways, lungs, and the respiratory muscles.

stress control and controlled breathing, can be influenced by consciousness). It is made up of the sympathetic and the parasympathetic systems, and during the development of research within brainstem assessments it is possible to observe that the sympathetic and parasympathetic systems are not in balance among participants with RTT. This may be due to immaturity of the brainstem (Julu, et al., 2001). This disequilibrium lies behind the considerable concern and anxiety noted by healthcare professionals and carers.

Participants with RTT are easily excitable and experience stress, finding it difficult to relax and calm down, and have difficulties in breathing. The two sub-divisions of the autonomic nervous system influence the most basic functions of the body via the brainstem (Julu, et al., 2001). The sympathetic activity has a very close relationship with changes in the mean arterial blood pressure (Sun & Guyenet, 1986). When the sympathetic system is stimulated we blush, become excited, alert and are ready to fight or flee. The pupils dilate, the small air bubbles in the lungs inflate and the digestive system slows down almost to a standstill, since its blood is re-routed to the brain and muscles to facilitate a reaction to danger. The sympathetic part increases blood pressure and pulse to deal with sudden changes. Therefore, the changes in mean arterial pressure can be used as a non-invasive index of the brainstem's sympathetic activity, and it is possible to monitor mean arterial pressure beat by beat continuously using non-invasive methods. This is highly relevant for this study, since sympathetic activity is one of the measured parameters.

Moreover, it is also possible to monitor cardiac vagal tone (CVT) continuously in real-time by non-invasive methods (Julu, et al., 2001) and CVT represents the brainstem parasympathetic activity. The parasympathetic part functions as a natural brake that prevents the sympathetic part from getting out of control. When the parasympathetic part is in action it slows down the pulse, the pump rate of the heart diminishes, blood pressure sinks, pupil size lessens, and salivation and intestinal movement increases. The parasympathetic nervous system creates rest and calm in situations when the body's reserves are being replenished. Contrary to the sympathetic system, which is always active, the parasympathetic system is active only when it is called for (comparable to the action of applying the brake of a car).

Since it is possible at the Swedish Rett Center to monitor cardiac vagal tone, this means that present advances in medical technology enable the monitoring of both sympathetic

and parasympathetic activities in the brainstem using non-invasive methods simultaneously and continuously in real-time. This new advance in medical technology is used in this current study to monitor brainstem autonomic activity as an index of emotional output in response to music and vibroacoustic stimulation in RTT patients and a group of normally developed children (the non-clinical group). The following measured parameters are used for analysis in this study: cardiac vagal tone (CVT), cardiac sensitivity to baroreflex (CSB), mean arterial blood pressure (MAP), variability of blood pressure (MAP-CV), carbon dioxide partial pressure in the blood (pCO₂) and oxygen partial pressure (pO₂) (see 3.6.1.).

2.3.5. *Measurable autonomic parameters using the NeuroScopeTM*

Blood pressure is a useful and a measurable autonomic parameter. The physiological regulation of blood pressure is managed by three different systems (Appenzeller & Oribe, 1997). The autonomic nervous system controls short-term blood pressure regulation using tonic neural discharges, which means an ever-present sympathetic “motor” and in addition the regulating parasympathetic tones (Appenzeller & Oribe, 1997). The present study focuses only on autonomic regulated blood pressure, particularly mean arterial blood pressure (MAP).

There was no appropriate technique for monitoring brainstem autonomic function in real-time until a neurophysiologist from the UK, Peter Julu, invented the NeuroScopeTM (Medifit Instruments LTD, London, UK). The development of the autonomic monitoring started in 1987, and in 1993 there were investigations of autonomic brainstem functions in neurological patients in Scotland. The NeuroScope makes it possible to observe, on a monitor screen, the intensity of the communication between the heart and the brain in real-time. The use of the NeuroScope to monitor the brainstem’s control of the autonomic nervous system is a welcome development in medical technology. The first article focusing on treatment based on investigations using the NeuroScope was published 2008 (Julu, et al., 2008).

Dr Alison Kerr, an RTT specialist in Scotland, persuaded Dr Julu to start monitoring RTT patients, and this led to an international workshop in 1998 featuring brainstem assessments at the Swedish Rett Center (Julu, et al., 2001). There is now a Swedish database of about 100 RTT patients with brainstem registrations that can be used for research purposes (Bergström-Isacsson, et al., 2007; Julu & Witt Engerström, 2005; Smeets, et al., 2006).

An illustrative example of the positive outcome of a brainstem assessment, using the NeuroScope, and how it could be of benefit to the patient, has been described by Dr Eric Smeets and colleagues (Smeets, et al., 2006). They explained in a case study how the daily life of a girl with RTT in the Netherlands was considerably improved following brainstem examination and recognition of her severe disorder of carbon dioxide metabolism due to over-breathing. Doctors succeeded in finding treatment for sleep disturbances and to prevent the most severe breathing dysrhythmias. This is an illustrative example of the positive outcome of a brainstem assessment and how it could benefit the patient. The various suggestions for treatment are still in the early stages, but all of them are based on experimental knowledge gained mainly from research at the Swedish Rett Center. It is now possible to monitor brainstem function in RTT patients in Sweden, England, the Netherlands and Italy.

Brainstem monitoring using the NeuroScope method has also been carried out on patients with other diagnoses than RTT, such as autism (Ming et al., 2005; Ming, Julu, Wark, Apartopoulos, & Hansen, 2004), diabetic patients for early detection of autonomic neuropathy (Julu, 1993; Julu & Mutamba, 1991; Kenefick, Parker, Slater, & Boswood, 2007), epilepsy (Delamont, Julu, & Jamal, 1999a), general neurology (Julu et al., 2000), sleep studies (Delamont, Julu, & Jamal, 1999b), syncope (Julu, Cooper, Hansen, & Hainsworth, 2003) and veterinary cardiology (Little, Julu, Hansen, & Reid, 2005).

The basic and neurophysiological method of monitoring brainstem autonomic function in people is the same, whether they develop normally or have developmental disabilities, and whether they are children or adults. The assessment takes approximately one hour and is painless and not invasive. In the Methodology chapter the method for brainstem assessment is described in detail.

2.3.6. Brainstem assessment carried out using other techniques and methods

Other techniques and methods have been developed by various inventors. One group uses a device they call a NeuroScope. These methods are not used in this research study but they are mentioned as it is necessary to clearly define the differences. L. Hazan in G. Buzsáki's lab (CMBN, Rutgers Newark, USA) has developed a NeuroScope described as an advanced viewer of electrophysiological and behavioural data with limited editing capabilities (Hazan, Zugaro, & Buzsáki, 2006). Hazan's NeuroScope allows the comparison of analysed data with original recordings. It can display original and

processed local field potentials (EEG), action potentials recorded from single neurons on groups of electrodes (e.g., tetrodes or multisite silicon probes), behavioural events, as well as the position of the animal in the environment. The Hazan method only uses a multi-channel EEG machine to collect the data. Hazan uses a NeuroScope, but it is quite different and not comparable with yet another method called the Medifits NeuroScope method and does not monitor brainstem functions.

The Medical Unit for neonatal care and the unit for physiology and pharmacology at Karolinska Institutet (KI) in Stockholm, Sweden, have developed a method for monitoring some autonomic functions (Rohdin, et al., 2007). This method investigates cardiorespiratory functions, focusing on heart rate and breathing, and is used as an apnoea detector. Heart rate and breathing in the KI method are recorded via a standard three-lead electrocardiograph. Depth and frequency of respiratory movements are measured via changes in electrode impedance. Registration continues day and night for one week in the patient's home environment. The KI method has been applied on some patients with RTT, and the registration demonstrated clear results of existing breathing difficulties and autonomic dysfunctions, but no details on the regulation processes in the brainstem. With this method it is possible to detect changes in heart rate but not why the variations appear. Heart rate may change due to many factors, for example temperature, hormones, blood gases, calcium and potassium values. Again, with breathing, there were no details of why and how changes took place. The method detects changes in breathing patterns (see section 2.3.2) but cannot diagnose what kind of breathing patterns the patient has. Feeble breathing, breath-holding, Valsalva's manoeuvres and apnoea are all detected as apnoea. These respiratory patterns require completely different types of treatments based on clinical experience (Rohdin, et al., 2007). The KI method should be seen as complementary to the type of brainstem assessment performed at the Swedish Rett Center and other locations.

2.3.7. Short summary related to the research questions

The above-mentioned studies have presented some of the brain and brainstem functions, and techniques to carry out brainstem assessment. Brainstem assessments among people with RTT have indicated that the RTT population in general have an immature brainstem and that autonomic nervous system dysfunctions are consequences related to this immaturity.

The studies mentioned in 2.2. have managed to capture how emotions were expressed through songs in music therapy. With the help of brainstem assessment, this present study goes “inside” the participants and measures physiological brainstem responses to their preferred music as well as music which they do not know. In addition the investigation identifies facial expressions related to the music and to measured brainstem responses.

2.4. Rett syndrome and emotions

Since people with RTT cannot express their emotions verbally, emotions and emotional facial expressions communicated by the RTT population are interpreted by other people, in clinical work as well as in their daily life. Recent knowledge about the immature brainstem indicates that some facial expressions might emanate from abnormal brainstem activity and not primarily be due to affects or emotions (Bergström-Isacsson, et al., 2007; Julu, 2001). This abnormal brainstem activity complicates interpretations of facial expressions and emotions in the RTT population. How emotions, as phenomena, are defined may differ depending on the perspective of the discipline, whether it is neurophysiology or psychology, but one thing everyone agrees upon is the importance of emotions!

The previous section has explained the background for the measurement of autonomic functions. Now the next part of the literature review will concentrate on the understanding and assessment of emotional reactions in people with RTT, in accordance with the research questions. As this research study includes observations of facial expressions and interpretations of emotions, it is important to explain that it is possible to differ between expressed emotions elicited by cortical activity and brainstem responses such as an arousal response.

2.4.1. General introduction to arousal and the arousal systems

Arousal is the fundamental force for all bodily and mental activities. It is the force behind almost everything we do.

The most fundamental force in the nervous system is arousalThe primitive arousal responses I discuss comprise the very first, most elementary responses to any sensory stimulus, preparatory for every behavioural response that follows. (Pfaff, 2006, p. 5)

It is impossible to think, feel, perceive, or move voluntarily without support of the arousal system and it acts specifically and rapidly in milliseconds. An arousal response is part of the body's defence system. A condition without arousal (extreme deactivation) goes beyond sleep and into coma (Pfaff, 2006).

According to Pfaff (2006), there are multiple arousal systems and the ascending arousal pathways can be divided into two groups. The first group, the general arousal system, is responsible for sleep and wakefulness. This system arises from the network between the brainstem and higher centres or below as a "reticular activating system", and this is the oldest part from an evolutionary standpoint.

In the second group, specific ascending pathways serve as a force for specific arousal states such as hunger, thirst, fear, aggression and sex. The second group includes five different ascending pathways and they all have different neurotransmitters:

norepinephrine (sensory alertness and emotions), dopamine (motor acts), serotonin (emotional behaviour and control of the autonomic nervous system), acetylcholine (cortical arousal), and histamine (general arousal). All arousal systems are located in the brainstem and also called the reticular activating system (Stern, 2010). The signals flow up from the brainstem to higher cortical centres, and from the cortex and emotion centres down to the arousal systems. They constantly regulate one another but they can act alone, e.g. an internal startle and momentary arousal peak. An arousal response in itself is neither positive nor negative, it is simply a physiological response, and it is the next step in the process that might lead the response further to a positive or negative experience of the arousal (Pfaff, 2006).

2.4.2. The connection between arousal, affects and emotions

The autonomic nervous system is involved in everything we do, and together with the arousal system it is the pathway into our emotions. There is no absolute agreement regarding how to define affects and emotions, and there is an ongoing discussion about definitions in many areas such as psychology, anthropology, pedagogy, sociology and philosophy. These are all disciplines where discussion about emotions has increased, which is why definitions overlap in the literature.

Most researchers agree that we are born with affects such as anger, happiness and sadness, and that they are also connected with our survival (Havnesköld & Mothander, 2002). The brainstem is closely related to affects, and this is something we cannot control by will, whereas emotions are defined as the experience of affect and are connected with

cortical competences (Hart, 2008). The hierarchy of the brain, given a simplified picture, means that higher (cortical) function can only work on the basis of lower (e.g. brainstem) functions, whereas lower functions can work on their own, independently of higher functions (Hart, 2008). Due to the interaction of the limbic system with higher brain areas there are no emotions without thoughts, and many thoughts evoke emotions, whether the thoughts are verbalised or not.

The limbic system, also called the emotional brain (Hart, 2008), plays an important role in how we respond to any stimuli, e.g. a sound. The limbic system evokes different kinds of emotions manifested in behaviour, level of motivation, aggression, sexual activity, mood changes such as sadness, happiness and joy. As previously mentioned, one part of the limbic system called the amygdala is especially important for processing our emotions in various ways. The amygdala is involved in affective behaviours; it is strongly activated by fear, anger, horror, and closely connected with the defence response system. Any frightening sound evokes a defence response in which the amygdala participates, followed by the hypothalamus and the midbrain. Appropriate autonomic responses follow. In the case of fright, sympathetic and parasympathetic responses are similar to what is seen in defence responses with signs of cardiovascular stress. Stereotype responses to stress or pleasure are important for learning because they condition a person's behaviour towards a stimulation that is pleasant and to avoid other stimulations that give unpleasant emotions.

When explaining how signals (relating to sound, vision, touch, smell, and taste) are transmitted through various systems in the brain, it is important to mention arousal and the system that executes it. The experience following an arousal in a person depends on the stimulus, its interpretation and past memory of the stimulus, if any. The responses of the autonomic nervous system (mainly brainstem functions) include variations in heart rate and blood pressure steered by cardiac vagal tone (3.6.1.) and baroreflex sensitivity (3.6.1.). If the higher cortex and the limbic system interpret the stimulus to mean "no danger", then normal function is restored in the brainstem and to heart rate and blood pressure, and indeed the person will return to normal. In RTT this control may fail because of the immaturity of the brain and the brainstem (Berthold, 2009; Vetenskapsrådet & Forskning.se, 2005).

Processing the memory of sounds involves the hippocampus which belongs to the limbic system. The limbic system interacts with other parts of the brain, including the temporal

lobe of the cortex, which is important for memory and learning (2.3.1.). If the experience of a particular sound (for example, a song) is emotionally charged, it is stored in different places in the brain and will be associated with the emotional experience. During the storing process, nerve synapses may change connections and/or strengths of nerve signals. This process is called synaptic plasticity and is important for long-term memory. Synaptic plasticity can create a permanent process to allow us to remember the sound, the experience and the emotion connected with that actual sound. The hippocampus part of the brain makes it possible for us to access the memory the next time we want to recall the sound, or when the same or similar sound is heard.

Because the limbic system interacts with lower parts of the brain there are no emotions without physiological consequences, and many of those changes in the body might also regulate the tone in the emotional system, as some kind of feedback loop (Hart, 2008). As emotions refer to the *experiences* of affects, this is a key part of the process of an individual's interaction with stimuli. Facial, vocal, or gestural behaviour serves as an *indicator* of both affect and emotion. Emotions are present in our bodily consciousness, in memories, in our perception, in our relations with others and also as part of our communicative competence. They construct a meaning, irrespective of disability or normal development. Emotions can create support in the search for how to behave in the world, and in a person's understanding of it, both on a bodily and a verbal level. The above-mentioned literature has expressed how affects and emotions are processed in the brain. As this research study includes interpretations of expressed emotions by analysing facial expressions, a background for interpretations theories will now be presented.

2.4.3. *Affects and emotions observed in facial expressions*

Darwin noticed that non-verbal emotional expressions were similar, irrespective of culture (Darwin, 1872/1965). This inspired him to study facial expressions more closely and he undertook a comprehensive study that showed how emotional expressions have fixed patterns of facial expression. His hypothesis was that this ability is biologically based. He described fear, anger, sadness, discomfort, surprise, happiness and interest, designating them as basic emotions, and asserted that they had an important role for human survival. Some of these emotions, such as fear and discomfort, appear at birth, while others develop during infancy.

Izard (Izard, 1977, 1979) has observed facial expressions amongst infants and found that they are capable of expressing happiness, sadness, disgust and surprise. She also states that it is possible to observe shame and fear or combinations of expressions. Izard argues that emotional development is important for the development of the child's perception and cognition.

Facial expressions have also been thoroughly observed by Ekman & Friesen (Ekman & Friesen, 1972). Their work provided the rationale for developing a fine-grained measurement that was necessary and useful for understanding emotions. After many years of research and by including an American psychologist, Silvan Tomkins, in their research team, they were able to confirm Darwin's hypothesis that emotions such as happiness, anger, disgust and sadness are always expressed by the same facial expressions, irrespective of cultural background.

Ekman, Friesen and Tomkins decided to create a system for measurements of facial activity, and the first attempt was called Facial Affect Scoring Technique (Ekman, Friesen, & Tomkins, 1971). This first attempt was later abandoned, as they realised that they needed to know more about anatomy. After studying the evolution of the nervous system and parallel elaborations of the facial musculature, a new detailed system for measuring facial movements was developed, called Facial Action Coding System (FACS) (Ekman, Friesen, & Hager, 2002).

As FACS was used for analysing facial expressions in this research study, a brief description will follow here, but the method will be presented in detail in the Methodology chapter.

FACS is a comprehensive, anatomically based system for measuring all visually evident facial movements on the basis of 44 unique Action Units (AUs), as well as several categories of head and eye positions and movements (Ekman, et al., 2002). Every AU has a numerical code and a name/descriptor (Appendix 6). It is important to point out that while FACS is anatomically based, there is no one-to-one correspondence between muscle groups and every single AU. Muscles act in different ways and contract in different regions to produce visible actions. One example is the frontalis muscle of the forehead. Contraction of the lateral portion of the frontalis raises the outer brow only (AU2), while contraction of the medial portion raises the inner brow (AU1); in other words, the same muscle but different AUs because of the direction of muscle activity.

FACS has been found useful for measuring facial behaviour in a variety of areas such as psychiatry, psychotherapy, psychophysiology, trial processes, communication and teaching (Ekman & Rosenberg, 2005).

Ekman and Friesen also developed a selective system based on FACS for identifying and scoring expressions of single emotions called EMFACS (EM = emotions). There are differences in how to code when using FACS or EMFACS. A FACS coding requires frame-by-frame and slow-motion viewing, while in the EMFACS everything is observed in real-time. EMFACS coders also describe only those facial events that include AUs or combinations of AUs that are “core” to certain emotions (examples can be found in Figure 20, in the Discussion chapter).

EMFACS is used in this study during the music analyses, as a method to quickly identify facial expressions and then correlate those expressions with findings from the brainstem assessment. FACS is used only during the last minute.

2.4.4. The problems of identifying emotions amongst people with intellectual disabilities

The literature concerning the meaning of emotions or expressed emotions does not include a population of intellectually disabled people. Interpretations described in the literature are mainly made based on a population with a normal development, and then directly transferred to the population of disabled people. According to Adams & Oliver, 2011, a reference I found after I started my study, the expression of emotions by people with intellectual disabilities is a comparatively under-researched area (Adams & Oliver, 2011).

From my own clinical experience I have noticed how parents, carers and therapists often interpret a smile as a yes, a sign of comfort, joy, or as a demonstration of interest in an activity. As previously stated, most people with RTT have either lost or never developed spoken language, but they use their voice in laughing and making sounds (commonly loud sounds) when expressing happiness. Dislikes and discomfort are also expressed in different ways. This could be through screams, tears, a serious face, a frowning face, or a blank face. As they have lost their verbal ability they need to make people understand what they feel or experience in other ways. Facial expressions and vocal sound are two media of emotional communication. Emotions are abstract phenomena which individuals with RTT may find difficult to understand because of their intellectual disability, and difficult to express because of their lack of spoken language. Therefore the people closest

to them always need to observe and act on the person's expressions, but these are generally not easy to interpret due to their dyspraxia and immature brainstem and cortical capacity. Bergström-Isacsson et al. (2007) hypothesise that a person with RTT might not always show a "true" facial expression. It is not a false expression, in the sense of a pretended expression, but more a brainstem "misfired" expression, which naturally might lead to facial movements that can be misunderstood. This misfiring is caused by the abnormal brainstem activity that is found in all monitored individuals with RTT. One reason for misinterpretation might also be that parents, carers and therapists do not know what to really look for.

The Polish/Swedish Psychologist Hautaniemi has published an overview of the philosophical discourse, and from this review developed a doctoral study where she described the meaning of emotions in the life-world of children with intellectual disabilities, not specifically RTT (Hautaniemi 2004). The children were studied by video recordings (no specific method to analyse e.g. facial expressions) in *Händelseriket*, a centre organised to give them different kinds of rich stimulation. In her study she did not find it difficult to distinguish a rich repertoire of emotions amongst these seriously disabled children. She states that they express themselves with their face and with body movements as a complement to facial expressions. Hautaniemi found individual variation in how the participants expressed emotions, in that some children could be stiffer in some parts of their face or body than others, which influenced how they expressed their emotions.

An Israeli research group, Defrin, Lotan and Pick (2006), searched for a way to identify pain during vaccinations among a group of adults with varied levels of cognitive impairment. They compared two methods: FACS and NCCPC-R (Non-Communicating Children's Pain Checklist) for identifying facial expressions of pain. They concluded that both methods were highly reliable tools to measure acute pain, and that NCCPC-R was sensitive to changes in all levels of cognitive impairment, whereas FACS was more sensitive to changes occurring in individuals with mild or moderate cognitive impairment. According to the authors, FACS was less able to differentiate in the PDD population, because the impact of sudden, unanticipated pain (inoculations) in this population caused a "freezing" response which they considered did not fit into the coding system (Defrin, Lotan, & Pick, 2006). However, from personal conversation with FACS specialist Erika

Rosenberg on this subject, it is feasible to add a new code for a specific and consistent response to stimuli in FACS:

If there is an AU on the face that includes comprise “freezing”, for example, then break it down into the constituent AUs. There is no need to create a separate FACS category, unless you want to also label this combination “freezing” and give it a numerical code. If it is something that you cannot describe in the existing AUs, then you should feel free to make up a numerical code for it in your own work.

(Personal conversation with FACS specialist and tutor Erika Rosenberg, Department of Psychology, University of California, March 2011)

As described above, there is no agreement about identifying emotions only by observing facial expressions in groups with intellectual disabilities. Hautaniemi does not find it difficult, whereas others do (Adams & Oliver, 2011; Bergström-Isacsson, et al., 2007; Defrin, et al., 2006). But this might just as well be because their experience is with different groups and in different contexts.

2.4.5. Short summary in relation to the research questions

The above-mentioned literature has presented the arousal system, and the connection between arousal, affects and emotions. Together with vocal sounds, affects and emotions are mainly interpreted by observing facial expressions in people with intellectual disabilities without verbal language, RTT included. As FACS is a comprehensive analytical method, it can be used to carry out detailed analyses.

After reviewing the literature, it is clear that music is commonly used with people with RTT in many different situations, e.g. for stimulating or calming effects. Therefore it is of interest to combine a brainstem assessment and facial analyses with the use of different musical stimuli. Since a definition of “stimulative” or “calming” music is somewhat ambiguous, the last part of this review will concentrate on this subject.

2.5. Rett syndrome, stimulatory music and sedative music

In general it is problematic to define music as either sedative or stimulatory, since the experience of music is linked, among other things, to musical preference. The way in which musical sounds are experienced is also individual and depends on personal memories and experiences connected with the music. This is confirmed in the literature (Berger & Schneck, 2003; Bever, 1988; Juslin & Sloboda, 2001; Juslin & Sloboda, 2010;

Merker & Wallin, 2001; Taylor, 2002), but some parameters in the music, such as rhythm and tempo, can give the music a calming or a stimulatory character. The following section will present what is generally known about how music is processed in the brain, and some important methods for analysing parameters in the music which can define music as having either a sedative or stimulatory character. This section is of importance for this current study as the definitions of “activating” music and “calming” music are commonly used among parents, carers and professionals.

2.5.1. Musical structures processed in the brain

It is difficult to determine how humans interpret musical structures in relation to whether it is stimulating or sedative. Music contains melody, rhythm, harmony, and dynamics. These elements influence our responses, individually or in combination. There are several researchers who agree that our music cultures are something we have to learn and that forthcoming musical sounds are based on earlier information stored in the brain (Ahlbäck, 2004; Berger & Schneck, 2003; Bever, 1988).

Berger & Schneck (2003) go deeper into understanding the brain and brain functions. They bring emotions into the discussion about how we understand music:

Cognition is not the precursor to behaviour. Humans are not thinking machines that feel, but rather feeling machines that think. To believe otherwise is to exhibit a naïve understanding of the most basic of physiologic processes – the instinctive drive for survival that is coded into automatic responses to perceived threats endangering survival.

Understanding ourselves as being, first and foremost, emotional animals forces us to rethink fundamental aspects of physiological function. That realization immediately places into perspective the role of music in physiologic accommodation.

(Berger & Schneck, 2003, p. 689)

Music can be linked to different emotions depending on when the person was first exposed to the specific tune. The same tune might evoke positive emotions among some people and negative emotions among others; and a sudden sound most often evokes surprise, and maybe also fear. Berger & Schneck (2003) describe the brain as the “emotional brain” which becomes a key player in determining how the system will respond to perceived threats. Taylor (2002) describes how the process of auditory

transmission (sensory information) is automatic and involuntary until the sound reaches the cerebral cortex. How it is interpreted, recognised, stored, responded to and later recalled, depends upon the type and level of activity taking place in each person's brain at the time of stimulation. According to Taylor, any single emotional response consists of three components: behavioural, autonomic and hormonal. Taylor mentions the hypothalamus as a very important and sensitive area for musical stimulation. Musical stimuli reaching the hypothalamus can, for example, inhibit or elicit aggressive behaviour (Taylor, 2002).

Research has earlier been carried out in this area and one can find extensive literature on musical structures and emotional expressions (Bonde, 2009; Juslin & Sloboda, 2001; Juslin & Sloboda, 2010). Music theorists and philosophers have discussed the expressive qualities of music since antiquity, and today the same discussion continues also amongst music therapists, psychologists and neurophysiologists.

2.5.2. Parameters important for analyses of sedative and stimulatory music

Over the years a considerable amount of research has been carried out to investigate musical parameters, and how to define music as sedative and relaxing (Bengtsson, et al., 2005; Dileo & Bradt, 2005; Gabrielsson & Lindström, 2001; Hevner, 1937; Hooper, 2010; Schou, 2008). Sedative music has naturally been used in music therapy, and to a high degree also in music medicine (Dileo & Bradt, 2005; Dileo Maranto, 1994; Nilsson, Rawal, Enqvist, & Unosson, 2003; Nilsson, Rawal, Unestahl, Zetterberg, & Unosson, 2001; Nilsson, Rawal, & Unosson, 2003; Schou, 2008). Music medicine is an enormous area and used as a complement, or an adjunct, to traditional medical treatment, but the field of music medicine is an area too big to be covered in this review. When reviewing all this literature it seems that there has been more focus on sedative music than stimulatory music.

In the current study I am not defining music as sedative or stimulatory; I use the concepts of favourite music that activates or calms, music that evokes different kinds of emotions. Before exposing the participants to the brainstem assessment I ask the parents or carers to bring what they believe is calming and activating favourite music. Calming music chosen by me, and music that is expected to cause an arousal (chosen by neuro scientist Björn Merker) is also included. It is therefore important to analyse all the music used in the

study. Different tools for analysis can be found in the literature and those which are of importance for this current study will be presented as follows.

With the work of Hevner (1937) and others as their starting point, the Swedish psychologists Gabrielsson & Lindström (2001) have summarised results from reviewed empirical research that investigated the influence of different factors in musical structure on perceived emotional expressions. Inspired by their work, but also by his own studies in VT (Wigram, 1996), Wigram developed a tool called “Potentials in Stimulatory and Sedative Music” (PSSM) for selecting music for relaxation or stimulation (Wigram, Nygaard Pedersen, & Bonde, 2002). According to Wigram, the following parameters influence whether a piece of music affects stimulation or relaxation: tempo, stability or gradual changes in volume, rhythm, timbre, pitch and harmony, harmonic modulation, texture, melody, repetition, structure and accents. In general, Wigram stresses that predictable musical parameters create relaxation, whereas unpredictability and sudden changes creates a higher level of arousal and stimulation.

Inspired by the work of Wigram, amongst others, music therapist, Professor Denise Grocke developed a comprehensive tool for analysing music, “A Structural Model for Music Analysis” (SMMA), during her doctoral study (Grocke, 1999). This tool consists of twelve categories of musical elements and furthermore three categories containing states of mood, symbolic and associative meaning and performance. This tool has been developed to analyse GIM (Guided Imagery and Music), music that is predominantly classical and orchestral, and often has a very complex musical structure.

Based on the work of Gabrielsson & Lindström (2001), Wigram (2002), and Grocke (1999), music therapist Jeff Hooper PhD has defined properties of sedative music, Record of Predictable Musical Factors (RPMF) and Predictable Factors in Sedative Music (PSFM) (Hooper, 2003, 2010). PSFM was mainly developed to provide a systematic way of defining elements in the music so that it could be classified as sedative.

PSFM identifies six musical factors: form, tempo, volume, texture, melody and harmony. As part of PSFM, every factor has a description of predictability; e.g. tempo predictability is described as: “Remaining stable with gradual increases (accelerandos) or decreases (ritardandos)” (Hooper, 2010, p. 123)²⁷.

²⁷ I have followed Hooper through his doctoral research, as we have been enrolled on the Aalborg PhD programme at the same time. My analysis tool has been influenced by his work, even though he did not defend his thesis until 2010.

This current study includes music chosen by parents and carers, and their choices are mainly children's music and pop music. The analysis methods described above are multifaceted and detailed but miss some elements when it comes to analysing pop-, rock- and children's music. The music teachers and sound technicians Aare, Grønager & Rønnefelt (2003) present some models of analysis which approach the music from different angles, such as *time and room*, *hook*, *break* and *gimmick*, which are all relevant parameters for the music used in this present study.

Aare et al. (2003) define the term *time and room* in music as something taking place here and now; they also include *development* from which tension and relaxation, conflict and reconciliation arise. If the music does not lead to development they talk about an *infinite now*, which instead of development can fill the room and create or mediate a condition. In rock and pop music, phenomena such as *hook*, *break* and *gimmick* are important details. *Hook* is exactly what the word says, a hook: something that the listener immediately notices and remembers. The writers explain the hook as "the face of the music" (ibid p.23). A common understanding is that a hook could be something really obvious in the music or a lyric phrase, but a hook might also be characteristic chords, a special sound or groove that makes it impossible to keep still. Examples of hooks are: "She loves you, yeah, yeah, yeah" with the Beatles and the guitar riff/motive in Deep Purple's "Smoke on the water". A *gimmick* is in a way the opposite of a hook. It is something you might not notice the first time you listen to the music. The gimmick, which is noticed after the hook, is something that is special about the piece of music, something that stands out but is not as obvious as a hook. A gimmick can give the music a new dimension. In "She loves you" with the Beatles you can hear them singing the chorus in high falsetto voices, which could be looked upon as a gimmick, as well as the drum triplets in the chorus. A *break* is more connected with the groove than with the concepts of hook and gimmick. A break stops or affects the groove over one or two bars with a pause or a rhythmical break where everyone plays in unison, or a break which is filled with a soloist. A break can be interesting in itself but it also has the function of focusing on the groove it is interrupting. In "She loves you" with the Beatles there is a break in the last chorus: "with a love like that". The break comes again at the end of the song.

All the above-mentioned methods have been fundamental for the development of the method used in this study. As mentioned earlier, the character of the music, brought by

parents and carers, mainly fitted into the genres of pop and rock and children's music (Appendix 9), so inspired by Hooper and Grocke, but mainly by Aare, Grønager, & Rønnefelt, the Tool for Music Analysis (TMA) was developed for this study by me and musicologist Erik Christensen (Appendix 10 and 4.8.). Music analysis was not included in the main research questions, and therefore a brief but still informative analytical method was needed. TMA includes parameters such as:

1. Surface, Energy and Mood (volume, tempo, pulse, timing, sound)
2. Presence and Attention (effects, voice, time/space)
3. Coherence and Memory (melody, harmony, structure/form)

This is not a very detailed tool, but it is sufficiently structured to be able to identify different characteristics in the music. (For further information see Appendix 10 and 4.8.)

2.6. Formulated hypotheses

The previous sections of this chapter have presented what is currently known about RTT and the related major difficulties. One aspect of this knowledge is the importance of favourites and preferred music among this group of people. Music therapy, music as activity, and receptive music provide considerable motivational power for people with RTT, regardless of which approach is chosen.

The RTT population suffer from major communication dysfunction and are therefore dependent on the ability of caregivers to interpret their communicative and emotional signals. As seen in 2.3. and 2.4., people with RTT generally have an immature brainstem which, among other things, can generate abnormal facial activity. This abnormal facial activity can make it difficult for the parents and carers to interpret facial expressions, which can create tremendous problems of misinterpretations. In spite of the fact that music in daily life, in treatment situations, and in therapy makes such a difference for people with RTT, there are still some issues to be investigated. Some pieces of music seem to have a calming effect, while others with a supposed "calming" character cause increased breathing patterns and other responses, indicating that the music does not have the expected effect.

As a consequence of the immature brainstem in the RTT population the autonomic nervous system is dysfunctional, which has an influence on emotional reactions. Emotional responses elicited by the music might therefore differ from abnormal

spontaneous brainstem activation (ASBA), but it might also be possible that music elicits ASBAs. It is therefore essential to combine findings from brainstem assessment with identification of facial expressions and musical structures in order to try to differentiate the expressions. Little basic research has been carried out with this population, and no in-depth investigation of beneficial intervention, e.g. music, has been conducted. This lack of knowledge means that there is a need to examine physiological response, and determine which stimuli cause what responses.

The following three basic clinical questions lead to the six hypotheses for the current study.

Questions:

1. What effects do different musical stimuli have on autonomic functions and cortical emotional reactions in participants with RTT?
2. What effects do different musical stimuli have on autonomic functions and cortical emotional reactions in non-clinical participants, children between 1 and 5 years old with a normally developed brainstem?
3. Is it possible to observe any differences between the two groups?

The hypotheses of this current study have been formulated on the basis that cortical emotional output would influence brainstem autonomic activity in three different ways (Bergström-Isacsson, et al., 2007):

First: Emotional excitement increases brainstem sympathetic activity above the resting baseline level, manifested in physiological responses such as changes in blood pressure and heart rate.

Second: A relaxing or calming emotional response increases brainstem parasympathetic activity above the resting baseline level, also manifested in physiological responses such as changes in blood pressure and heart rate.

Third: An arousal response without evoking a relaxed or an excited state only causes physiological arousal that is measurable in brainstem autonomic activity. The definition of brainstem activity will be described in detail in Table 2, section 3.6.2.

Hypotheses:

The following six hypotheses are formulated to investigate responses within subjects when a participant is monitored with the most consistent baseline measure concerning normal breathing, blood gases within normal range, waking state and without epileptic

activity, and to compare responses between RTT and non-clinical participants, children between 1 and 5 years old.

1. *A piece of unknown music, specially chosen for this purpose*, causes only an arousal (a physiological arousal response) without a sympathetic or parasympathetic increase.
2. *Activating music* chosen by parents or carers causes a sympathetic response (an activating response).
3. *Calming music* chosen by parents and carers causes a parasympathetic response (a relaxing response).
4. *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 music that is played in the combination of VT and music, but now played on its own (Mu)* causes a parasympathetic (a relaxing response).

CHAPTER THREE

3. Method

The aim of this study was to investigate autonomic activity and emotional behaviour in response to music and vibroacoustic therapy in RTT patients referred to the Swedish National Rett Centre over a period of two years (2006-2007). An identical analysis was made of a non-clinical participant group of eleven children ranging in age from 1 to 5 years with a normal developmental pattern. The aim was also to investigate if preliminary observations from an earlier study (Bergström-Isacsson, et al., 2007) were reproducible in another group of the Rett population. A quantitative approach and a within-subject study was the most suitable technique regarding the kind of measurable data collected (baseline and six independent variables) and a laboratory-like situation (Prickett, 2005).

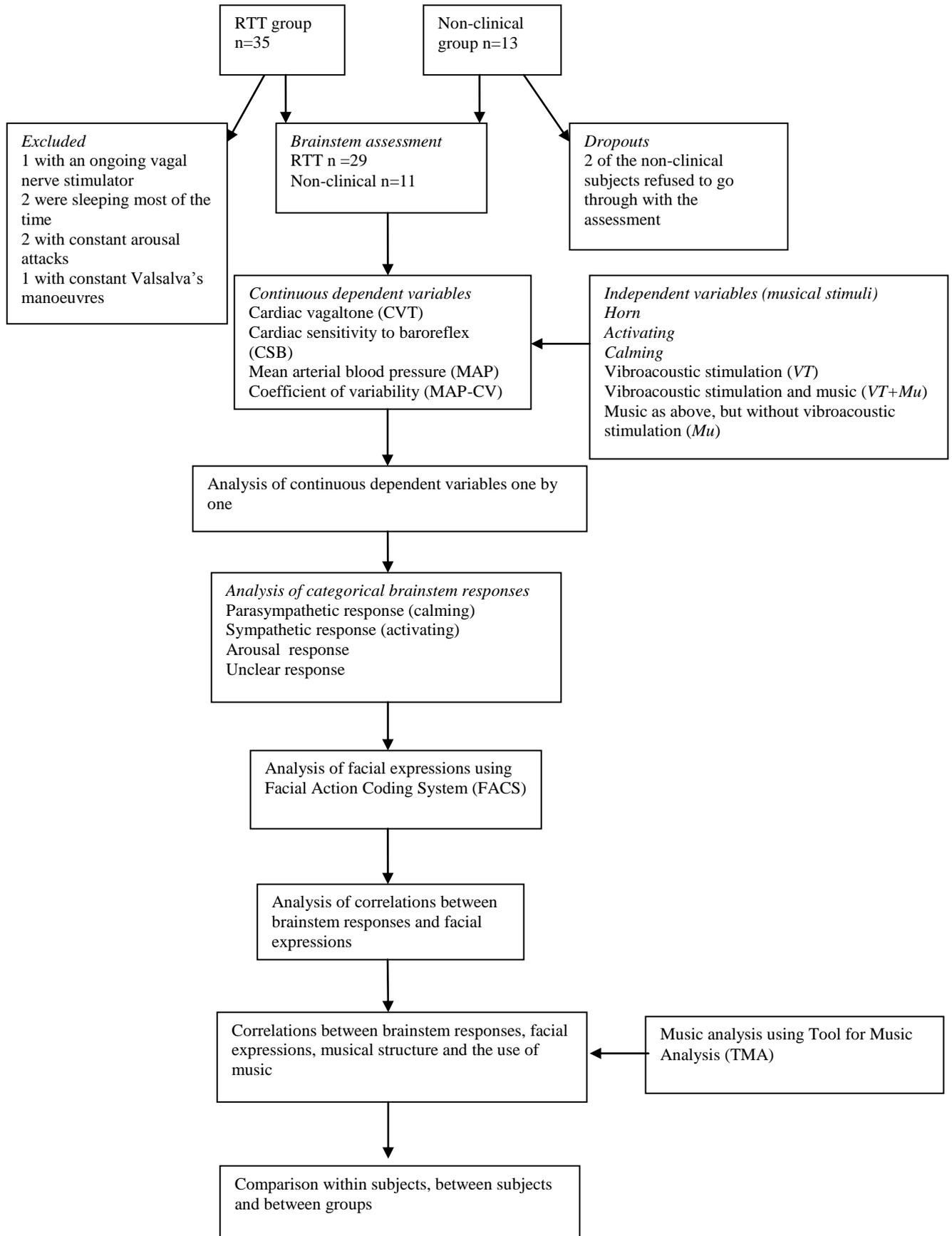
3.1. Design

This experimental study was designed as both a between-groups and a within-subject study (also called a repeated measures design). Figure 2 provides an overview and a visual understanding of the study procedure. Participants in the RTT group were compared with participants in the non-clinical group, and the baseline scores for each participant in both groups were compared with the scores for the six stimuli used in the study. There was an element of randomisation in the study as the six musical stimuli the participants received were randomly ordered. Allocation concealment was achieved as one member of the team, not involved in the study, used a random generator (Excel) and gave the order of the stimuli for each person before every test situation. People in general inevitably differ (from one another), and in a population of people with disabilities participants can differ a great deal. In a between-groups design these differences among participants are uncontrolled and are treated as an error. In within-subject designs, the same participants are tested in each condition. Therefore, differences among participants can be measured and separated from errors in this type of design.

In this repeated measures experiment, stimulus was a *within-subject factor* because different measurements on the same participant occurred at different times. The repeated measures design was used to increase the sensitivity of the test, since participants served as their own controls, and thus across-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 normal participants was recruited to establish differences and similarities in responses, where they occurred, between a non-clinical and clinical population.

Figure 2 An overview of the Rett Center study procedure



3.2. Power calculation

Test power was difficult to specify for this study due to lack of similar research on which effect size estimates could be based, and also because of the within-subject design of the study. In the absence of any usable previous research, I assumed a medium effect size ($f = 0.25$, corresponding to $d = 0.50$). I assumed further that the baseline measurement would explain 36% of the variance ($R^2 = 0.36$, corresponding to $r = 0.6$). Alpha level for testing was set to 0.05. I aimed to identify the sample size that would lead to 80% power. In a parallel (between-subjects) design, 35 cases would be needed in each stimulus to achieve 80% power (using ANCOVA with one covariate in the programme Power and Precision, using the numbers specified above). If a large effect ($f = 0.40$) was assumed, 15 participants for each stimulus would be sufficient to achieve the same test power of 80%. It was not possible to calculate test power directly for this within-subject study. The target number of 35, where each participant received each stimulus, was used for the RTT sample. I was able to recruit 35 participants to the experimental group, of whom 29 remained as participants when exclusion criteria had been applied (Figure 2). The target number for the non-clinical group was 10; no power calculation was attempted for this comparison. In this study, 13 were recruited to the non-clinical group, 11 of whom became participants (Figure 2).

3.3. Ethical approval and patient register procedure

An application and details of the study were sent to the regional ethics committee at Umeå University, Sweden for approval. The application was accepted after some clarification about the power calculation had been provided and some of the information sent to the participants had been reformulated. I also needed to gain approval from the county council to keep a register of patient information; this was given when the application had been approved by the ethics committee. As described earlier, the parents received information about this study in a document sent out by the Rett Center's social worker (Appendix 1). This document clearly stated that participation in the study was voluntary, and that the musical stimuli used would not affect the medical assessment. The participants' parents or guardians were also asked to sign a form of consent (Appendix 2).

3.4. Participants

3.4.1. Recruitment of participants with Rett syndrome: excluded participants

All patients with RTT referred to the Rett Center within the selected period (January 2006 – December 2007) were potential participants for the study. A total of 35 participants, 33 females and 2 males, were examined for possible inclusion in the study. Of these, 6 were excluded due to the exclusion criteria (see Figure 2): 1 had ongoing vagal nerve stimulators (VNS), 2 were sleeping most of the time, 2 had constant arousal attacks and 1 had constant Valsalva's manoeuvres. Relevant results could not be obtained from participants with VNS, because of the electrical impulses that affected the heart, and therefore also the brainstem control function. The reason for excluding those who were sleeping most of the time, and those who had constant arousal attacks and Valsalva's manoeuvres was that the data were too unreliable, as well as difficulties in establishing a reliable baseline, and potential floor or ceiling effects.

3.4.2. Included participants with Rett syndrome

The remaining 29 participants with RTT were included in the study. The parents or the guardians were supplied with information about the research project before they came to the Rett Center (Appendix 1). They then consented to the participation of the person they were responsible for by signing an approval (Appendix 2). Parents and guardians were fully informed about their right to withdraw from the study at any time, and that this decision would not affect the medical assessment they came for. The participants (27 female, 2 male; see Table 1) were aged between 6 and 40 years and came from seven different European countries (Sweden, Norway, Finland, Denmark, the Netherlands, Greece and Poland). The mean age was 16.58 years with standard deviation 9.57. Eleven of the participants had Valsalva's manoeuvres as a complication of breathing (Table 1, section 3.4.3.). All RTT participants had abnormal breathing and were classified into breathing phenotypes (Table 1): forceful breathers, feeble breathers and apneustic breathers (see section 2.3.2.). These classifications were made by Julu (Julu & Witt Engerström, 2005) and they represent the different cardiorespiratory phenotypes. RTT in its classical form was found in a majority of the participants (Table 1). In order to take part in the study a person, female or male, had to have been diagnosed with RTT before referral to the Rett Center and the brainstem examination. It was not necessary for a genetic test to have been carried out, as RTT is still considered a clinical diagnosis. Of the

participants in the study, 16 had undergone a genetic test before coming to the Rett Center and 13 were not tested. At the time of data collection the Rett Center did not carry out any blood tests, but as from 2009 all patients are offered genetic tests.

3.4.3. Non-clinical comparison group

The participants in the non-clinical group were recruited via child-welfare centres in the municipality of Östersund. The nurses were asked to give the first document (Appendix 4) to all parents; if the parents then came back and asked questions about the project they were to be given the second document (Appendix 5), informing them how to contact me for further information. Before their children were assessed the parents had to indicate their consent by signing an approval, the same as the one signed by the RTT parents. Of 13 children invited to the non-clinical group, 11 participated in the study, and 2 refused to participate. The children were between 1 and 5 years old, the mean age was 3.36 and the standard deviation 1.96 (Table 1). The non-clinical group, 6 girls and 5 boys, had had a normal birth and a normal physical and cognitive development, reaching normal milestones as expected.

Table 1 Characteristics of participants

Variable	RTT (n = 29)	Non-clinical (n = 11)
No. female	27 of 29 (93%)	6 of 11 (54%)
Age: Mean (SD)	16.58 (9.57)	3.36 (1.96)
Diagnosis	23 classical RTT (79%) 1 congenital (3%) 3 variants (10%) 2 male variants (7%)	None
Mutation	2 R133C (7%) 2 11.56DEL44 (7%) 2 R106W (7%) 1 R168X (3%) 1 R294X (3%) 1 P302A (3%) 1 R294X (3%) 1 PR255X (3%) 2 unknown mutations (7%) 3 no mutations (10%) 13 not tested (45%)	None
Breathing phenotype	13 forceful breathers (45%) 10 feeble breathers (34%) 6 apneustic breathers (20%)	None
Valsalva's manoeuvre	11 (38%)	None

3.5. Independent variables (stimuli)

The study data were collected during approximately one hour when the person was exposed to registration of basic functions: the brainstem's control function of the autonomic nervous system. The control situation was the person's own baseline which was measured when the person was resting, breathing normally, awake, and with no epileptic activity registered on the EEG. As regards neuronal maturity, the group studied was homogeneous (Armstrong & Kinney, 2001).

The stimuli used are described in terms such as activating, calming or favourite music, based on the participants' previous and known behaviour in connection with their favourite tunes, as described by the author, parents and carers. A total of six stimuli were applied consecutively to each participant in this study. The sequence in which the musical stimuli were presented was randomised to prevent order effects (the possibility that the effect of the stimuli could be confounded with the effect of the sequence in which they are played). To ensure allocation concealment, a member of the team who was not involved in the study used an Excel spreadsheet to generate a random sequence before each participant began their trial, and gave instructions regarding the order of musical stimuli. After the presentation of each stimulus, the participants were taken back to baseline, or as close to baseline as possible, through a wash-out period. The time for that period differed between participants and depended on how long it took for each participant to show values similar to baseline.

Parents and carers were asked to bring one piece of music they interpreted as activating, a piece of music that made the person happy and ameliorated anxiety or a tantrum. They were also asked to bring a piece of music they believed had a calming effect, not necessarily relaxing, but something the participant really listened to and music that created a moment of concentration, something that "touched" them and had an emotional effect. The choice of the participant's music is often a matter of interpretation, which is not always easy. The parental choices will be reported and analysed in the Results chapter (4.8.) and a list of all music used can be found in Appendix 9.

3.5.1. Stimulus one: *Horn music (Horn)*

Horn music was played to the participant during the brainstem measurement. The initial concept of basic music stimulation was that *Horn* should evoke physiological arousal. The aim was that the music should be: short, simple and distinct (without being childish), memorable and in some way "striking", if possible a musical theme with a conclusion, music with a clearly defined start, part of the participant's cultural sphere (something not culturally exotic) and preferably not known by the participants.

Calle Hernmarck's tune (Figure 3) met many of the above requirements. The foremost criterion was that the tune should provide an entire musical theme with a signal-like start and a well-defined melody, over a short span of time. It would seem most improbable that any of the participants had listened to the tune before, since circulation has been very

limited. The tune is very local; it is not a commonly known piece of music and it could confidently be assumed that the participants would not have heard it before. The music (“Vid Svarttjärn” on the CD *Ekon från Vallskogen*, Calle Hernmarck & Sten Andersson, Twin Music TMCD-19) is a piece of goat-horn music composed by Calle Hernmark.

A horn call embedded in music might be one appropriate stimulus for humans. For example, in fox-hunting the horn is used to call hunters, and in military operations in former times a horn or bugle was used for calling the soldiers. One of the oldest pictures of a man blowing in the horn of an animal is a motive from the Bayeux tapestry, a Norman tapestry from the late 11th century, illustrating the disembarkation of William the Bastard (otherwise known as William the Conqueror) in England. One of the oldest horns found in Sweden could be from around 500 BC (anecdotal from Calle Hernmarck).

Vid Svarttjärn

Calle Hernmarck

Horn

4

7

10

13

Figure 3 The score of the horn music

Note. Printed by kind permission of Calle Hernmarck

3.5.2. *Stimulus two: Activating music (Activating)*

This was music chosen by the parents or carers, and hypothesis 2 anticipated a sympathetic response. Earlier research shows that generally this music has an up-tempo beat; the lyrics and refrain are catchy and clear, and there are repeats and clear rhythms (Merker, et al., 2001). This kind of music can provide responses such as smiling, body movement, increased breathing rate, rising of body and increased contact.

3.5.3. *Stimulus three: Calming music (Calming)*

This was also music chosen by the parents or carers, and hypothesis 3 anticipated a parasympathetic response. This music usually has a low beat with a general perception of physical nearness, climbing towards a refrain (expectancy); it also has soft lyrics and a supportive basic rhythm (see section 4.8.). This kind of music can provide responses such as calmness, concentration and lack of movement.

3.5.4. *Stimulus four: Vibroacoustic stimulation (VT)*

Here the participant was exposed to vibration only. The frequency 40Hz was chosen from earlier studies and experience, showing that frequencies under 60Hz are most effective for people with RTT (Skille, 1991; Wigram & Dileo-Maranto, 1997a). The vibrations come from a CD record created by Olav Skille, Norway. The chosen frequency has a sinus curve with a duration of 5 seconds and a peak of 89dB at the point where the person sits. Hypothesis 4 anticipated a parasympathetic response

3.5.5. *Stimulus five: Vibroacoustic stimulation combined with calm music (VT+Mu)*

A further stimulus consisted of being exposed to the same vibration, 40Hz, but in combination with calming (relaxing) music. The basic criteria for the music were that it should be: calm, structured, non-vocal, a distinct melody and part of the participant's cultural sphere²⁸.

I found that Jens Andreasson and Bengt Wittje (INDIGO) had composed two pieces that met these requirements. These two pieces, track 4 "Dawn" and track 5 "Timeless" on the CD *Keeper of time*²⁹, could be played directly after each other, combined with VT.

This is one way of examining whether VT embedded in music increases the parasympathetic response more than VT alone. It also provides information about brainstem competence, thus giving an indication for further treatment with one stimulus at a time, or both together.

²⁸ While these criteria were developed for VT, there is no real evidence that vocal music should be excluded, and it has been used quite successfully by me, and many others.

²⁹ Theta, JBCD 044

3.5.6. *Stimulus six: Calm music without VT (Mu)*

The last of the six stimuli consisted of exposing the participant to the music from the CD *Keeper of time* alone. Hypothesis 6 anticipated a parasympathetic response. This music was the same as that described above, in *VT+Mu*, and the reason for using only the music was to clarify whether any response to *VT+Mu* depended on the music alone or the combination with *VT*.

Explanations and definitions for calming (sedative) music can be found in the literature review (section 2.5.3.).

3.6. **Dependent variables and monitoring equipment**

3.6.1. *Continuous physiological variables*

This study was specifically designed for collecting physiological data during a brainstem assessment, which basically entails monitoring pulse and heart rate, respiration movements and cardiac function, i.e. the brainstem's regulation of three parts of the autonomic nervous system. The method used is painless and non-invasive. The computerised integrated monitoring equipment, the NeuroScope quantifies the extent of communication that exists between the brainstem and the heart, and the following parameters were measured simultaneously and in real-time.

1. *Cardiac vagal tone (CVT)* (measured in units of the Linear Vagal Scale, LVS³⁰). Cardiac parasympathetic neurons or cardiovagal motor neurons, the only parasympathetic input to the heart, mediated by the vagal nerve, generate the cardiac vagal tone, which gives information about how strong the cardioinhibitory reaction is. It originates from the caudal part of nucleus ambiguus in the brainstem and slows down the heart rate – a process described as cardioinhibition. CVT is maintained through reflexes, just like other parasympathetic activity in the body. It can be defined as the pulse-synchronised prolongation of the diastolic period.
2. *Cardiac sensitivity to baroreflex (CSB)* (ms/mmHg). CSB is also a parasympathetic response, giving information about how sensitive the heart is to the blood pressure, and can be defined as the increase of pulse intervals in milliseconds per unit change in systolic blood pressure.

³⁰ Cardiac vagal tone (CVT) is measured in arbitrary but clinically validated atropine-derived units of a Linear Vagal Scale, LVS. In this scale zero represents complete clinical atropineization, and 10 units is the average young adult level.

3. *Systolic blood pressure (SBP)* (mmHg). SBP represents the peak blood pressure that opens the aortic valves to let out blood into the aorta during systole. This is the maximum blood pressure during a cardiac cycle.
4. *Diastolic blood pressure (DBP)* (mmHg). DBP represents the blood pressure during diastole just before the heart reopens the aortic valves after closing them at the end of systole. This is the minimum blood pressure during a cardiac cycle.
5. *Mean arterial blood pressure (MAP)* (mmHg). MAP is used as an indicator of the activity of the sympathetic nervous system. This is the mean or average arterial blood pressure.
6. *Heart rate (HR=beats/min)*, also called the pulse rate or the “speed” of the heartbeat.
7. *Electroencephalogram (EEG)*. The electrical activity of the cortex is monitored and measured, to obtain information about the maturity of the brain, depending on patterns and frequencies, and possible pathological epileptogenic activities.
8. *Electrocardiogram (ECG)*. The ECG demonstrates the heart’s electrical activity and possible cardiac origins of arrhythmia.
9. *Carbon dioxide (pCO_2) and oxygen (pO_2)*. The partial pressures of blood gases in mmHg are measured transcutaneously. They represent tissue oxygenation and are more useful in this type of experiment than oxyhaemoglobin saturation, which represents use of the oxygen carriage capacity of the blood.

The NeuroScope from MediFit Instruments Ltd, London, UK was used to record the beat-to-beat heart rate from ECG R-R intervals (see section 2.3.5.).

Systolic and diastolic blood pressure were also recorded beat to beat by using the Portapres model 2 (FMS Finapres Medical System BV, Netherlands).

A photoplethysmographic finger cuff is used to obtain a continuous digital arterial blood pressure in the Portapres. The Portapres sends the signals to a computer that calculates the recorded signals into beat-to-beat blood pressure: systolic, diastolic and mean blood pressure.

As described in section 2.3.5., the sympathetic activity is very closely related to mean arterial blood pressure (Sun & Guyenet, 1986), and this activity can be monitored from the calculation of mean arterial blood pressure (SD divided by mean value = MAP-CV,

Coefficient of Variation measured in percentage). With the help of this technique, the sympathetic stimulation to the heart could be deduced from the heart rate in conjunction with cardiac vagal tone (CVT) that was measured independently. During the registration, pre-jelled electrodes on the participant's chest registered ECG (Figure 4). Cardiac vagal tone was monitored continuously in real-time from ECG signals, using a modification of principles described by Julu (Julu, 1992) and now implemented in the NeuroScope. CVT (LVS units) represents parasympathetic activity in the brainstem. Cardiac sensitivity to baroreflex (CSB) also represents parasympathetic activity in the brainstem, defined as the change in pulse intervals in milliseconds per unit change in systolic blood pressure (ms/mmHg). The method for measuring CSB is based on an observation by Eckberg (Eckberg, 1976), and CSB is now registered by the NeuroScope. CVT and CSB are integrated into a computer using a Medulla Lab (MediFit Instruments, London, UK), which is part of the NeuroScope system. The computer calculates everything in real-time (Julu, et al., 2001).

Breathing was registered with a piezoelectric plethysmographic belt round the lower part of the rib cage. All breathing movements were also integrated in the computer, together with pressure of oxygen and carbon dioxide levels registered transcutaneously by using electrodes fastened immediately above the liver and connected to a technical unit, TINA, TCM3 made by Radiometer, Denmark. The equipment for breathing movements, arterial blood pressure, and the transcutaneous measures of oxygen and carbon dioxide, were all connected to the computer via the Medulla Lab (MediFit Instruments, London, UK). The computer calculated all data and made it possible to study the details beat by beat.

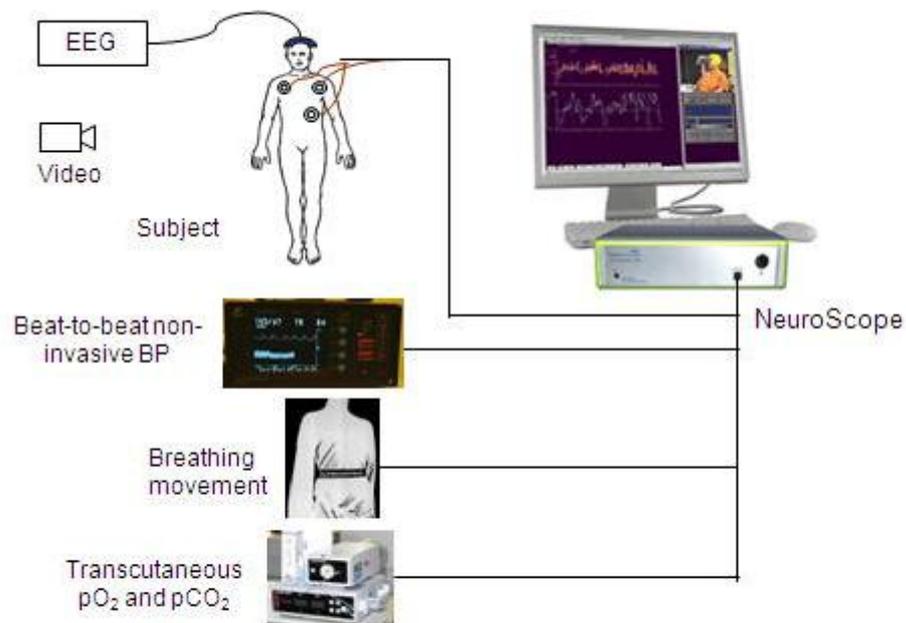


Figure 4 Technical equipment used for brainstem assessment, and how wires and electrodes are connected to the participant

Note. The figure is printed with the permission of Peter Julu.



Figure 5 A young woman connected to the technical equipment used for brainstem assessment

Note. An electro cap measures EEG and a photoplethysmographic finger cuff is used to obtain a continuous digital arterial blood pressure in the Portapres. The photo is printed by kind permission of the young woman and the photographer Stig Hansen.

Breathing movements and breathing patterns were not analysed in detail in this study but the different RTT phenotypes categorised from breathing patterns are partly discussed in the results. An electroencephalogram (EEG) (see section 3.6.1.) was also produced using an electro cap (ECI) with built-in electrodes, which is worn like a swimming cap (Figure 5). The EEG machine used was a paperless Nervus, Magnus 32/8 polygraphic channels (Figure 6) made by Cephalon, Denmark.



Figure 6 The screen on the EEG machine

Note. The photo is printed with the permission of the photographer Stig Hansen.

All data were registered in a computer and could be seen as graphs on the screen, which gave the opportunity to discuss the developments minute by minute during the registration. The whole process was time-synchronised with two digital video cameras and filmed, 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 registration. The video from the EEG camera and the EEG machine were also used for coding facial expressions. During registration the participant sat on a beanbag named "Musik-Molly" from the Swedish firm "Kom i Kapp" with built-in loudspeakers (Figure 7). 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 and an amplifier (YAMAHA Natural Sound Compact Disc Player CDC-585 and YAMAHA Natural Sound Stereo Amplifier AX-396) were connected to the "Musik-Molly", which produced the vibrations. An additional CD player (SONY CD Walkman, G-protection) was connected to external loudspeakers (Wharfedale Diamond 7.1 No. DA001008) to provide the music played during *VT+Mu*, as well as the music selected by parents or carers.



Figure 7 Technical equipment used for brainstem assessment, including the beanbag used for vibroacoustic stimulation

Note. The photo is printed with the permission of the photographer Stig Hansen.

3.6.2. *Categorical brainstem responses*

Continuous and categorical brainstem responses are closely linked together. The detailed measuring of all continuous variables separately was crucial for later identifying the different categorical brainstem responses. The categorical brainstem responses included in the hypotheses were the ones describing the expected responses to the six different stimuli. *Physiological arousal* could be explained as the first response: alertness. A *parasympathetic response* is described as a calming response, and a *sympathetic response* as an activating response. An unclear response is explained as an increase or a decrease in all continuous variables. The technique used for monitoring brainstem responses in RTT has been applied at the Swedish Rett Center since 1998. The NeuroScope, invented by Julu (see section 2.3.5.) was market-prototyped in 1994 and patented by the University of Glasgow in 1999. The instruments are very precise and the method reveals the exact result for the same participant under the same conditions.

Table 2 illustrates the definitions used in the study hypotheses, guided by the physiological definitions of arousal as part of the defence response (see section 2.4.1.). Increased *parasympathetic activity* in the brainstem is similar to what happens in drowsiness, or the desire to go to sleep, and indicates a calming response (Delamont, Julu, & Jamal, 1998). On the other hand, increased *sympathetic activity* in the brainstem, as in

the preparation for a physical exercise (Jordan, 1991), requires increased arterial blood pressure facilitated by the reduction of parasympathetic activity. The relevant indicators for both alternatives are shown in Table 1. The initial phase required for increasing arterial blood pressure is a reduction of CSB, which is the negative feedback control of arterial blood pressure. Therefore, CSB is the index that reacts most quickly, and if there is only mild physiological arousal, it may be the only measurable response. Variability in CSB can occur without changing MAP. Increases in either sympathetic or parasympathetic activity will increase the variability of the arterial blood pressure. According to neurophysiologist Peter Julu, the average coefficient of variation of MAP-CV is 5% or less. If variability of MAP is above 5%, changes in the autonomic tone above the baseline are indicated; this is illustrated in Table 2. For a person to react according to the expected parasympathetic increase, a calming response requires an increase in CSB or CVT, or both, in relationship to the baseline. CSB is the parameter that reacts most quickly and shows that the braking effect is on the alert. It is an advantage if the CVT also increases, because that *is* the brake. If there is a good parasympathetic response it may be followed by a stabilisation of blood pressure. The coefficient of variation of blood pressure (MAP-CV) can nevertheless be allowed to vary <5%. An arousing or exciting response *may lead to* a sympathetic increase. To constitute an arousal response, the CSB must be lowered in relationship to the baseline. If there is also an increase in MAP and an increase in MAP-CV of 5% or more, then the excitement has led to an increased sympathetic output, and the person is activated.

Table 2 Survey of the autonomic responses defined by CVT, CSB, MAP and coefficient of variations in MAP compared with baseline

Responses (categorical brainstem responses)	CVT Cardiac vagal tone (LVS)	CSB Cardiac sensitivity of baroreflex (ms/mmHg)	MAP Mean blood pressure (mmHg)	MAP-CV Coefficient of variation in %
Parasympathetic response (calming)	CVT and/or CSB must increase	CSB and/or CVT must increase	Decrease or no change	Less than 5%
Sympathetic response (activating)	Decrease or no change	Decrease or no change	Must increase	Must be 5% or more
Arousal	Decrease or no change	Must decrease	Increase or no change	Not important

Note. This table was originally constructed by Peter Julu (reproduced from Bergström-Isacsson, et al., 2007)

3.6.3. Facial Action Coding System (FACS)

A video analysis of facial expressions and vocal sounds from the last minute of each stimulus was carried out simultaneously with the analysis of CVT, CSB and MAP. This video analysis was carried out using the FACS method. By using the video synchronised with the EEG machine it was possible to code and mark both frequency and duration for every single facial expression in the EEG, 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 (Appendix 7) and expressions caused by abnormal brainstem activity. Each AU was identified and marked (start and stop of the AU) and transformed into facial events³¹. FACS itself is purely descriptive and based on 44 unique Action Units (AU) (Appendix 6). Thanks to its descriptive power, FACS has emerged as the criterion measure of facial behaviour in multiple fields, e.g. facial expressions and emotions, pain research, psychology, psychiatry, management and in the judicial system (Ekman & Rosenberg, 2005; Sayette, Cohn, Wertz, Perrott, & Parrott, 2001). Eye- and head movements were not coded in this research, since these movements are not very important for expression of emotions, and therefore not relevant for this study.

³¹ An event is a period where AUs related to each other appear.

A researcher must take a specific training course to be recognised to use the method in research. He or she also has to pass the comprehensive Final Test for Coders to receive a Certificate and thereby be accepted, and also internationally registered, as a FACS coder. The training can be carried out via the Internet, or by attending a course at Berkeley University, USA. I became an internationally registered FACS coder in 2008, and have been a registered coder in micro-expressions³² since 2009.

The next step was to narrow the data down into a manageable quantity. This was done by focusing on AUs connected with emotions and micro-expressions (Appendix 7). The data were taken from the same moment as the last minute of the video started – if and when there was something going on in the participant’s facial expression. The video analysis was intended to correlate physical expression with the results from the brainstem monitoring by using the possibility of interpreting facial expressions. All scores were transferred into an Excel document, where musical stimuli, time and AUs were listed, making it possible to transform AUs into facial events and then into emotions. The scores also made it possible to calculate frequency and duration of AUs, which was important as a reliability check, for identifying events and individual facial movement patterns. A second brief video observation was made of the total time the participants were exposed to musical stimuli. This part included facial expressions, micro-expressions, connected with the music and the variations in the music, and checked against responses from the brainstem. This was undertaken in order to investigate whether it was possible to interpret facial expressions (as emotional responses or brainstem responses) and whether changes in facial expressions were caused by or correlated to what was happening in the music.

3.6.4. Analysis of musical material: Tool for Music Analysis (TMA)

The Tool for Music Analyses (TMA) covers basic changes which were important for different emotional responses. The Results chapter will include the music results from the analysis of the music (4.8.). A record of all music used can be found in Appendix 9. TMA was constructed by me and Erik Christensen, who is an experienced Danish musicologist and a PhD student at Aalborg University (2009-12). He has worked for the Danish Broadcasting Corporation as editor of contemporary music programmes and has published *The Musical Timespace. A Theory of Music Listening* (1996).

³² Emotional expressions coded in real-time and not frame by frame

During the process of developing the TMA we tested the analysis tool by analysing the same pieces of music and comparing the results. The TMA was discussed and revised until agreement was acceptable. Music analysis was not one of the main research questions, and therefore TMA was considered acceptable for the current study.

In this present study, TMA (Appendix 10 and section 4.8.) was used as a tool to identify basic changes in the music which might be important for different emotional responses. TMA was developed from previously used methods of analysis, based on Grocke (1999), Hooper, (2003, 2010) and Aare, Grønager & Rønnefelt (2003). TMA also made it possible to compare the parents' and carers' choice of the participants' favourite tunes. *Surface, Energy, Mood* provides basic knowledge about the music such as volume, tempo, pulse, timing and what the music "sounds like", timbre.

Presence, Attention provides information about what experience the music presents, what the music wants to "tell us", such as effect (hook, break, gimmick, see section 2.5.3.) and if the music is non-directed (more of a floating condition than development) or forward-directed (e.g. tension vs. easing of tension, or conflict vs. reconciliation).

Coherence, Memory provides information about the character and the structural form of the music, such as major or minor, and features: repetitions, sequencing (immediate repetition but at another pitch), call-and-response (the answer is not identical to the call but there are similarities in rhythm and context), ready-steady-go (e.g. in "Blue Suede Shoes": Well it's one for the money (*ready*), two for the show (*steady*) three to get ready, now go, cat, go (*go!*))

3.7. Procedure

3.7.1. Parent interview – data collection

Before each registration, I interviewed a parent or a carer. During that interview the parents or carers were asked about the participants' favourite pieces of music used for activating and calming purposes, respectively. They were also asked questions about whether the person had previously had or was currently having music therapy, which therapy method was used, and if and how they used music at home. The interviewer asked the parents or carers how they interpreted different emotional meanings from facial expressions, and if the participant vocalised or used their voice in other ways to express themselves. The verbal data from the interview was collected with the help of a form (Appendix 3).

During the interview the parents were again fully informed about their right to withdraw from the study, and that this decision would not affect the medical assessment they came for.

3.7.2. Video recording – data collection

Every participant was recorded by two video cameras. One camera focused on the participant, and on the person sitting next to her or him. It was important to be able to check afterwards if someone talked, touched, played, or did something else that might have contaminated the data. The second video camera focused on the face of the participant. This camera was connected to the EEG machine where the video file was saved. The analyses of the facial expressions were carried out on the screen of this EEG machine.

3.7.3. Preparation of participant and parent or carer

Before or after each interview, and always before the brainstem monitoring, the participants were given a medical examination; this was carried out by a child neurologist. The participant and the parents or carers were then introduced to the assessment room, the environment and the technical equipment, and every detail was explained. The participants had a chance to sit on the beanbag (“Musik-Molly”), and the parents/carers had time to ask questions. The parents or carers were also informed about the importance of silence and no interaction during the time the participant was exposed to the stimulus. The non-clinical participants were not given a medical examination since the criteria stated that the child should be healthy and normally developed. For the same reason no EEG registration was carried out. The non-clinical participants came only for brainstem assessment, but they all had time before the monitoring to get acquainted with the technical equipment, the assessment room and the people in that room. Some of the children in the non-clinical participant group were insecure about the situation. The team spoke English and that made some of them suspicious.

When the assessment started, the participant was put on the beanbag (“Musik-Molly”) with built-in loudspeakers. All the electrodes for ECG and oxygen and carbon dioxide, the breathing belt, finger cuff and EEG cap were connected to the participant and to the technical equipment. The video cameras, the microcomputer and the EEG machine were time-synchronised and the monitoring could start. First of all, it was necessary to establish a baseline.

3.7.4. *Baseline measurement*

A baseline for the brainstem autonomic function of participants with RTT (recorded during a set period) is established when the participant is breathing normally, blood gases are within the normal range, the participant is awake, and there are no signs or evidence of agitation and no epileptic activity (Julu, et al., 2001). For the non-clinical group, the same criteria applied for establishing a normal baseline, with the exception of epileptic activity, as EEG activity was not monitored. One minute was usually sufficient to establish the baseline, but longer periods of up to five minutes were used when this was necessary.

3.7.5. *Procedure of administering stimuli and return to baseline*

When the baseline had been established, the participant was exposed to the first stimulus. Due to the randomisation this could be any of the six musical stimuli. Nothing else went on in the assessment room when the participant was exposed to the stimulus. The start and the stop of the music and the vibrations were controlled by me. The person was exposed to two-minute excerpts of *Horn*, *Calming* and *Activating*. The brainstem responses were continuously measured but the data analysed were the mean values during the last minute of the music. This was decided because the initial minute of the stimulus presentation is likely to have an 'adjustment' response to the new stimulus after the baseline period. The pieces of music that were of an activating or calming character were generally on for approximately two minutes, and therefore the excerpts were to last no longer than that during the monitoring process. Exposure to *VT*, *VT+Mu* and *Mu* lasted for a period of 10 minutes each. The mean value of the brainstem responses was measured and calculated from the last minute of each stimulus. The time difference between *VT* and the stimuli with only music was due to an attempt to resemble a normal situation of treatment as far as possible. A *VT* session normally lasts for approximately 25 minutes but it would have been too lengthy to expose the participants to 3 x 25 minutes during the monitoring. Therefore, it was necessary to make a choice. The last minute was chosen because 10 minutes is the minimum period of time for using *VT*, and to optimise the result as much as possible, the last minute was selected for analysis. Between the presentations of each new stimulus (2 minutes or 10, depending on the randomisation) the participant settled down and returned to baseline, or as close to baseline as possible.

3.7.6. Ending of the procedure

The monitoring ended after presentation of the last stimulus. Many of the parents or carers – and most likely also the participants – expressed a feeling of relief when all the monitoring and tests were over. The difficult part of the monitoring was keeping more or less still for such a long time. As expected, this was easier for the participants than it was for the non-clinical group. Healthy children aged between one and five would not usually expect or want to be calm for over an hour, and especially not to have one hand, to which the monitoring photoplethysmographic finger cuff was attached, immobilised. To distract attention from the hand it was covered with a towel, but the children were obviously relieved to be able to use both hands again. For the participants the ending also meant that the EEG cap, the electrodes and cables, and all the other paraphernalia were taken away.

3.8. Methods of analysis

3.8.1. Preparation and screening of data

The times when the introduction and cessation of different stimuli began and ended were marked in the computer. The exact time was important for the later video analysis of facial expression. The data used were the mean values of the physiological responses during the last minute of each musical stimulus (see section 4.3.5.). All the different values were entered into an SPSS database where the baseline, the classification of diagnosis, the breathing phenotype and personal data for each person could be found. The procedure for analysing data, in order to determine and define the different results of the brainstem assessment, is described below.

For continuous variables, the distribution was checked with graphical methods to obtain an overview of the collected data. If the data were clearly skewed, methods that could deal with such distributions were used. Specifically, log transformations were taken for the purpose of testing differences in means (t-tests), and graphical displays were calculated using geometric means. (Means are used to characterise the central tendency of a set of numbers. The most well-known type of mean, the arithmetic mean, is only applicable and unbiased in the case of symmetric data. In contrast, the geometric mean is used to represent the central tendency in data that are right-skewed. The numbers are multiplied and then the n th root of the result is taken. This is equivalent to taking the arithmetic mean of the log-transformed data and exponentiating it again to bring it back to the original scale.)

3.8.2. Reliability analysis of FACS

This study used traditional FACS coding method, but some departures from the FACS manual have been made (Ekman, et al., 2002). These modifications were made because of the poor quality of the video that made it difficult to distinguish between similar AUs. The modifications were thought to be permissible because the AUs were sufficiently well identified for the purpose of reliable coding.

The modifications were (a) 23 (lip tightener) and 24 (lip presser) have been coded as agreements; (b) 25 (lips part), 26 (jaw drop) and 27 (mouth stretch) were coded as agreements; (c) 43 (eye closure) and 45 (blink) were coded as agreements; and (d) 73 (entire face not visible) and 74 (unscorable) have also been scored as agreements between the coders. After email discussion with Dr. Harriet Oster (FACS tutor and the author of Baby FACS), another change has been made. Observations where the researcher's reported code of AU81 (chewing) appears at the same time as inter-observer reported coding of the same facial movements with AU8 +25/26/27 (lips together) +80 (swallowing), have been transformed into a new code, AU88, because the *character of this series* of movements in the face is *closely connected with the pathology of RTT*.

There are at least four types of inter-observer reliability that are relevant to the interpretation of substantive findings (Sayette, et al., 2001). Most studies report reliability averaged across all AUs. Using this method, it is more or less impossible to look at reliability between individual AUs, but this might be of little concern when investigators analyse total measures. A second type of reliability involves using temporal resolution within time frames (tolerance windows) of up to ½ second, while a third type is to explore different levels of intensity. A fourth option, used in many studies, is where investigators are interested in testing hypotheses about emotion-specified expressions, which are considered to represent combinations of AUs. The reliability of emotion-specified expressions depends on the constituent AUs. By assessing the reliability of these aggregates directly, one can more accurately estimate their reliability.

In this doctoral study, FACS was primarily used to identify different facial expressions, and to investigate if it is possible to use FACS as a method of reporting and interpreting facial expression in a group of people with RTT. An independent observer coded 9 out of 29 of the participant group and 3 out of 11 of the non-clinical group. Therefore the first of the four methods described above was used: an average across all AUs, but with time and AUs clustered into events, has also been taken into consideration. The agreements were

evaluated on event-by-event basis, i.e. Coder A scores: AU1+ AU2 and Coder B scores AU1+AU2+AU4. According to the agreement index described in the investigator's guide (Ekman, et al., 2002), the agreement between coders A and B using this ratio is the number of AUs both coders agreed upon multiplied by 2, and that sum divided by the total number of AUs scored by both coders. In this example, the ratio is $4/5 = 0.80 = 80\%$ agreement. If one coder scores something and the other does not, the agreement is 0; the index is also 0 if there is no agreement about AUs. Every paired observation is calculated and then the mean scores across those ratios are taken to find the total agreement.

In both the RTT group and the non-clinical group, 30% were selected for inter-rater reliability analysis using the last complete minute of each stimulus. The level of agreement between the coders within that period of time was calculated.

3.8.3. Analyses of effects on continuous brainstem responses

Changes in all continuous variables were analysed one by one, stimulus by stimulus. By using graphical and statistical methods (see 4.3.) this process made it possible to gain a first impression of observed responses, and how they differed within and between the two groups (RTT participants and non-clinical participants). It also made it possible to answer the hypotheses on a general level for the groups. The mean values of the continuous variables were important to be able to determine the individual categorical brainstem responses. All continuous mean values were analysed together and compared within subjects. In order to fully answer the research questions and hypotheses, it was necessary to explore the individuals' changes in CVT, CSB, MAP and MAP-CV in detail, compared with their respective baseline for all musical stimuli. Difference scores (delta scores, or change scores from baseline) in continuous variables of physiological data were calculated, and parametric statistical analyses were used to examine data for significant changes.

3.8.4. Analyses of effects on categorical brainstem responses

Cross tables and chi-square tests were used to identify and organise the participants' different categorical brainstem responses, and to test the level of significance within the groups of participants and between the groups, in relation to the formulated hypotheses.

3.8.5. Analyses of effects on FACS

Cross tables and chi-square tests were used to identify and organise the participants' facial expressions, to organise these expressions into emotional events, and to test whether observed emotional facial expressions were statistically significant within the

groups of participants. Categories were combined into three groups of categories to test whether tendencies were significant.

3.8.6. Analyses of the music used

Parents and carers were asked questions about the participants' use of music and the answers were reported in numbers and percentages. The Tool for Music Analyses, TMA, was used in this current study to identify the character and structure of the music. TMA was also used to investigate whether there were correlations between the character and structure of the music, and categorical brainstem responses.

3.8.7. Analyses of four case vignettes

While conducting the study and gaining more insight, it became obvious that it could be important to look at CVT, CSB, MAP, MAP-CV together with pO_2 , pCO_2 and FACS. Continuous and categorical brainstem responses might mean one thing when standing alone, but might become something else in another, more complex context.

Three clinical participants were selected as typical participants with RTT, meaning that they were all diagnosed with classical RTT. During the assessment and the analyses it became obvious that all three RTT participants had a minimum of five different, randomly occurring, abnormal breathing patterns and frequent ASBAs. The non-clinical participant was picked at random.

ASBA (Abnormal Spontaneous Brainstem Activation) is a brainstem abnormality found in participants with RTT. ASBA is a condition whereby the brainstem neurons spontaneously depolarise, sending signals to different effector organs, including the heart, in an abnormal or erratic manner. This can result in what we observe as cardiac arrhythmia and cardiac instability, manifest in random fluctuations in heart rate and blood pressure. ASBAs can be indirectly measured during brainstem assessment by abnormal spontaneous cardiovascular behaviour. An ASBA can be observed on the monitoring equipment as a sudden increase in CVT, CSB, DBP (diastolic blood pressure), SBP (systolic blood pressure) and HR (Heart rate), and then a sudden drop in all parameters at almost exactly the same time. This looks like a sudden explosion, a peak, on the computer screen. Unbalanced blood gases seem to trigger the frequency of ASBAs. Examples of this are when the level of pCO_2 is too high, but also when the levels of pO_2 and pCO_2 come too close to each other (reach the same values).

Table 3 values represent the normal, expected values for non-clinical adults (as there are no existing normal values for children aged 1-5 years old) without pathology, compared with values that could typically be expected in participants with RTT (Julu, 1992).

Table 3 Values of measured brainstem parameters representative of a normal population and normal values for participants with Rett syndrome

Normal values for adults		Normal for RTT, any age	
CVT (LVS)	5-10	CVT (LVS)	3-5
CSB (ms/mmHg)	6-12	CSB (ms/mmHg)	4-6
MAP (mmHg)	80-100	MAP (mmHg)	65-80
pO ₂ (mmHg)	100	pO ₂ (mmHg)	60+
pCO ₂ (mmHg)	30-40	pCO ₂ (mmHg)	39-44

CHAPTER FOUR

4. Results

4.1. Sample characteristics: selection of participants and baseline data

4.1.1. Selection of participants

A total of 35 RTT participants, 33 females and 2 males, were recruited to the study. During the data collection six RTT participants were excluded due to not meeting the inclusion criteria: one with ongoing vagal nerve stimulator (VNS), two who were sleeping most of the time, two with constant arousal attacks and one with constant Valsalva's manoeuvres. Therefore 29 participants (27 females, 2 males) remained for analysis. The study also included a group of non-clinical participants, 6 girls and 5 boys, who had had a normal birth and a normal development both physically and cognitively. The basic demographic details of the groups (age, sex, and diagnoses) have been described in the Methods chapter (3.4.).

4.1.2. Participants' relation to music

All parent and carers were asked if participants with RTT and non-clinical participants had music therapy, now or in the past, and in that case, what kind of music therapy. They were also asked whether they used music, and if so, how. Non-clinical participants did not practise music therapy (Table 4). Among the RTT participants, 11 (38%) had access to some kind of music therapy, while 18 (62%) had nothing. Some of the participants' parents and carers in the RTT group reported having had problems gaining approval for music therapy as a treatment procedure from their respective county councils. Music therapy is not a natural or fully accepted form of therapy within the healthcare system, and is therefore difficult to get. Another problem mentioned was the lack of qualified and well-trained music therapists.

Table 4 The number of Rett syndrome and non-clinical participants who had received any kind of music therapy

Population		Frequency
RTT participants	FMT*	1 (3%)
	Analytic	7 (24%)
	Other	3 (10%)
	Nothing	18 (62%)
	Total	29
Non-clinical participants	Nothing	11

Note. * FMT = Functionally oriented Music Therapy, a specific music therapy method which stimulates the body's development

The amount of music around all participants in their daily lives gives a different picture (see Table 5). In the RTT group, 24 of the 29 participants have and have had a great deal of music around them in their daily lives, as have 8 of the 11 in the non-clinical group. In the RTT population it is well known that music is of great importance, but Table 5 gives an overview of how and in what situations music is used.

Concerning the participants in the RTT group, 23 persons (79%) used music to calm down compared with 2 (18%) in the non-clinical group. The parents and carers in the RTT group used music in many different situations to calm the person down. The parents in the non-clinical group mainly used the calming music when driving with their children, and to draw attention away from something that was boring or frightening. Music for activating reasons was more evenly used within and between the groups (51% vs. 36%). Eleven (38%) of the RTT participants used music “as medication” in situations when nothing else worked. None of the children in the non-clinical group had the same need. Sometimes music was used to help the participants relax and get to sleep; this included both lullabies and other kinds of music. At bedtime, 9 (31%) of the RTT participants and 3 (27%) of the non-clinical participants were exposed to some kind of music.

In the RTT group, music was used by 9 (31%) as signals; for example, for a new activity, a person or a place, a way to illustrate and clarify what is going to happen next. The non-clinical participants did not use music as signals. Other important situations when music was used, according to the parents and carers, were e.g. during dental and medical examinations, in shopping centres and at meetings. These were situations when music was a working tool for 9 (31%) of the RTT participants. All non-clinical participants used

music in this way. As many as 27 (93%) of the parents and carers in the RTT group said that they used music deliberately, compared with 7 (64%) from the non-clinical group.

Table 5 Questions asked about the use of music among Rett syndrome participants and non-clinical participants

	RTT n=29	Non-clinical n=11
Lots of music around them in daily life *	24 (83%)	8 (73%)
Use of music to calm down	23 (79%)	2 (18%)
Use of music to activate	15 (51%)	4 (36%)
Use of music as "medication"	11 (38%)	0 (0%)
Use of music in sleeping situations	9 (31%)	3 (27%)
Use of music as a signal	9 (31%)	0 (0%)
Use of music in other situations	9 (31%)	11 (100%)
Deliberate use of music	27 (93%)	7 (64%)

Note. * The carers did not know about the amount of music around 2 of the participants.

4.1.3. Success of matching: physiological parameters at baseline

The non-clinical group was intended to be matched to the RTT group in terms of their brainstem maturity. As described earlier (2.3.2.), the brainstem is immature in RTT, sometimes as immature as that of a baby, and may remain thus throughout life. This was the reason for choosing children aged 1-5. In fact, the non-clinical group could have been even younger; however, this was not possible, since the technical equipment was far too big for children under the age of 1. There were differences between the groups (Table 6). CVT and CSB were higher in the non-clinical group, and MAP was significantly lower. These parameters added together give information about a more stable and well-functioning brainstem, a more mature brainstem in the non-clinical group at baseline level. The MAP-CV was slightly higher in the same group, but the difference was not statistically significant. The matching was partly successful, but some differences existed concerning brainstem maturity.

Table 6 Baseline differences in continuous dependent variables between groups of Rett syndrome and non-clinical participants

	RTT		Non-clinical		Diff
	N	M (SD)	N	M (SD)	M
Bas_CVT	29	4.23 (2.90)	11	8.42 (9.05)	-4.19
Bas_CSB	29	3.48 (2.88)	11	7.25 (8.59)	-3.77
Bas_MAP	29	58.36 (14.81)	11	47.74 (5.83)	10.62 **
Bas_MAP-CV	29	6.53(2.65)	11	7.27 (2.31)	-0.74

Note. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

4.2. Data preparation: screening of distributions and reliability tests

4.2.1. Screening and transformations of continuous variables

The distributions of the continuous variables were examined visually to determine if parametric statistics could be applied, possibly after an appropriate transformation. After looking at the distribution of the data using histograms (Appendix 8), it became apparent that almost all variables were right-skewed. Therefore a natural log transformation was done on all continuous variables. This successfully removed the skewness. The delta values reported below (differences from baseline) are based on these log-transformed values (Table 8). For graphical analyses, log-transformed values were transformed back into their original scale (“geometric mean”).

4.2.2. Inter-observer reliability of FACS analyses

Reliability can be assumed for the physiological data, but for the analysis of facial expression (FACS), an extensive reliability analysis was undertaken. After organising all codes into events, 30% of the data, relating to eight clinical participants and three non-clinical participants, were randomly selected and analysed for inter-observer reliability (Table 7). The overall level of agreement between researcher and independent observer was 0.69, according to the model and transformations described earlier, in the Methods chapter. In the RTT group the agreement had a ratio of 0.62 and in the non-clinical group the ratio was 0.89. In this study an observational window of ½ second was allowed, which gave a low reliability on location, but the most important part here was the description, whereas the reliability is high. According to the FACS manual (Ekman, et al., 2002) and earlier research (Sayette, et al., 2001), a ratio of 0.60 to 0.75 is considered to be good or adequate reliability, and 0.75 or higher indicates excellent reliability. The inter-reliability check indicated that FACS was a possible method to use, but it also clearly

shows lower agreement in the RTT group. This is due to the author's earlier experience and knowledge of the syndrome and movements which are closely connected with the syndrome, such as jaw-pressing, teeth-grinding and chewing, and do not exist in the non-clinical group. One disagreement in the RTT group was AU14 vs. AU12. They *could* be contrary, but in this case AU12 and AU14 stood for themselves, and even if AU12 is strongly connected with happiness, more AUs need to be involved to constitute a genuine smile (see Appendix 7). In this case both AUs indicated some kind of dissatisfaction and therefore the disagreement could be explained. Another disagreement between the coders was AU11 vs. AU12.

Table 7 Inter-observer reliability agreement for eight participants with Rett syndrome and three non-clinical participants

RTT	Horn	Activating	Calming	VT	VT+Mu	Mu	Mean
1	0.57	0.69	0.75	0.57	0.32	0.55	0.58
2	0.52	0.89	0	0.76	0.75	0.57	0.58
3	0.61	0.74	0.70	0.30	0.62	0.71	0.61
4	0.66	1.0	0.80	0.40	1.0	0.90	0.79
5	0.46	0.62	0.30	0.66	0.59	0.40	0.50
6	0.89	0.48	0.50	0.20	0.97	1.0	0.67
7	0.65	0.64	0.67	0.60	1.0	0.80	0.73
8	0.16	0.54	0.65	0.64	0.41	0.33	0.46
Total mean/stimuli	0.56	0.70	0.58	0.52	0.70	0.66	0.62
Non-clinical							
1	0.93	0.93	0.76	0.90	1.0	1.0	0.92
2	0.80	0.62	0.94	0.85	1.0	0.86	0.84
3	0.93	0.98	0.94	0.92	0.77	0.95	0.92
Total mean/stimuli	0.89	0.84	0.88	0.89	0.92	0.94	0.89
Overall/stimuli	0.68	0.74	0.64	0.62	0.77	0.73	0.69

4.3. Analyses at group level of the four continuous dependent variables in participants with Rett syndrome compared with a sample of non-clinical participants

These hypotheses formulated in section 2.6. were first analysed at group level, using the original continuous variables. Analysing the continuous variables as continuous variables is more powerful than analysing count data, as the information about magnitude is retained. The changes in the continuous variables, analysed one by one, present a first impression of observed responses, and how they differ between the stimuli and groups.

4.3.1. CVT

CVT is an indicator of the parasympathetic part of the nervous system. The changes and the variability in CVT are presented here as geometric means and their standard errors (SE) (Figure 8). In the RTT group, the mean CVT values tended to increase compared with baseline in all musical stimuli. In contrast, the non-clinical group responded to all stimuli with a decrease in CVT. Overall, as an indicator of a parasympathetic (i.e. relaxing) response, CVT only responded in the predicted direction for some of the stimuli. According to this indicator, the RTT participants appeared to become more relaxed under all stimuli, whereas the non-clinical participants appeared to become less relaxed.

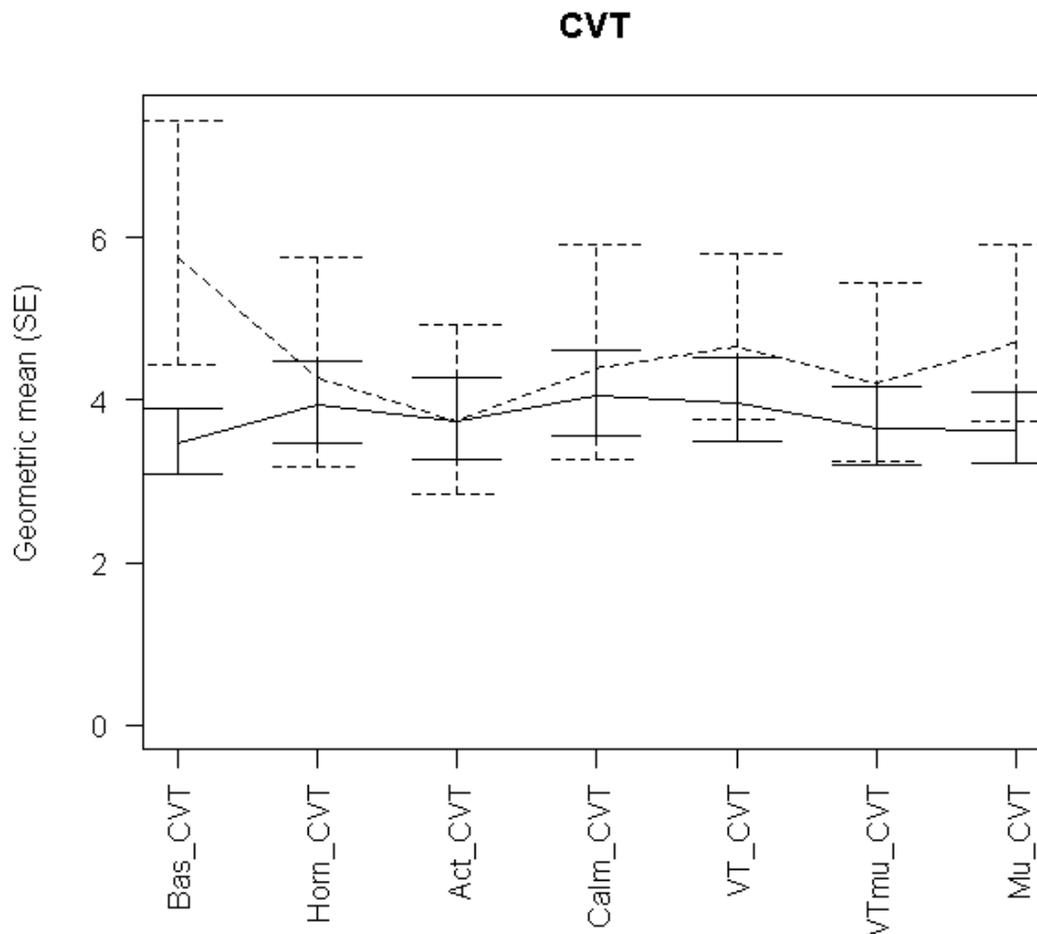


Figure 8 CVT geometric means and Standard Errors (SE) at baseline and under six different musical stimuli.

Note. CVT responses to six different musical stimuli compared with baseline, for the group of 29 RTT participants (solid line) and 11 non-clinical participants (dashed line)

4.3.2. Changes in CSB

Like CVT, CSB is also an indicator of the parasympathetic part of the autonomous nervous system. By comparing means between the two groups (Figure 9), it is clear that the CSB baseline was higher in the non-clinical participants, already at baseline. As expected, the RTT group responded with a decrease in CSB during *Horn* and, more markedly, during *Activating*. A slight increase was noticed during *Calming* and *VT*, again as expected. The non-clinical group also responded with a decreased CSB in *Horn* and *Activating*, as expected. However, this group also decreased in CSB during other stimuli

that were designed to have a relaxing effect (*Calming*, *VT+Mu* and *Mu*), contrary to the expected direction.

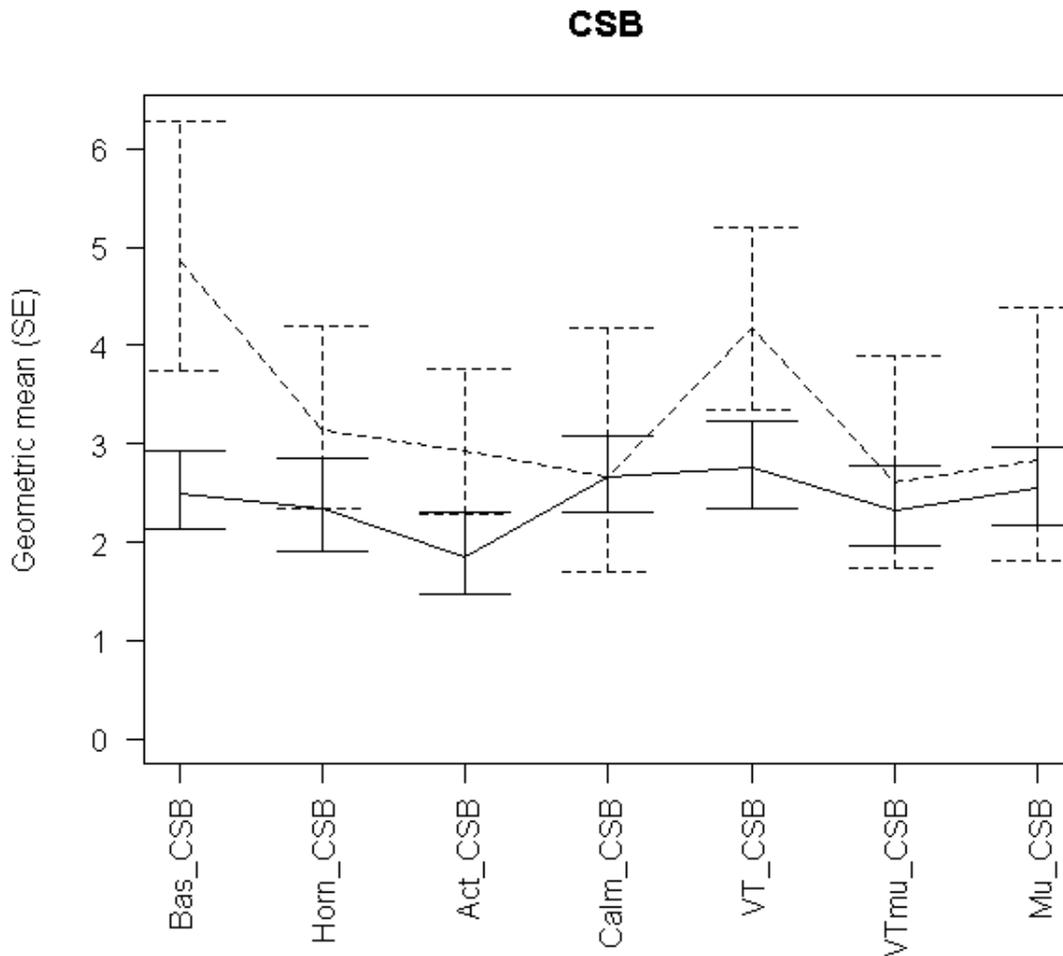


Figure 9 CSB geometric means and Standard Errors (SE) at baseline and under six different musical stimuli.

Note. CSB responses to six different musical stimuli compared with baseline, for the group of 29 RTT participants (solid line) and 11 non-clinical participants (dashed line)

4.3.3. Changes in MAP

MAP is an indicator of the sympathetic part of the autonomic nervous system. From Figure 10 it is clear that the MAP was significantly lower in the non-clinical group than in RTT participants under all stimuli and at baseline. The RTT participants appeared to increase in MAP during *Horn* and *Activating* (as would be expected), but also during

Calming. During VT, both groups responded (expectedly) with a small decrease in MAP, at least compared with the other stimuli.

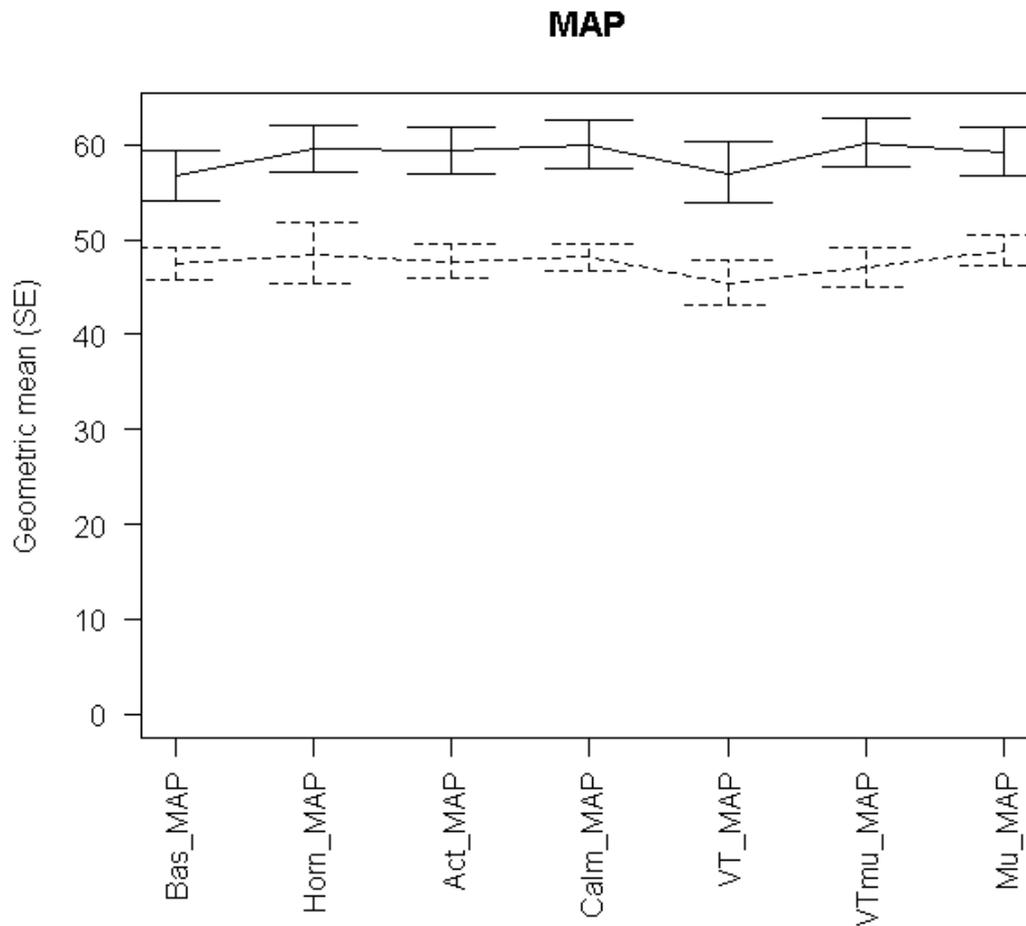


Figure 10 MAP geometric means and Standard Errors (SE) at baseline and under six different musical stimuli.

Note. MAP responses to six different musical stimuli compared with baseline, for the group of 29 RTT participants (solid line) and 11 non-clinical participants (dashed line)

4.3.4. Changes in MAP-CV

MAP-CV is an indicator of the sympathetic part of the autonomic nervous system. Figure 11 illustrates that baseline MAP-CV was similar in the two groups. All stimuli increased MAP-CV in the RTT group. *Horn* showed the most marked increase in both RTT and non-clinical children. *Activating* also showed the expected increase in RTT children, but less clearly so in the non-clinical group.

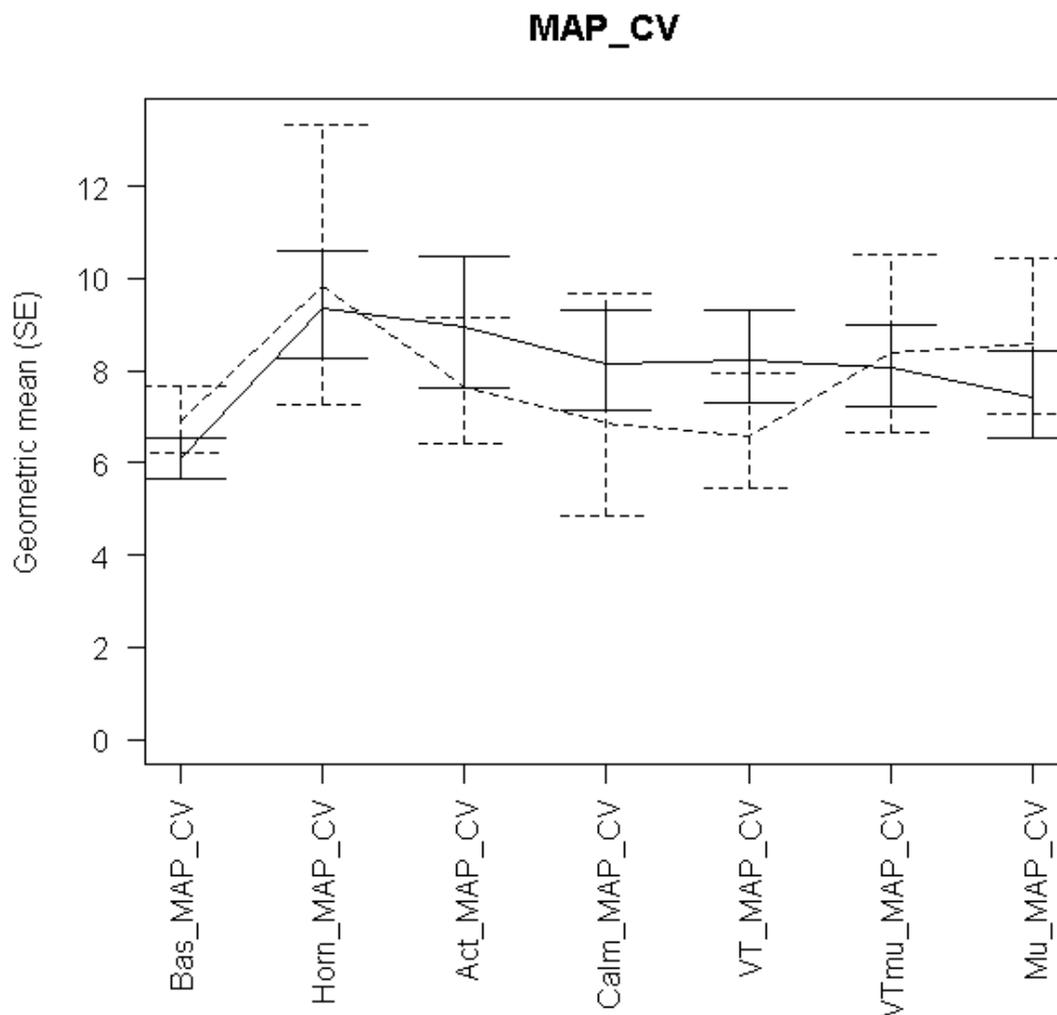


Figure 11 MAP-CV geometric means and Standard Errors (SE) at baseline and under six different musical stimuli.

Note. MAP-CV responses to six different musical stimuli compared with baseline, for the group of 29 RTT participants (solid line) and 11 non-clinical participants (dashed line)

4.3.5. Tests of significance for changes in continuous variables

Following these descriptive analyses, significance testing was undertaken to confirm which of these tendencies were stronger than could be explained by chance. Table 8 shows the mean changes in the different neurophysiological brainstem responses to each stimulus for the two groups. Subsequent statistical significance testing was done by one-sample t-tests. There were some missing data due to constant Valsalva's manoeuvres or arousal attacks.

Table 8 Analyses of brainstem responses to the six musical stimuli in the Rett syndrome and non-clinical groups

	Delta In CVT M (SD)	Delta In CSB M (SD)	Delta In MAP M (SD)	Delta In MAP-CV M (SD)
RTT n=29				
Horn	.128 (.446)	-.069 (.857)	.049 (.158)	.432 (.743)**
Activating	.045 (.475)	-.340 (1.085)	.048 (.135)	.386 (.894)*
Calming	.184 (.440)*	.089 (.602)	.053 (.198)	.313 (.730)*
VT	.135 (.326)*	.083 (.558)	.003 (.158)	.323 (.660)*
VT+Mu	.080 (.345)	-.048 (.507)	.056 (.192)	.301 (.543)**
Mu	.047 (.391)	.016 (.562)	.043 (.137)	.200 (.759)
Non-clinical N=11				
Horn	-.296 (.530)	-.438 (.423)**	.022 (.251)	.355 (.833)
Activating	-.431 (.541)	-.505 (.581)*	.007 (.129)	.105 (.383)
Calming	-.268 (.489)	-.602 (1.092)	.016 (.177)	-.008 (.950)
VT	-.209 (.461)	-.152 (.551)	-.044 (.132)	-.049 (.455)
VT+Mu	-.312 (.428)*	-.622 (1.031)	-.007 (.206)	.192 (.727)
Mu	-.200 (.381)	-.541 (1.015)	.030 (.134)	.220 (.434)

Note 1. Mean delta scores and one-sample t-tests in the analyses of continuous brainstem responses

Note 2. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

MAP-CV (Table 8) was significantly increased in *Horn*, *Activating*, *Calming*, *VT* and *VT+Mu* in the RTT group, which indicated poor brainstem control function. CVT increased significantly in *Calming* and *VT*, as expected. *Horn* and *Activating* caused a significantly decreased CSB, an arousal, in the non-clinical group which was in accordance with the hypothesis, even though an increase in MAP and MAP-CV was needed for it to be a sympathetic response (activation). *VT+Mu* significantly increased CVT, as expected.

4.3.6. Summary of the group-based results

Horn, *Activating* and *VT+Mu* gave the same overall responses in both groups. *Horn* was supposed to cause an arousal, which it did. *Activating* was supposed to cause activation but it did not, and *VT+Mu* was supposed to cause a calming response but this did not happen. The only stimulus which gave the same and also expected response in both groups was *Horn*. The non-clinical group responded with an arousal response to all stimuli.

4.4. Results of the analyses of categorical brainstem responses in participants with Rett syndrome compared with a sample of non-clinical participants

The results presented above show the group-level responses to each variable separately. In addition, I also looked manually at each participant's data separately, using Table 2 for analyses, in order to determine each participant's categorical response to each stimulus. Table 9 gives information about individual responses to the different musical stimuli. The responses are: parasympathetic, sympathetic, arousal, no response and an unclear response (also equal to a non-expected response).

Table 9 Number of individuals' categorical brainstem responses to six different musical stimuli

Responses	Horn		Activating		Calming		VT		VT+Mu		Mu	
	RTT n (%)	Non- clinical n (%)	RTT n (%)	Non- clinical n (%)	RTT n (%)	Non- clinical n (%)	RTT n (%)	Non- clinical n (%)	RTT n (%)	Non- clinical n (%)	RTT n (%)	Non- clinical n (%)
Parasympathetic	8 (28)	3 (27)	8 (29)	2 (20)	11 (39)	1 (1)	14 (52)	4 (36)	9 (32)	5 (45)	8 (28)	1 (1)
Sympathetic	7 (24)	5 (45)	10 (36)	4 (36)	8 (29)	4 (36)	11 (41)	2 (20)	10 (36)	2 (20)	5 (17)	4 (36)
Arousal	2 (7)	2 (18)	3 (11)	1 (9)	3 (11)	1 (9)	0	1 (9)	1 (0,5)	1 (9)	1 (0,5)	1 (9)
No response	0	0	0	1 (9)	0	0	0	0	0	0	1 (0,5)	0
Unclear	12 (41)	1 (9)	7 (25)	3 (27)	6 (21)	5 (45)	2 (29)	4 (36)	8 (29)	3 (27)	14 (49)	5 (45)
Total	29	11	28	11	28	11	27	11	28	11	29	11

Note 1. The sample size differs between 27 and 29 in the RTT group because of missing data in some musical stimuli due to constant Valsalva's manoeuvres or arousal attacks. No missing data in the non-clinical group.

Note 2. The numbers of expected responses are in bold.

Briefly summarised, the expected categorical responses related to the hypotheses (2.6) were observed in 7% (*Horn*), 36% (*Activating*), 39% (*Calming*), 52% (*VT*), 32% (*VT+Mu*), and 28% (*Mu*), respectively. The non-clinical group showed the expected categorical response in 18% (*Horn*), 36% (*Activating*), 9% (*Calming*), 36% (*VT*), 46% (*VT+Mu*), and 9% (*Mu*), respectively. Comparing the two populations, one can say that (a) the expected response was usually seen in a minority of cases, both in RTT and non-clinical children; (b) expected responses to three stimuli (*Activating*, *VT*, *VT+Mu*) occurred in over 30% of both RTT and non-clinical children; (c) the expected calming response to *Calming* was more common (39%) in RTT than in non-clinical children (9%); and (d) *Horn* rarely produced the expected arousal response, either in RTT or in non-clinical children.

4.5. Effect of stimuli on facial expressions (FACS) of participants with Rett syndrome

As regards RTT participants, it is difficult to ask them whether they like the music or not. Therefore parents and carers have to interpret their facial expression and from this draw conclusions as to whether the chosen music is good or not for the person. Some expressions may show genuine emotions and some may not. Facial expressions might not be as easy to interpret as people generally think.

4.5.1. FACS analysis

The results from Table 10 indicate that more participants (15) *smiled* during *Activating* than under any other stimulus; *false smiles* were found most often during *Calming*; and *disgust* was most frequently (20) expressed during *Mu*. Overall, *disgust* (37), *smile* (36), *false smile* (25) and *surprise* (12) were most frequently encountered. *Activating* and *Mu* elicited most reactions. The results from Table 11 indicate that *smile* (8) and *false smile* (8) were also common in the non-clinical participants during *Activating*. *VT+Mu* commonly elicited *smiles* (9). As in the RTT group, *Activating* (17) evoked many reactions, but so did *VT+Mu* (19). Overall, *smile* (37), *false smile* (24) and *surprise* (16) were most frequently encountered.

To test whether these tendencies were statistically significant (chi-square tests), the following categories of similar reactions were combined: Group 1: *Smile, Laugh, Surprise*; Group 2: *False smile*; Group 3: *Anger, Anxiety, Fear, Disgust*. Table 12 shows that *Activating* evoked more smiles and similar reactions (21) than any other stimulus. Conversely, the *Mu* stimulus evoked more negative responses such as anger or anxiety (23), and *Horn* also evoked many such reactions (10). In comparison, Table 13 shows the results for the non-clinical participants. Smiles were most often seen in *VT+Mu* (14) and *Calming* (11), but were also reasonably common in *Activating* (9). Negative reactions were seldom observed overall (6 in non-clinical vs. 55 in RTT). False smiles during *Activating* were common in both populations. In general, the pieces of music selected by parents (*Activating* and *Calming*) elicited the most positive responses.

Table 10 Occurrence of facial expressions among participants with Rett syndrome (n=29) under different stimuli

RTT	Horn	Activating	Calming	VT	VT+Mu	Mu	Total/Expression
Smile	3	15	7	0	6	5	36
False smile	4	7	8	2	3	1	25
Laugh	0	2	0	0	0	0	2
Sadness	0	0	0	1	1	1	3
Anger/Anxiety	3	1	1	0	3	0	8
Surprise	0	4	3	1	3	1	12
Fear	1	3	1	0	1	3	9
Disgust	6	2	2	5	2	20	37
Total	17	34	22	9	19	31	132

Note. Multiple occurrences of each facial expression per stimulus and participant were possible.

Table 11 Occurrence of facial expressions among non-clinical participants (n=11) under different stimuli

Non-clinical	Horn	Activating	Calming	VT	VT+Mu	Mu	Total/Expression
Smile	6	8	5	5	9	4	37
False smile	5	8	4	3	3	1	24
Anger/Anxiety	0	0	0	0	1	0	1
Surprise	1	1	6	3	5	0	16
Fear	1	0	0	1	1	0	3
Disgust	1	0	0	0	0	1	2
Total	14	17	15	12	19	6	83

Note. Multiple occurrences of each facial expression per stimulus and participant were possible. Categories with zero occurred in all stimuli (Laugh, Sudden laugh, Sadness) are not shown.

Table 12 Number of expressions among participants with Rett syndrome (n=29) exposed to six types of musical stimuli by groups of emotional expressions

Groups of expressions	Horn	Activating	Calming	VT	VT+Mu	Mu	Total
Positive response (Smile/Laugh/Surprise)	3	21	10	1	9	6	50
Ambiguous response (False smile)	4	7	8	2	3	1	25
Negative response (Anger/Anxiety/Fear/Disgust/Sadness)	10	6	4	5	7	23	55
Total	17	34	22	9	19	30	130

Note1. Pearson's chi-square test with simulated p -value (based on 2000 replicates): $\chi^2 = 37.91$, $df = NA$, p -value < 0.001

Note 2. Multiple occurrences of each facial expression per stimulus and participants were possible.

Table 13 Number of expressions among non-clinical participants (n=11) exposed to six types of musical stimuli by groups of emotional expressions

Groups of expressions	Horn	Activating	Calming	VT	VT+Mu	Mu	Total
Positive emotions Smile/Laugh/Surprise	7	9	11	8	14	4	53
Ambiguous response (False smile)	5	8	4	3	3	1	24
Negative emotions Anger/Anxiety/Fear/Disgust	2	0	0	1	2	1	6
Total	14	17	15	12	19	6	83

4.6. Comparison of facial expressions and categorical brainstem responses in the Rett syndrome group

By comparing neurophysiological categorical brainstem responses (Table 9) with scored facial expressions by the RTT individuals (Table 10), the following general observations can be made.

1. *Horn*. The results from brainstem assessments gave unclear categorical brainstem responses to a high degree (41%). These responses agree with the output from the facial expressions.
2. *Activating*. The most common response was the expected sympathetic response (36%). This corresponds with the frequent occurrence of 15 smiles, but some participants (29%) responded with a parasympathetic response (which is equal to a calming response). Seven false smiles and 6 negative expressions were also observed. The overall indication is that even though this music was pleasing and stimulating for some participants, and pleasing and calming for others, the false smiles and negative expressions indicate that some of the RTT participants' brainstem control functions were out of control. These responses agree with the output from the facial expressions.
3. *Calming*. The most common response was the expected parasympathetic response (39%) which corresponds with the occurrence of 10 smiles, but some participants (29%) responded with a sympathetic response. Eight false smiles and four negative emotions were also observed. The overall indication here is that this music was pleasing and calming for some participants, and pleasing and stimulating for others, but the false smiles and negative expressions indicate that some of the RTT participants' control functions were out of control. These responses agree with the output from the facial expressions.

4. *VT*. The most common response was a parasympathetic response (52%), as expected. These responses do not agree with the observed facial expressions
5. *VT+Mu*. The most common response was a sympathetic response (36%) but some participants responded with a parasympathetic response (32%). These responses agree with the output from the facial expressions.
6. *Mu*. The most common response was an unclear response (49%) but some participants responded with a parasympathetic response (28%) and some with a sympathetic response (17%). These responses agree with the output from the facial expressions.

Overall the analysed categorical brainstem responses agreed with the output from the participants' facial expressions, except in the case of *VT*.

4.7. Four case vignettes

In the following case studies there will be a more detailed description of the brainstem assessments of three clinical participants and one non-clinical participant when they were exposed to the music already known to them (calming and activating music chosen by their parents or carers). Blood gases (pO_2 , oxygen and pCO_2 , carbon dioxide) correlated to facial expressions were included in the analysis. The clinical participants were selected as typical participants with RTT, which means that they had all been diagnosed with classical RTT, and were very similar in their contact and expressions. They all liked and used music in different situations, but they differed with respect to musical preference and physical status. They represented two of the cardiorespiratory phenotypes: feeble breathers (2) and apneustic breathers (1). All three RTT participants had a minimum of five different, randomly occurring, abnormal breathing patterns and frequent ASBAs (3.8.7.). This description is intended to explain the importance of studying the whole picture of both physiological and behavioural responses in order to be able to interpret the individual. The non-clinical participant was picked at random. Continuous and categorical brainstem responses might mean one thing standing alone, but might become something else in another, more complex context. It should be emphasised that most measured values are close to the individual's own baseline values regardless of musical stimulus. But as people with RTT in general have low values of all continuous variables (an indication of an immature brainstem) except for pCO_2 , all changes are important. The values fluctuate, as the NeuroScope allows measures every heart beat, and this fluctuation in itself is normal. This is also a reason for choosing a mean value in this study.

4.7.1. Case vignette 1: Paula

Paula is a woman with classical RTT, stage III. No genetic test has been carried out, she is classified as a feeble breather (2.3.2.) and has frequent ASBAs (almost one every minute) throughout the brainstem assessment, with or without external stimuli. In Paula's daily life her parents and carers use music to calm her down. She has never had access to music therapy or music as remedial teaching at school, but she likes to sit down and listen to music when she comes home after her daily occupation and duty.

Table 14 Paula's baseline and mean values from the last minute of calming and activating stimuli

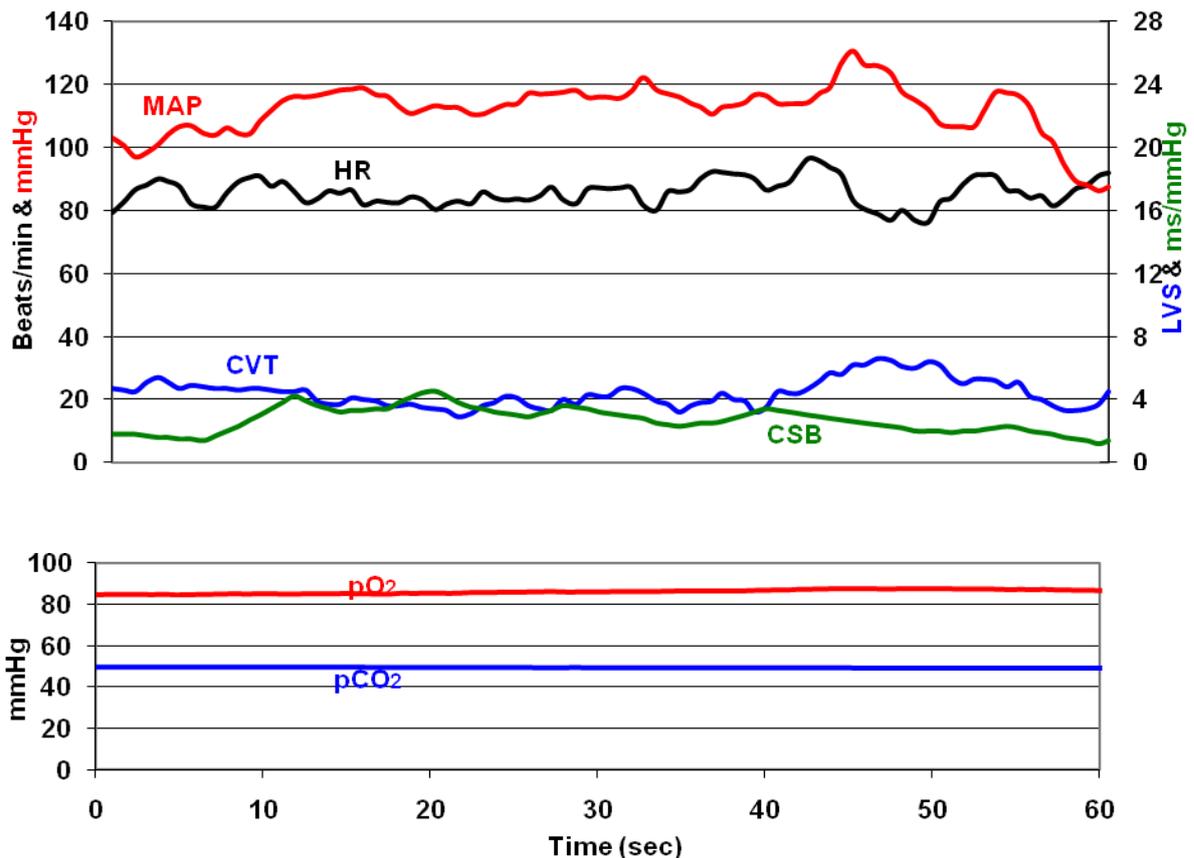
Continuous variables	Baseline	Calming	Activating
CVT (LVS)	6.09 ¹	5.08 ¹	6.37 ¹
CSB (ms/mmHg)	5.1 ²	3 ³	4.6 ²
MAP (mmHg)	107.2 ⁴	105.9 ⁴	112.2 ⁴
MAP-CV (%)	not relevant	10.19	2.90
pO ₂ (mmHg)	60.6 ²	85.2 ²	71 ²
pCO ₂ (mmHg)	50.9 ⁴	49.7 ⁴	52.4 ⁴

Note. ¹ normal; ² normal for RTT; ³ too low; ⁴ too high (cut-off values, see Table 3).

Her baseline values (Table 14) are near to normal except for her level of blood gases. Her oxygen level is normal for participants with RTT, but the level of carbon dioxide is high, even for a person with RTT. Her pathological blood gases might be one reason for the irritated brainstem and thereby also one reason for the frequent ASBAs. Paula has an *individual facial movement pattern*, which is something observed repeatedly, irrespective of what is happening around her. Her facial muscles are moving more or less all the time and her tongue is also very active. When measured, using the coding in FACS analysis, this facial activity includes AU1+AU2+(AU5)+AU10+AU12+AU25+AU26+AU27 (Appendix 6). *This pattern creates ambivalence among the people trying to interpret her.* It sends out signals of surprise, disgust, happiness and sometimes also fear, and all this happens in the same event. Her active face is caused by an abnormal activation starting in the retro-facial area of the brainstem where nuclei of corresponding cranial nerves are located. From the results of her brainstem assessment it is clear that her pattern starts with facial activity; then it affects the blood pressure and then her tongue, and sometimes an

increased flow of saliva that is a sign of parasympathetic activity. *Why* this happens is difficult to understand, but it is important to know *that* it is happening. Her carers find it difficult to know what she is expressing with her face. To be able to guide them it is necessary to observe her “normal face” and compare that with emotional expressions.

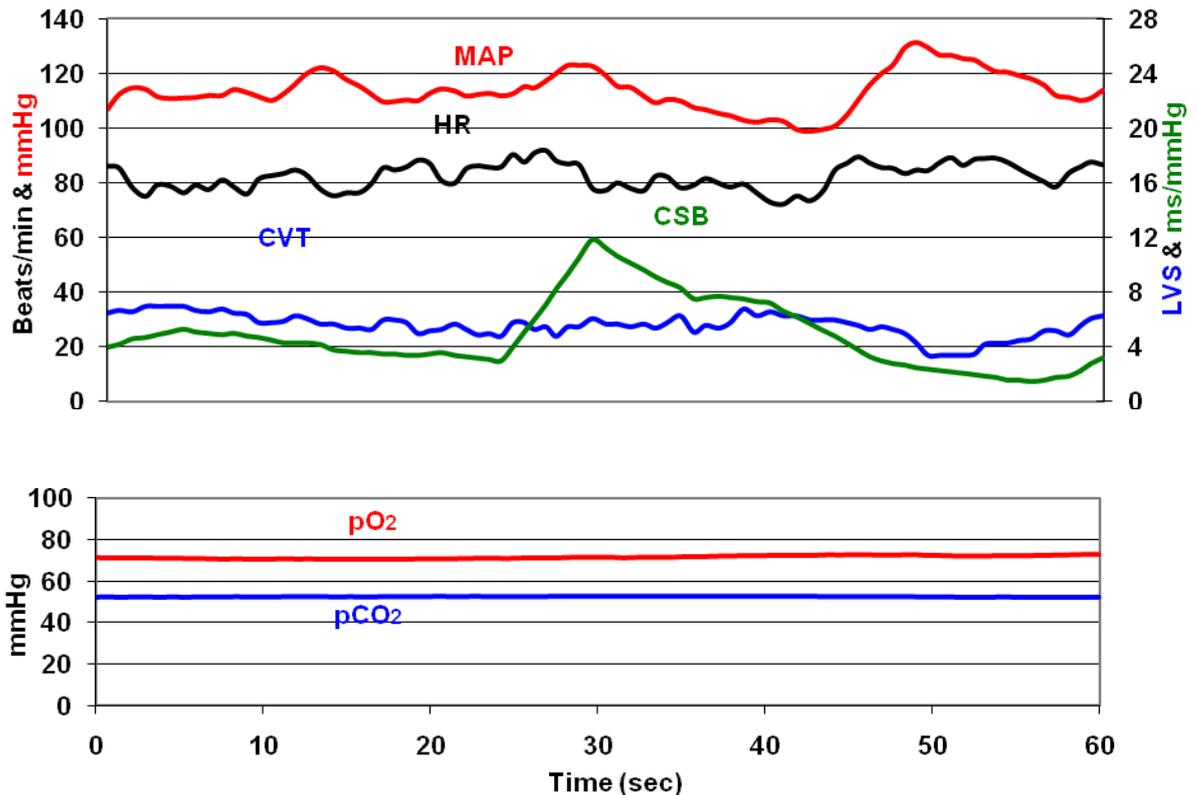
Figure 12 Brainstem assessment graph of the last minute of Paula’s favourite calming music, including blood gases



This is an unclear response (Figure 12). CVT and CSB decrease compared with baseline (Table 14) but there is no increase in MAP, which is necessary for a sympathetic response, i.e. activation. However, it is clear that during the presentation of her chosen calming music on this occasion, she responds in another way than the carers expected. She is not calmed or focused at all. Paula’s pO₂ is slightly higher but the pCO₂ is still far too high, which is known to irritate her brain and brainstem (neurophysiologist Peter Julu, personal conversation, Östersund, 2010). This response appears to suggest that she neither prefers nor responds in a calming way to this music, and it does not help her to reach a relaxed state. Her face expresses mixed signals that correspond well with the brainstem curves. She starts the last minute with AU4+AU6+AU12 (false smile) – 2 seconds (sec),

blank – 2 sec, a very quick smile AU6+AU12 – 1 sec, blank 10 sec, AU6+AU10+AU12 (false smile) – 9 sec and finally AU1+AU2+AU4+AU5+AU12 (fear) throughout the music. Her facial movement pattern is also present on and off, which provides information about the irritated brainstem and frequent ASBAs.

Figure 13 Brainstem assessment graph of the last minute of Paula’s favourite activating music, including blood gases



This recording (Figure 13) gives information about a slightly parasympathetic increase: a calming response instead of the expected activating response. The pO₂ increases from 60.0 mmHg up to 71 mmHg (Table 14), which is helpful in balancing the high pCO₂, but the pCO₂ is still far too high when compared with a non-clinical participant without pathology. She does not exhale well enough. The music is not doing the brainstem any good, but nor does it do her any harm. Looking at her facial expressions as representing emotions, she starts with AU1+AU10 (disgust) – 7 sec. At the same time an arousal response is observed on the monitor screens, and she continues with AU6+AU7+AU12 (smile) – 2 sec. But during this time her individual facial movement pattern is also involved, which tells us that the brainstem is firing. This is then not a proper smile. After these 2 sec, AU7 disappears and leaves only AU6+AU12 (smile) followed by a reduction

of her individual pattern – 1 sec and finally a genuine smile AU6+AU12+AU25+AU26 without her brainstem firing at all at the same time.

Summing up case vignette 1

Paula liked her activating favourite and she responded to it with positive emotions towards the end, but she was very much disturbed by abnormal brainstem activity. Her calming favourite was not calming in any way, and her activating favourite was slightly calming (parasympathetic response) instead of activating, but decreased her breathing pattern. None of her favourite music seemed to help her to reduce ASBAs or balance her blood gases on this occasion, but during her activating music there was a period at the end when the parasympathetic system managed to balance the blood pressure, pO₂ was slightly higher compared with baseline, there were no ASBAs, and she smiled with a genuine smile. None of her musical favourites are harmful, but the music that makes her smile genuine smiles instead of her individual movement patterns and increases her breathing is preferable.

4.7.2. Case vignette 2: Lisa

Lisa is a young woman with classical RTT, stage IV, and a typical mutation (R106W) on the MECP2 gene. She is classified as a feeble breather (2.3.2.), has clinical epilepsy and frequent ASBAs. In Lisa's life there is, and always has been, lots of music. Her parents and carers use music to activate her and to calm her down, as “medicine/first aid”, as signals and for sleep. Music is essential for her, both for communication and for leisure time. All through school Lisa has had individual music as remedial teaching once or twice a week and also music in a group. She listens to recorded music as well as live music, and everybody around her is used to singing to her and with her.

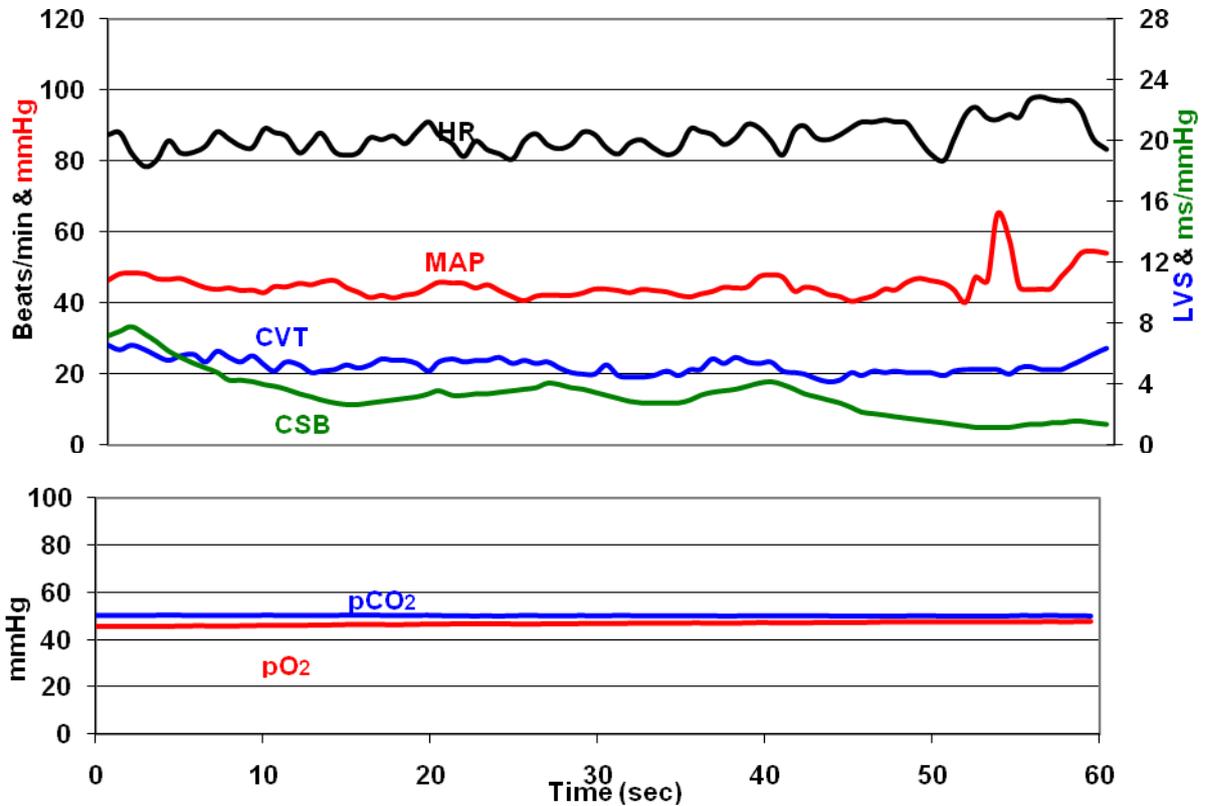
Table 15 Lisa's baseline and mean values from the last minute of calming and activating stimuli

Continuous variables	Baseline	Calming	Activating
CVT (LVS)	3.98 ²	3.24 ²	5.82 ¹
CSB (ms/mmHg)	2.40 ³	3.30 ³	3.70 ³
MAP (mmHg)	54.50 ³	45 ³	62.60 ³
MAP-CV (%)	not relevant	2.22	5.75
pO ₂ (mmHg)	62.30 ²	46.2 ³	65.2 ²
pCO ₂ (mmHg)	54.2 ⁴	50.1 ⁴	50.5 ⁴

Note. ¹ normal; ² normal for RTT; ³ too low; ⁴ too high (cut-off values, see Table 3).

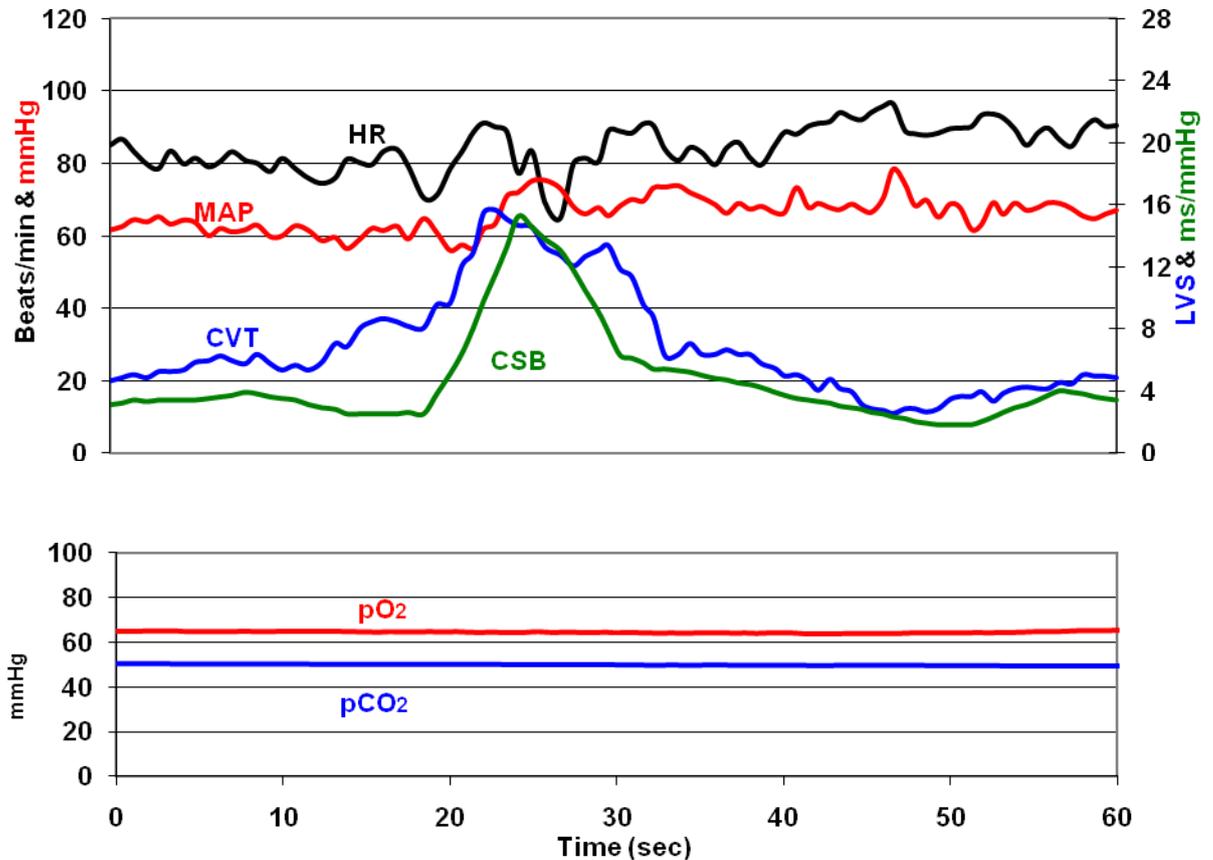
At baseline (Table 15) the CVT is in the lower end of what is normal for RTT, but CSB and MAP are low even for RTT. Her brainstem responds in a very immature way. Her CVT level shows that she *has* a capacity to calm down, but the very low CSB tells us that her heart has a weak ability to respond quickly to the signals from the brain. Her low MAP baseline value indicates that she also has a weak sympathetic drive. In other words, she has both poor sympathetic *and* parasympathetic potential. Lisa's pO₂ is acceptable, but the level of pCO₂ is far too high. Even if the brainstem is accustomed to this high pCO₂ level it is still a problem, as the high concentration irritates the brainstem and triggers off ASBAs. The correlation between high pCO₂ concentration and ASBAs can be observed during the assessment. In addition, the ASBAs affect pulse and blood pressure, which varies so much that it causes dizziness, instability and anxiety.

Figure 14 Brainstem assessment graph of the last minute of Lisa’s favourite calming music, including blood gases



During Lisa’s calming music her face is blank and she is very still. Not even her individual facial movement pattern (AU4+AU25+AU26) appears. Figure 14 shows that she responds with an increase in CSB, a parasympathetic (calming) increase, which is good for her – but not enough to balance her blood gases. Her breathing movements slow down and she becomes too relaxed. As a consequence her pO₂ level decreases from 62.30 to 46.2 (Table15) and the level of pCO₂ remains too high. When the pO₂ and pCO₂ are most equal, as in Figure 14, this elicits ASBAs and induces an epileptogenic pattern on the EEG that gives Lisa both a choking feeling and drowsiness. She is not ventilating as she needs to, in order to be adequately oxygenated and wash out pCO₂.

Figure 15 Brainstem assessment graph of the last minute of Lisa’s favourite activating music, including blood gases



These values (Figure 15) are in line with an activation of the upper and lower brainstem, and an unclear response; both a parasympathetic and a sympathetic response appear at the same time. Lisa also increases her breathing, which is good for getting rid of pCO₂, from the baseline value of 54.2, down to 50.5 (Table15). This response is very important for her, as it strengthens her parasympathetic system and at the same time increases her sympathetic system in a way that gives better balance in her blood gases and thereby reduces ASBAs. Comparing these findings with her facial activity gives a clear result. Her individual facial movement pattern immediately stops and instead she responds with AU6+AU12+AU25+AU26 (smile), which continues throughout the music. She also adds short vocal sounds (“ha, ha”) which together with the action units can be defined as a laugh.

Summing up case vignette 2

Lisa responded with a parasympathetic response to both favourites, but that response in itself was not enough to increase her breathing and thereby balance her blood gases to

prevent ASBAs. Activating music was good for her and gave her brain a short period of rest and time to replenish its reserves, and she also responded to her activating music with a genuine smile. It is worthy of note that this music was live music sung by her carers in a very interesting way. Lots of play, expectation, pauses, dynamic changes and communication through eye-contact went on between Lisa and her carers during the activating music. Lisa's response indicated that live music she recognised, in combination with personal interaction, is preferable to calming music, which seems to put her into too relaxed a state.

4.7.3. Case vignette 3: Felicia

Felicia has classical RTT, stage III, with no mutations identified, and she is classified as an apneustic breather (2.3.2.) with frequent ASBAs. She is a young woman who considers music to be one of the most important things in life, according to her parents. During childhood she worked with a music therapist (FMT method) but this did not work out very well. The family decided rather quickly not to continue with that therapy, and instead they started to use music in a structured way at home and at school. Both her class teacher and the music teacher were very sensitive to her signals and needs, so she was allowed to use music as she wished and according to her own needs.

Felicia likes to listen to recorded music as well as live music, and she lets everybody know if they play the wrong tune or the wrong recording. Her parents and carers use music to calm her, to activate her, "as medicine" and to make her feel well.

Table 16 Felicia's baseline and mean values from the last minute of calming and activating stimuli

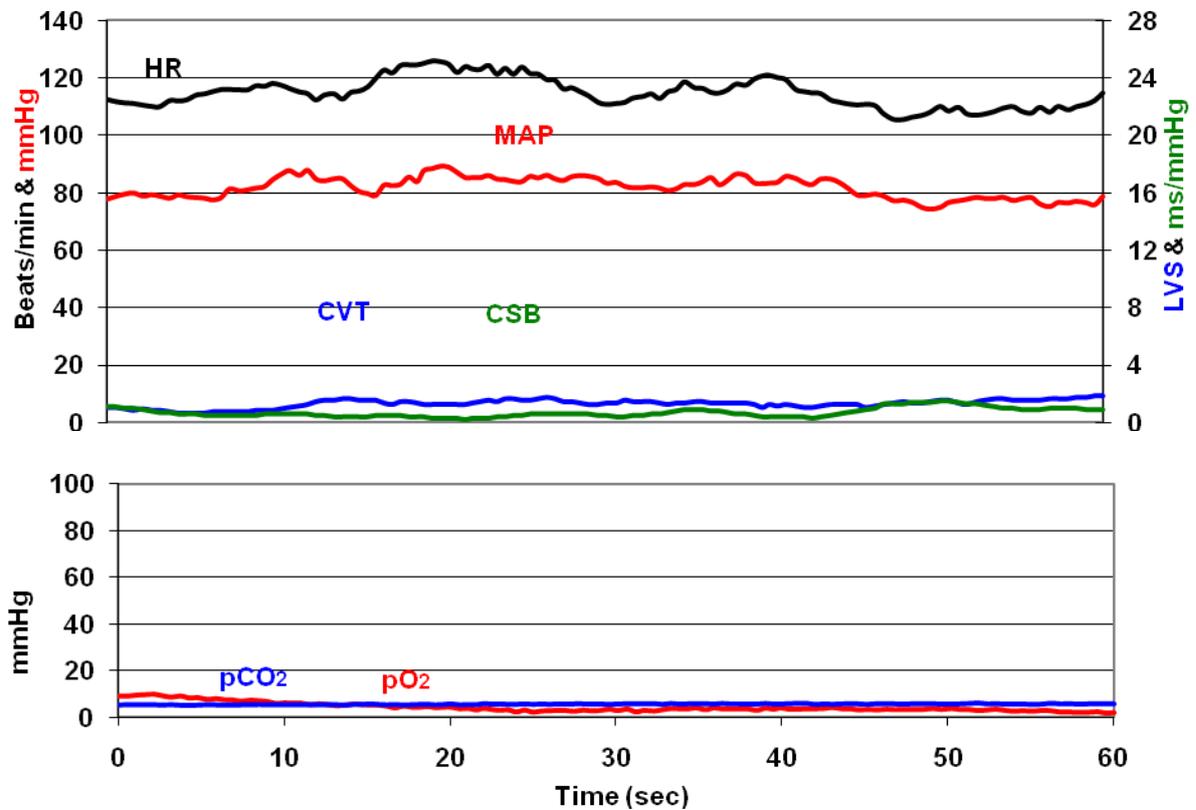
Continuous variables	Baseline	Calming	Activating
CVT (LVS)	1.36 ³	1.35 ³	2.43 ³
CSB (ms/mmHg)	0.9 ³	0.7 ³	1.6 ³
MAP (mmHg)	72.2 ²	81.8 ¹	73.5 ²
MAP-CV (%)	not relevant	4.40	5.75
pO ₂ (mmHg)	103 ¹	4.4 ^{3*}	29.8 ^{3*}
pCO ₂ (mmHg)	47 ⁴	5.4 ^{3*}	6 ^{3*}

Note 1 * The technique must be questioned when blood gases are as low as these.

Note 2. ¹ normal; ² normal for RTT; ³ too low; ⁴ too high (cut-off values, see Table 3).

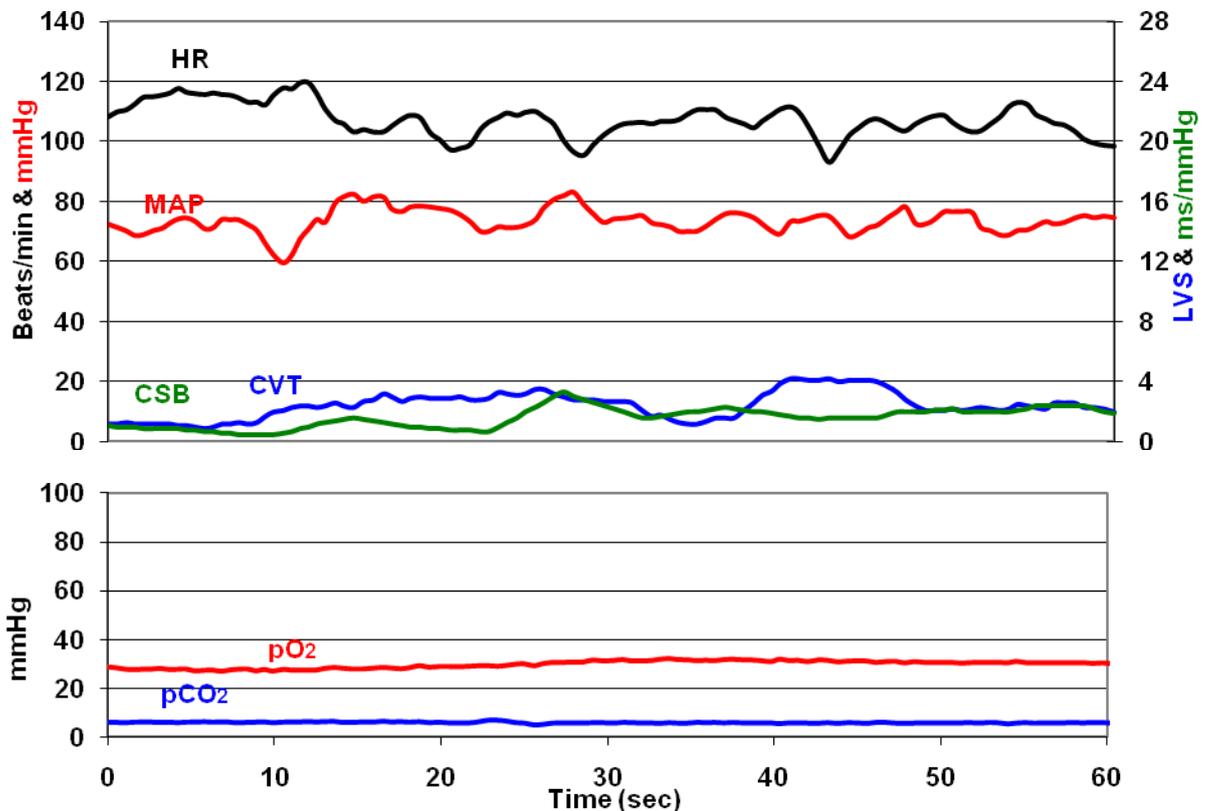
Felicia has a baseline (Table 16) CVT which is very low, and her CSB is also low. Both are lower than is usually found in people with RTT. Her MAP is normal for RTT but her CVT and CSB are too weak to be able to control her blood pressure. Her brainstem is very immature and therefore does not function very well when she is exposed to stress or sudden inputs. In spite of this, her pO₂ is within the normal range but her pCO₂ level is slightly too high, even for people with RTT.

Figure 16 Brainstem assessment graph of the last minute of Felicia's favourite calming music, including blood gases



During the calming music Felicia is very upset to begin with. She screams and she is really angry but in the last minute (Figure 16), when the mean values are taken (Table 16), she becomes still and quiet. No facial expressions can be coded. She does not respond to the music with either a parasympathetic or a sympathetic increase, but the pO₂ and pCO₂ give us information that her breathing is abnormal (Table 16), confirmed by the instruments monitoring her breathing pattern. She does not inhale deeply enough, which causes the extremely decreased pO₂. She exhales and then loses far too much pCO₂.

Figure 17 Brainstem assessment graph of the last minute of Felicia’s favourite activating music, including blood gases



During her activating music (Figure 17) Felicia responds with an immediate increase in both CVT and CSB compared with baseline (Table 16), which affects her blood pressure and pulse. This is a parasympathetic response and therefore good for her, as it helps her to balance her blood gases. Looking at her facial expressions, her individual pattern AU6+AU12+AU25+AU27 (smile) is observed almost from the very start to the end of the music. She also responds with rocking movements in pace with the music. Her blood gases are still not accurate, but it is important to get Felicia interested and happy enough so that she will take an active part in the music and move, which will help her to increase her breathing, wash out pCO₂ and increase oxygenation.

Her facial expressions are easy to misinterpret, and it is easy to mix up her sometimes false smile with a genuine smile because of the normal structure of her face (wrinkles and furrows). AU6 has to be present to constitute a real smile. If it is not there, the smile might be caused by abnormal brainstem activity and then it is not connected with emotions. It is important to notice this false smile, because it can be observed when Felicia has ASBAs and suddenly goes blank, as if she is taking a short pause. What is

happening is that all of a sudden her heart slows down, which may give her a feeling of missing beats and a sense of experiencing an air pocket.

Summing up case vignette 3

Felicia had a low baseline, indicating a poor brainstem function. Her calming favourite did not increase her parasympathetic system or her breathing on this occasion. She managed to increase her parasympathetic system when she was exposed to her activating favourite, which should have helped her to balance her blood gases. By observing her facial expressions she smiled almost from the very beginning to the end of her activating favourite, and she responded with rocking movements in pace with the music. She was happy and she was moving, which helped her to increase her breathing pattern. Music that she recognises and enjoys, music that makes her active, does her good, as it seems to increase her parasympathetic system and her breathing.

4.7.4. Case vignette 4: Liam

Liam's clinical development has been normal. He is a young boy who has had lots of music around him, both at home and during his time at preschool. His choice of music is primarily children's songs, but also pop and rock music. His parents are very observant and pay attention to his reactions when he responds to something played on the radio or TV.

Table 17 Liam's baseline and mean values from the last minute of calming and activating stimuli

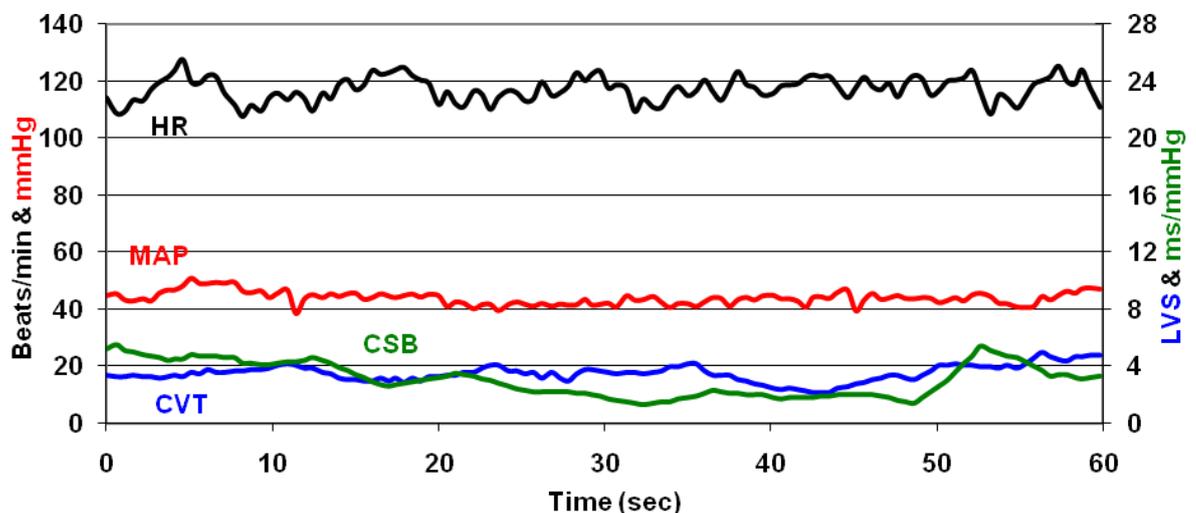
Continuous variables	Baseline	Calming	Activating
CVT (LVS)	3.87 ²	3.53 ²	3.65 ²
CSB (ms/mmHg)	4.3 ²	3.0 ¹	4.0 ²
MAP (mmHg)	46.7 ³	43.90 ³	45.80 ³
MAP-CV (%)	not relevant	5.01	6.98

Note 2. ¹ normal; ² normal for RTT; ³ too low; ⁴ too high (cut-off values, see Table 3).

From his baseline it is clear that his CVT, CSB and MAP are lower than normal (Table 17), but it is important to realise that these values represent normal, healthy *adults*. This study is the only one that has been done, so far, where it has been possible to monitor healthy children between 1 and 5 years old, and there are no normal values for children

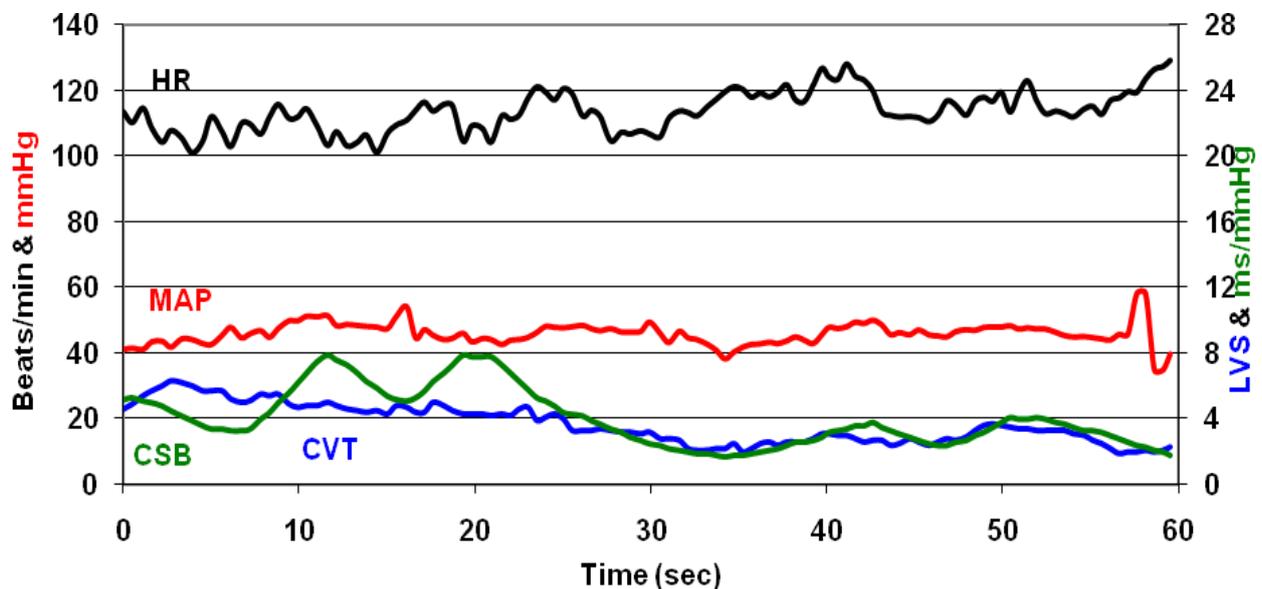
aged 1-5 years old. When Liam's baseline values are compared with the mean value for the non-clinical group in this study, his values are in the lower range also amongst this group, due to his low age. Values for pO₂ and pCO₂ could not be trusted due to technical problems, but we had no reason to believe that this would be abnormal in any way. The assumption is based on his normal development, his well-functioning brainstem parameters and his normal breathing pattern, which was registered during the brainstem assessment.

Figure 18 Brainstem assessment graph of the last minute of Liam's favourite calming music. No blood gases registered



When Liam is exposed to his calming favourite there is an immediate response in his face and a clear parasympathetic response which lasts for the first minute. But when the mean values from the last minute are monitored (Figure 18), there has been a decrease in CVT, CSB and MAP, compared with baseline (Table 17), which gives an unclear response. This response (a decrease in all parameters and a low baseline CSB) can be explained as a deactivation of the brainstem, which is a sign of immaturity. His initial facial expressions are AU1+AU12, which are equal to a false smile, and he ends up with AU12+AU25+AU26, which also indicates a false smile. Liam is attentive, he listens to the music and he communicates with his mother and his aunt by looking from one to the other and also looking at the CD player. His false smile might be a communicative smile to share the musical experience rather than an expression of emotional happiness.

Figure 19 Brainstem assessment graph of the last minute of Liam’s favourite activating music. No blood gases registered



As soon as the music starts Liam gives everybody a big genuine smile (AU6+AU12+AU25+AU26). The intensity of AU6 and AU12 is really strong, and the peak of his expression comes at the beginning of the chorus. In the first minute of the music there is a parasympathetic increase but in the last minute, when the mean value is taken (Figure 19), there is a decrease in CVT, CSB and MAP compared with baseline (Table 17). This is again a deactivation of the brainstem, a sign of immaturity. Liam is emotionally happy and this is a song he really likes.

Summing up case vignette 4

Liam responded to his activating favourite with a parasympathetic response and with genuine smiles. He managed to control his blood pressure, which indicated that even if he had rather low CVT, CSB and MAP his brainstem is mature enough to be able to control its functions. He was also able to use his facial expressions in two different ways: first as a way to communicate (*Calming*) and to share the musical experience, and in addition to this, also to share and communicate genuine happiness (*Activating*). Liam can very well listen to music as often as he likes; and even if his brainstem is immature, it functions well.

By comparing Paula, Lisa and Felicia with Liam it was clear that music had an obvious effect on all four of them, but also that there was a difference in their ability to control experienced responses, and how to communicate experienced emotions.

4.8. An analysis of the music used as stimuli in the study

The music used in this study was registered and can be found in Appendix 9. The register includes all details (wherever possible) about artists, composers, CD titles and numbers and category. Parents and carers were asked to bring two pieces of music that differed in character: one piece which was supposed to give an activating response, and another one with an expected calming response. They were instructed to bring music that was familiar and often played, and maybe actively used in different contexts and situations. In the dialogue with the parents and carers, it was clear that the participants' parents and carers were very stringent and exact in their choices compared with the parents of the non-clinical participants. Music is not used in the same way in the non-clinical group as in the RTT group, and therefore the parents were not sure about their children's favourites. The total number of pieces of calming music brought by the families was 31, and some pieces were chosen by two or more families. The total number of pieces of activating music brought by families was 35, and some of these pieces were also chosen by two or more families.

Table 18 The most common musical structures in activating and calming music, parents' and carers' choices

	Activating music	Calming music
Surface, Energy, mood		
<i>Volume:</i>		
Loud	9	2
Medium	26	19
Quiet	0	10
<i>Tempo:</i>	Mean 109.2 SD 20.36	Mean 75.8 SD 18.7
<i>Pace:</i>		
3	1	3
4	34	28
<i>Pulse:</i>		
Regular pulse	35	25
Free flow	0	4
Mixed	0	2
Timing:		
Pushing	10	4
Laid back	3	12
On beat	22	12
Not possible, ex. speech		3
Sound/timbre:		
Sharp	19	3
Medium sharp	15	9
Blending in	1	19
Rough	12	
Medium rough	21	6
Smooth	2	24
Not possible, ex. speech	0	1
Accented	19	4
Medium accentuated	15	8
Not accentuated	1	18
Not possible, ex. speech	0	1
Staccato	7	1
Medium staccato	26	8
Legato	2	21
Not possible ex. speech	0	1
Presence, Attention		
<i>Effects (can be more than one):</i>		
Hook	39	15
Break	27	10
Gimmick	30	12

Voice (can be more than one):		
Male	18	7
Female	12	12
Child	6	1
Solo	27	19
Group	15	3
Lyric	35	22
No lyric	0	9
Time/space:		
Non-directed	0	8
Medium directed	23	12
Forward-directed	12	10
Not possible, ex. speech		1
Coherence, memory		
<i>Melody:</i>		
Major	35	29
Minor	0	1
Modal	0	1
Short phrases	17	7
Medium long phrases	18	15
Long phrases	0	9
<i>Harmony:</i>		
Simple/predictable	29	13
Medium predictable	5	7
Varied/unpredictable	1	10
Not possible, ex. speech	0	1
<i>Structural form:</i>		
Predictable form	26	17
Medium predictable form	8	3
Unpredictable form	1	10
Not possible, ex. speech		1
<i>Features (can be more than one):</i>		
Repetitions	29	20
Sequencing	7	4
Call-response	9	2
Ready-steady-go	4	2
No form		3

TMA (Appendix 10) was used as the tool for music analyses. There were many common structures in the activating and calming music, but also some differences (Table 18). Medium volume, a non-syncopated and a regular pulse (on the beat) in 4/4 seemed to be the most common structures in both *Activating* and *Calming* but the tempo was mainly slower in the calming music. Hook, gimmick and break, in that order, were also important

for both *Activating* and *Calming*. However, there were also some differences mainly regarding *Sound/Timbre*. Sharp, medium rough, accentuated, medium accentuated and medium staccato were the characteristics that were most commonly found in *Activating*, whereas the characteristics of *Calming* were more “blending in”, smooth, not accented and legato. Other ingredients were also observed, but not to a common degree. Some further differences were found with regard to *Voice*, where the female solo voice was preferred in *Calming*, and the male solo voice was preferred in *Activating*, and also in *Coherence*, *Memory* where short and medium-long phrases dominated in *Activating*, whereas medium-long dominated and quite a few long phrases were found in *Calming*. There are seven different genres represented in the record of music (Appendix 9): children’s songs (38), pop songs (20), ballads & trad songs (4), stories (2), folk music (2), classical music (3), and relaxation music (7). In four cases parents and carers sang live, which gave a different response compared with the recorded music. It was obvious that the live music created a high level of attention and focus. This personal interaction makes a difference compared with recorded music alone.

4.8.1. The effect of musical structures on categorical brainstem responses and facial expressions

By combining observations from brainstem analyses, facial activity and musical structures it was obvious that the hook in the music caused the most apparent response with changes in brainstem activity and with real smiles, laughs and also focus and attention. Examples of hooks were: “I tell you what I want, what I really, really want, so tell me what you want, what you really, really want” (*Wannabe* with the Spice Girls), and “I’m never gonna say goodbye, ‘cause I never want to see you cry.” (*Swear it again* with Westlife). The gimmick was another ingredient in the musical structure that caused different observable changes in brainstem activity, as well as in facial expressions with real smiles, focus and attention. One example of a gimmick was an oboe that appeared all of a sudden in the musical structure in *Ti-Ti Nalla, Yön Värin* (with Riitta Korpela). Both hooks and gimmicks may give the music identity and call for attention without changing the character of the music, or the regular pulse or tempo. Hooks and gimmicks can be found in pop music, some children’s music and in some ballads & trad songs.

CHAPTER FIVE

5. Discussion

The discussion begins with a short summary of the main findings of the study followed by a discussion in relation to previous research and literature referred to in chapter 2. This is followed by a discussion of the design and methods used, as well as limitations, generalisation and the need for further research. Finally there will be a discussion of aspects related to clinical applications followed by reflections on the research process.

5.1. Short summary of the main findings

This current research showed that 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, which will be discussed in section 5.2.1. An immature brainstem, observed in RTT, is not capable of balancing functions of the autonomic nervous system (2.3.). When people 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 brainstem that happiness sometimes changed into a physiological condition of stress. To be able to avoid this transition, it is extremely important to be observant of changes in facial expressions. When analysing facial expressions it became clear that a majority of the individuals with RTT had a unique specific disorder-related movement pattern, which could easily be misinterpreted as expressions of emotions. These movement patterns (see section 4.7.1. and also 5.2.4.) seemed to originate from abnormal brainstem activation; they occurred spontaneously, and did not appear to express emotions. Individual movement patterns were not observed among the non-clinical participants.

From a clinical perspective the findings showed that, based on the correlation between results from brainstem assessment and FACS, it was possible to interpret facial expressions among the RTT participants and thereby hopefully diminish the risk of misinterpretation. This will be further discussed in section 5.7.

5.2. Discussion of findings

5.2.1. Continuous and categorical brainstem responses to musical stimuli

From the brainstem assessment it was obvious that the non-clinical group had higher CVT and CSB and significantly lower MAP values at baseline compared with the RTT group, even if the two groups were supposed to be matched with respect to brainstem maturity (Table 6, section 4.1.3.). These differences in baseline values affect the regulation of autonomic brainstem functions, but not necessarily the first responses to the musical stimulus. It was noticeable that all participants (both RTT and non-clinical participants) responded with an arousal to musical stimuli to begin with. This is a normal response, as the arousal system is the fundamental force in the nervous system (Pfaff, 2006) and the system that responds first of all. The main difference between the two groups appeared after some time. These findings were observed during the music analyses and responses to musical structures. The RTT group seemed to “stay with the music” to a greater extent compared with the non-clinical group, and the physiological response to the music also “stayed” for the RTT group.

The mean values used for the statistical analyses were taken during the last minute of each stimulus. By that time a majority of the non-clinical participants were focusing on something else (e.g. playing or looking around), while the RTT group still seemed to respond to the music. There were, however, individual exceptions in both groups. During the last minute, the RTT group responded to *Horn* (4.3.5.) with an arousal, in accordance with the hypotheses (2.6.). In the case of *Calming*, there was a significant increase in CVT, which is equal to a parasympathetic response (a calming response), and in line with the hypotheses. A sympathetic response (activation) was expected when the RTT group was exposed to *Activating*, but instead they responded with an arousal. During *VT*, the RTT group responded with a significant increase in CVT, which was also in accordance with the hypotheses. The combination of *VT* and *Mu* (*VT+Mu*) was expected to cause a stronger parasympathetic response than *VT* alone, but instead it caused an arousal, a decreased CSB. The results from *VT+Mu* also showed significant variability in MAP-CV, indicating that the brainstem had to work hard to defend a stable MAP, perhaps partly *due to* dual stimuli. It is reasonable to assume that it could be too much for an immature brainstem to balance two very different musical inputs, music and vibrations, at the same time. It could also be because of the music, as *Mu*, which was

chosen by the therapist, did not seem to give the expected parasympathetic increase. *Mu* did not cause any significant response in any continuous variables.

The non-clinical group was expected to respond in a similar way to the RTT group, but instead they responded with an arousal response to all musical stimuli. This means that only the response to *Horn* (a significant decrease in CSB) was in accordance with the hypotheses (2.6.). One reason for the differences between the groups might be the parents' and carers' choice of favourite music. Parents and carers of the RTT participants were often very clear about what favourite music to play (4.1.2.). They used the favourite music in many different ways, e.g. as "medicine", to activate and to calm down (Table 5, section 4.1.2.). The situation in the non-clinical group was totally different. Most of the parents explained that they did not really know what favourite music to play, as they did not need or use music in the same way as parents or carers in the RTT group. Thus they had not paid attention to exactly what music their children preferred.

By looking at the individual values it was possible to compare every participant with their own baseline, and then, from Table 2, to categorise the continuous variables into categorical brainstem responses. The information that emerged from that categorisation was slightly different from the general group results (see Table 9, section 4.4.). *Horn* was one clear example. By comparing means from continuous variables on group level it seemed as if the RTT group responded with an arousal (Table 8, section 4.3.5.), but by analysing individual responses it appeared that only 7% responded in that way. However, their responses were very strong, which had an effect on the statistics. An examination of the individual picture of categorical responses, revealed that 28% of the RTT participants responded to *Horn* with a parasympathetic increase (a calming response), and 24% with a sympathetic increase (an activating response), whereas 41% responded with an unclear response, which might very well imply an increase in *all* continuous variables.

Similar differences were found for all musical stimuli in both the RTT group and the non-clinical group. Without the analysis of individual categorical brainstem responses, these differences would not have been found. None of the answers to the formulated hypotheses are unambiguous, and this was also the reason for analysing the data in different ways.

There seem to be strengths and weaknesses in all methods for analysis, but by looking at the results from different angles, and thereby observing different pictures, there might be a better chance of finding out more about the situation as a whole.

Identification of individual categorical brainstem responses was also important for further analyses of brainstem responses related to interpretations of facial expressions and emotions, which will be discussed in sections 5.2.3. and 5.2.4.

5.2.2. *Brainstem assessments and findings in relation to previous research*

The results from this study support earlier research, which indicated that there are individual differences in how people with RTT respond to music, and that these responses are not always the ones expected (Bergström-Isacsson et al., 2007).

Interest in measuring physiological responses to music has grown over the years (2.3.3.). Different methods and different parameters have been used, and it is therefore difficult to compare the results. Cardiovascular, cerebrovascular and respiratory changes induced by music have been investigated in Italy (Bernardi, et al., 2006; Bernardi, et al., 2001).

Bernardi et al. stated that breathing rate, blood pressure and heart rate increased with faster tempi compared with baseline, and especially amongst musicians. This present study has not measured exactly the same parameters, but to some extent there are points of agreement. The parents' and carers' *choice* of activating music had a higher tempo (mean 109.2) than the calming music (mean 75.8), and all activating pieces had a regular beat, in accordance with what Bernardi et al. describe (Table 18, section 4.8). On the other hand, some results are contradictory. Some RTT participants, as well as non-clinical participants, responded differently, with a calming response (RTT participants 29%, non-clinical 20%), instead of an expected activating response (RTT participants 36%, non-clinical 36%), *irrespective* of the tempo in the music. Contradictory results were also seen in *Calming*, where some participants responded as expected with a calming response (RTT participants 39%, non-clinical 1%) and some with an activating response (RTT participants 29%, non-clinical 36%). These findings indicate that tempo and musical structure are not the only important parameters. There are probably more factors to take into consideration when it comes to physiological responses to music, such as brainstem maturity, musical preference and emotional responses that might include memories connected with the music.

The technique used at Karolinska Institutet (KI) in Stockholm (2.3.6.) to monitor breathing and cardiac abnormalities also differs from the one used in the present study (Rohdin, et al., 2007). The KI technique is also very detailed, but not to the same extent as the one used at the Rett Center. But as the KI technique allows measurement over time, the two methods might complement each other.

5.2.3. *Brainstem responses in relation to facial expressions and emotions*

All participants responded with an arousal (decrease in CSB) to all musical stimuli to begin with. These findings were observed, but not statistically analysed, during the music analyses and responses to musical structures. The next step was to see what happened after that first reaction, when emotions came into play. Sometimes these emotions might be related to cognitive processes. What story does this music tell? What kind of emotion is evoked by this song or this piece of music? This process may of course go on intentionally, but when it comes to participants with RTT and very young children, this cannot be taken for granted; it might also be an unconscious process. In either case the physiological reaction can be monitored during a brainstem assessment and interpreted with the help of facial expressions, but everything starts with an activation of the arousal system (Stern, 2010).

To be able to identify emotions in the RTT population, people in general mainly observe facial expressions. Findings from this study indicated that it was possible to identify emotional facial expressions, but it became clear that this requires knowledge about how to interpret the expressions in a reliable way. When observing facial expressions during brainstem assessments it seems reasonable that some facial expressions originate from abnormal brainstem activation, e.g. ASBAs (3.8.7.). ASBA is a condition whereby the brainstem neurons spontaneously depolarise, sending signals to different effector organs, including the heart, in an abnormal or erratic manner. This activation might appear at any time, not only when the individuals are exposed to external stimuli, and involves areas in the brainstem where nuclei steering facial muscles around the eyes, mouth, tongue and saliva are situated. ASBAs may elicit facial movement patterns, which are then caused by this abnormal brainstem activation. These individual movement patterns may not directly indicate the emotion that the uninitiated observer would interpret as emotion, but this may not be the right interpretation. However, this abnormal brainstem activation might also secondarily cause emotions such as anxiety and fear, although this is an ongoing philosophical discussion in neuroscience (Panksepp & Bernatzky, 2002; Peretz, 2010; Pfaff, 2006): What happens first, and what causes what?

During the analyses I found it possible to distinguish expressions caused by brainstem activation from emotional expression. This could be done by identifying individual movement patterns in combination with breathing rate, breathing patterns, dilated pupils, vocal sounds and “freezing” of the gaze and body. These were all important parameters to

study when interpreting emotional expressions in the RTT population. As people with RTT have difficulty communicating (2.1.4.), it is even more important that their signals are interpreted as correctly as possible. It is mainly through their emotional expressions that they receive confirmation, and can communicate in different situations and environments. Therefore everyone around them must observe both positive and negative emotional expressions if they are to understand and guide them in a proper way.

5.2.4. Facial expressions and emotions: findings in relation to previous research

Physiological responses have been investigated from different perspectives. Some of them are based on emotions and communicative expressions (2.3.3. and 2.4.3.). Interpretation of expressions has been carried out with the help of video recordings and microanalyses (Ekman, et al., 2002; Ekman & Rosenberg, 2005; Kim, et al., 2009; Sayette, et al., 2001) and specific observation techniques (i.e. protocols) (Hautaniemi, 2004). These are well-functioning methods for collecting data, but the findings could be interpreted in different ways. It is natural to look for changes in facial expressions when interpreting people's responses or mood. This is something we all do; it goes far back in human history (Darwin, 1872/1965) and at that time it was also a matter of survival. As a whole, people – researchers included – do not have the fundamental knowledge to interpret facial changes in a systematic and reliable way. We have all lost a great deal of knowledge. Today we survive without interpreting people's facial expressions, although we still use some of that understanding unconsciously. This is, however, not enough for research purposes.

FACS (Ekman, et al., 2002) is a known (especially in the area of psychology), useful and comprehensive method for analysing facial expressions, but the different codes are constructed to suit a population with normal development(2.4.3.). In the article by Defrin, Lotan & Pick (2006), the authors wrote about comparing two methods (FACS and NCCPC-R) to identify expressions of pain. The authors stated that NCCPC-R was a more sensitive method than FACS to observe changes in facial expressions at all levels of cognitive impairment. Their study did not include RTT, but they wrote about how participants with intellectual disabilities responded to pain by “freezing” – an expression they considered was difficult to code in FACS. Unfortunately the researchers did not use, or know about, the possibility of creating specific codes for that specific observed behaviour. This might not have changed their results, but the full potential of the method was not used.

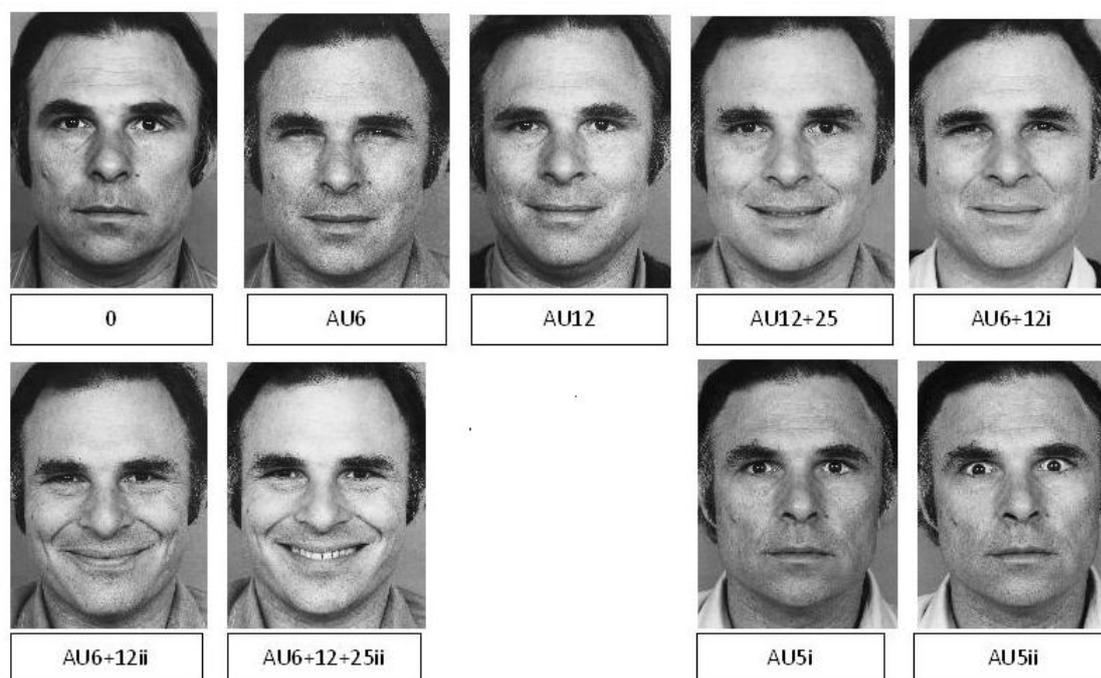
This present study is the first where FACS has been used as the main method to interpret facial activity and emotions amongst people with RTT. One important finding is that participants with RTT have individual facial movement patterns (4.7.), which are of great importance for coding and interpreting emotional expressions. A majority (55%) of the RTT participants had individual facial movement patterns which could easily be mistaken as emotional expressions if I had not been able to correlate with brainstem activities or a functioning method to analyse facial expressions. None of the non-clinical participants had these kinds of patterns.

For reliability purposes, 30% of all participants were coded by two trained FACS coders. Both coders identified the same facial movements but coded them slightly differently, probably because of diverse levels of experience of the syndrome. I had had many years of experience of RTT, but the independent observer was able to act in a truly objective way due to never having encountered people with RTT. Traditional FACS coding was used, but some departures from the manual have been used (see section 3.8.2. and 4.2.2.). The modifications were permissible because the AUs were sufficiently well identified for the purpose of reliable coding.

Hautaniemi (2004) described how she used facial expressions in her research, but she also added body movements as an important factor (2.4.4.). She did not find it difficult to distinguish a rich repertoire of emotions among seriously disabled children. It has been discussed how impossible it is for severely disabled people to show false facial expressions, to pretend, because of their limited cognitive ability (Vetenskapsrådet & Forskning.se, 2005). I partly agree with this, but when relating to the findings in this present study about individual facial movement patterns, there is some doubt. It is clear that even parents of participants with RTT have misinterpreted facial expressions because of, amongst other things, their individual patterns. Expressions that are automatically elicited from the brainstem could very well be called false. In that case the group of severely disabled people do indeed show false expressions, but *not* with an intention to pretend or express something false.

It is not easy to distinguish a “false smile” from a genuine smile. Figure 20, photos reproduced from the FACS manual, illustrates some AUs involved (Ekman, et al., 2002). 0 is a neutral face (the person’s baseline), which is important to have as a comparison. AU6 is called “cheek raiser”, which draws the skin towards the eye from the temple and cheeks as the outer band of muscle around the eye contracts. AU6 also raises the

infraorbital triangle, lifting the cheek upwards. AU12 is a “lip corner puller”, pulling the corner of the lips back and upward. For it to be a genuine smile, both of those have to appear together (AU6+AU12). AU25 (“lip part”) could also be involved (AU6+AU12+AU25). The level of intensity (i or ii added after the code) of the emotion also changes the intensity of the facial expression, in this case the smile. AU5i (AU5ii is stronger) is called “upper lid raiser”. This is when the upper eyelid is raised so that some of the eyeball outside the iris is visible. This AU is involved when a person is frightened, anxious or suddenly surprised. If that AU appears together with one of AU6+AU12 (+AU25), or in that combination, then it is *not* a genuine smile. When the level of intensity of AU5 was low it was easy to miss it, and instead interpret the above-mentioned combination as a genuine smile. This combination, AU5+AU6+AU12+AU25, was observed in RTT participants and not in non-clinical participants. The combination was related to an obvious sympathetic response (an activating response) when comparing the AU combination with results from the brainstem assessment.



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Figure 20 Important FACS codes involved in the difference between a genuine smile and a false smile

A sympathetic (activating) response is neither positive nor negative in itself. It is simply a physiological explanation of what is going on in the autonomic nervous system, but it

could be negative if the nervous system is unable to balance this activating response with a well-functioning brake system. We know that the baseline values for continuous variables are low (Table 6, section 4.1.3.) in the RTT group, approximately 50% lower in comparison with the non-clinical participants, which affects their ability to balance the autonomic nervous system. This brainstem dysfunction that is known in the RTT population could very well be the reason for the combination of AUs (AU5+AU6+AU12+AU25) being observed only in RTT.

One example might help to illustrate how easy it could be to misinterpret a smile – and I use the smile as an example because it is what we generally look for as an expression of happiness and comfort, and in communicative situations.

Favourite music elicits a genuine smile (AU6+AU12 (+AU25)) to begin with. After a while AU5i appears in the face, and the smile has suddenly changed to something else, even though this is hardly noticeable as the rest of the AUs are still there. The expression might change even more if AU6 disappears as well, which is most certainly will. Since the smile started as a genuine smile, and since AU12 (+AU25) is still present, and AU6 disappears after a while, it is easy to interpret this as an ongoing smile. The reason for this change might be that the brainstem was unable to balance a sympathetic response, to hinder MAP and MAP-CV from increasing too much, due to low CSB and CVT. If a sympathetic response increases without control it might very well cause an experience of stress which, in this case, was identified by observing that AU5 appears and AU6 disappears.

5.3. Discussion of the importance and the use of music in Rett syndrome

Music seems to be one of the most important ingredients in life for people with RTT, and for other specific neurological disorders such as Williams syndrome (Korenberg, Bellugi, Salandanan, Mills, & Reiss; Levitin & Bellugi, 1998; Merker & Wallin, 2001; Sacks, 2008). However, nothing is known about the reason for this, only that both one gene in the X-chromosome and several in chromosome 7 are important for the individual's interest in, and experience of music. This study included questions to parents and carers about how music was used. Almost all of the participants with RTT in this study (93%) used music in one way or another (4.1.2.). Music was also important for children in the non-clinical group (63%). Parents and carers described how they used music as a “drug” when nothing else seemed to help, in situations of anxiety, self-destructiveness, anger, fear and sadness.

Earlier research has described the importance of music and communication in numerous articles, and this is confirmed in the present study (Elefant, 2002; Trevarthen & Burford, 2001; Wigram & Elefant, 2009). The importance of music and responses to it indicate that the parts of the brain which receive and process music seem, according to the current study, to be intact in people with RTT, which may be one explanation for music being so important throughout life. However, neither *control* of the responses, nor ways of expressing feelings, emotion and body sensations evoked by music, are intact. In the literature there are numerous reports on how music is and should be used in relation to people with RTT (Coleman & Handsell, 1988; Elefant & Lotan, 2004; Elefant & Wigram, 2005; Hill, 1997; Houtaling, 2003; Lindberg, 2006; Merker, et al., 2001; Montague, 1988; Rett, 1982; Sigafos, et al., 2009; Sigafos, Laurie, & Pennell, 1996; Trevarthen & Burford, 1995, 2001; Wesecky, 1986; Wigram & Weekes, 1985a; Wigram & Elefant, 2009; Yasuhara & Sugiyama, 2001). I agree with the view of these authors on the importance of music, and how music could be used as motivation, as “medicine”, in communication, and for learning. However, hopefully this study, using both neurophysiological methods and FACS, can contribute with widened knowledge about the importance of *interpreting* expressed responses in general, but also to music being used in a better and more accurate way.

The literature presented in this study explains in section 2.3.2. the processes children are exposed to and how music affects the brain when they are very young, and even before birth (Berger & Schneck, 2003; Bergström-Isacsson, et al., 2007; Merker, et al., 2001; Merker & Wallin, 2001; Taylor, 2002). In most families, it seems that music, especially live music and rhythmical movements, is more important in relation to babies (Eckerdal & Merker, 2009), and it seems natural for parents to sing to their baby, even if singing is unusual in other situations. Parents’ voices change and become softer and more “musical”. Rocking movements are used, often in a stable tempo to establish comfort and security, and music is also used as an important way to communicate. These phenomena affect children and create a platform for interaction, communication, and musical preferences. In this period of children’s lives, parents do not know that their child might have RTT because the baby responds in the same way as any child. This “musical way” to communicate is important for all of us, but might be even more important for children with RTT. Even if the interest in music might be related to the genetic mutation in RTT, as mentioned above, the importance of music can also include other explanations.

Children with RTT have a regression period in life (2.1.1.), when they become anxious and generally lose many of their acquired abilities and functions, but the importance and function of music seems to remain. One can then speculate on the importance of music, what the music stands for, and how music was used during the first period in life when the parents did not know that their child had RTT. Maybe music can be looked upon as a stable base for a person with RTT to rely on, something that remains when many other things in their life suddenly change. Music might then be emotionally related to comfort, closeness and safety (a safe space), and can thereby later be used as a resource to create and recognise that safe space.

As music is obviously such a strong tool in relation to people with RTT, it can also be used as an effective form of intervention in different areas and for different reasons (2.4.4.). It is used by therapists, teachers, parents and carers (Bergström-Isacsson & Larsson, 2008; Grocke & Wigram, 2007; Wigram, et al., 2002). In this current study, 31% of parents and carers described that they sometimes used music as a signal for new activities (see Table 5, section 4.1.2.), as a way to illustrate what is coming next. None of the non-clinical subjects used music in this way. Again it is clear that music is a helpful aid for the RTT group and is used as a “language” in communication and also for understanding the world. For people with RTT it is necessary to use non-verbal tools which might also provide some information about their cognitive level. There are ongoing discussions about the cognitive level of people with RTT, but as long as verbal instructions are not enough, the level of understanding is clearly lower than normal, but of course with individual variations. This discussion concerning cognitive level is necessary, as it is difficult to use traditional test instruments, and this gives scope for speculation. There is no doubt that people with RTT are sensitive to a variety of input, and this is one reason why music can be used as described above. What this current study reports, and earlier research also shows, is the poor regulation of brainstem responses to different kinds of input, including music (Bergström-Isacsson, et al., 2007; Julu, 2001). Therefore it is relevant to wonder what effect all the music around us has? There is music going on everywhere: in shops, waiting rooms, lifts, at home, in buses and taxis, to mention only a few locations. Most of us with normal and well-functioning regulation of input can switch off, choose not to listen, and focus on something else if we are in situations where we cannot turn the music off. In people with poor regulation of the autonomic nervous system, as in RTT, this is probably impossible. All input seems to remain, which can

create an inner chaos. In the results from this research study it becomes clear that the RTT group “stays with the music” in a different way compared with the non-clinical participants, and I do not think the situation is very different in their daily life compared with this experimental situation. They might get used to the music situation at home, but they are strongly affected by all musical input when they are not at home. Nevertheless, this global musical environment is the reality. This general exposure to music of all kinds might explain why people with RTT suddenly display anger, anxiety and fear, as well as sudden laughs and joy, when they are in different environments.

It is well known that music is made up of vibrations that we hear, but low frequency sound is also used as a musical stimulus. Earlier research describes how low frequency sound affects humans in a dual way, both physiologically and psychologically (Bergström-Isacsson, et al., 2007; Hooper, 2002; Skille, 1991; Wigram, 1996; Wigram & Dileo-Maranto, 1997b). VT is also a treatment method that has been used in RTT both in England and in Sweden. The RTT group in this present study responded to 40Hz with a significant parasympathetic increase (calming effect), even if sympathetic increase was also observed among a few. This result confirms findings from an earlier study (Bergström-Isacsson, et al., 2007), but by analysing findings from different angles this current study shows that there are obvious individual variations. VT affects humans, but the experiences are very subjective.

5.3.1. Music analysis

There are models for analysing music where the aim is to understand how musical structure affects us, and what ingredients to look for when choosing music, if for instance we want something relaxing or stimulating (Aare, Grønager, & Rønnenfelt, 2003; Dileo & Bradt, 2005; Gabrielsson & Lindström, 2001; Grocke & Wigram, 2007; Hooper, 2003, 2010; Juslin & Sloboda, 2001; Juslin & Sloboda, 2010). They are all very detailed and well thought-out (2.5.2.). However, it has been difficult to use these analytical methods in this current study. One reason was the need to look at children’s music and pop music. The most helpful model was the one produced by Aare et al. (2003), and with some modifications the recently designed tool, TMA (Tool for Music Analyses), provided the information needed (4.8.).

There was no difference between clinical and non-clinical groups when it came to musical preference reported by Elefant (2002). The overall chi-square test in this study confirmed that the responses were not randomly distributed ($p < 0.001$), which might

indicate that people with RTT indeed have intentionality and music preference. But children's music is important also for adults with RTT. This has been confirmed in earlier research, but these reports do not say that adults with RTT only like children's music (Houtaling, 2003; Merker, et al., 2001); they listen to other kinds of music as well, if they have been introduced to other genres, but the songs they heard as children often remain important throughout their lives. Important ingredients in the music for both groups seem to be the hook, something that the listener immediately notices and remembers, regularly pulsed music (on the beat), major key and lyrics (4.8.). Another important detail is that live music seems to create another level of attention and focus compared with recorded music. This might be due to the interaction between performer and listener, which became very clear in the results from one of the RTT participants when the carers sang to her (4.7.2.). Similar findings were also observed in three other cases, even if the responses were not so obvious.

5.4. Discussion of research design and methods

This experimental study was designed as both a between-groups and a within-subject study. The groups were matched with respect to brainstem maturity, and data were collected during a brainstem assessment using the NeuroScope for measuring all physiological data, an EEG machine and two video cameras. The NeuroScope technique has been used in music therapy research once before (Bergström-Isacsson, Julu & Witt Engerström, 2007), but this is the first time a complete research study including music, VT, and facial expressions has been carried out. To eliminate any effects of order, the six different musical stimuli were randomly ordered and there was a wash-out period between each stimulus. The aim was to explore autonomic brainstem activity and emotional behaviour in response to music and vibroacoustic stimulation in participants with RTT. The same analysis was made of a non-clinical comparison group with a normal developmental pattern. Analyses of continuous brainstem responses at group level gave general and overall results, but these results were not sufficiently detailed for clinical application. It was therefore necessary to analyse data on an individual level. This process made it possible to compare results within subjects and between groups.

When starting to analyse the individuals with RTT in detail for the vignettes, it became evident how important balanced blood gases were for all of them. The RTT population generally have difficulties in regulating blood gases, due to breathing abnormalities, and Lisa was one clear example of this (4.7.2.). In her case, music and VT affected both

parasympathetic and sympathetic activity. The findings indicated that a parasympathetic increase was not enough. Lisa needed increased sympathetic activity as well to be able to increase her breathing pattern and thereby regulate her blood gases.

Another aim was also to analyse the participants' facial expressions in detail to find out if it was possible to observe whether they purely expressed effects of brainstem responses (e.g. individual movement patterns due to abnormal brainstem activity) or emotional expressions. This was carried out using FACS, a validated and established research method for identifying genuine emotional facial expressions (Ekman, et al., 2002). All parameters were time-synchronised, which made it possible to go back and study, and correlate everything in detail.

Analysis of facial expressions using FACS has not previously been used in combination with brainstem assessment. FACS is also a new method when investigating emotional responses to music in an RTT population. It has been shown that it could be difficult to trust the facial expressions seen in people with RTT without careful surveillance. For a valid observation, a detailed analysis is extremely important. It is necessary to study the participants' normal expressions, their individual facial movement patterns, and also have clinical experience of that group before it is possible to correctly judge their emotional expressions. This knowledge is of great importance, as the emotions of people with RTT are interpreted mainly through their facial expressions.

TMA was used as the method to analyse the music (Appendix 10 and 4.8.). Music analyses were not included in the main research questions, but were nevertheless important, as favourite music is something that is frequently used among the RTT population. Over the years there have been discussions about what kind of music they prefer, but also what music they should be offered (Elefant, 2002; Houtaling, 2003; Merker, et al., 2001). The analyses in the present study served to briefly identify differences and similarities in musical structure between activating and calming music, and, where possible, to identify changes in brainstem responses following the structure of the music. TMA is not a very detailed method, but it gave the necessary information for this research study.

5.4.1. Technical equipment

Brainstem assessment using the NeuroScope has been carried out in medicine and research (Bergström-Isacsson, et al., 2007; Julu, 1993; Julu, et al., 2003; Julu, et al., 2001; Julu, et al., 2008; Ming, et al., 2005; Ming, et al., 2004), which guarantees the technique,

even though it could be further developed (3.6.1.). It is a stressful procedure to put all the electrodes and breathing belt on the participant, and it is uncomfortable to wear the EEG cap and to have all the wires hanging around the body. All the leads connected to recording machines and the finger cuff measuring blood pressure limited the participants' ability to move. There is a risk that the patch does not achieve top quality contact, and this actually happened in the case of a few individuals. However, this is, today, the only continuous non-invasive technique available.

It is also difficult to establish an ideal situation in the assessment room. Many people are present, all the necessary technical equipment and many things have to be discussed during the procedure. It is therefore extremely important to use video recordings, and then identify disturbing events that may have had some influence on the data collected.

5.5. Limitations and generalisation

The methods used in this study, the results and the conclusions that are drawn are inevitably subject to different limitations that need to be critically reviewed.

Sample size is one issue that needs to be taken into account. There were 35 individuals with RTT included in the study, 6 of whom were excluded. Obviously a sample of 29 individuals, who were not randomly chosen, cannot be generalised and does not represent the RTT population. The results relate only to this sample.

Normally developed children aged between 1 and 5 years, the non-clinical participants, were recruited as comparisons. The RTT group and the non-clinical group were supposed to be matched with respect to brainstem maturity. However, the results showed that the brainstem was more immature among the RTT participants. For a complete match, the non-clinical group should therefore have been even younger. Children under the age of 1 were not chosen both for technical reasons, and because of unknown musical preferences. Parents of children under the age of 1 might not have thought about activating or calming favourites, but results from this present study showed that musical preference was difficult also in children who were 1-5 years old.

The technique used in this study has been used for brainstem assessment over the last 20 years and has functioned well. However, there are technical details which can be further improved, e.g. the finger cuff (blood pressure) and the patch (blood gases). It is also worth discussing that this is far from a natural situation. The assessment is laboratory-like, a new and strange situation for the participants, with new technical equipment, wires connected to the body, and unknown people in the room.

From the start, the method for analysing facial expressions in the study had not been chosen, which had an impact on the video recording. Some video excerpts were not sufficiently focused on the participant's face and thus not optimal for FACS coding. The analyses of facial expressions were difficult, and took a very long time due to the low quality of the video recording. This might also have had an impact on the results.

Detailed analyses of facial expressions using FACS have never been tested in an RTT population before. The EEG cap among the RTT group affected the FACS coding as it hindered identification of muscle activity, especially in the upper face. In this current study it was necessary to use the cap because the assessment was carried out for specific medical reasons on the RTT group.

There was a clear difference between coding the RTT group compared with the non-clinical group. There was 62% agreement in the reliability test for the RTT group, compared with 89% in the non-clinical group. Reasons for this difference might be that the EEG cap restricted upper facial muscular movements, but also because of the researcher's and the independent coder's different experience of RTT.

TMA, the tool for music analyses, had not been standardised or tested before, which is a factor that has to be taken into consideration. It was designed to be able to analyse a variety of music, mainly pop music and children songs, but also music from other genres. This seems to be a good enough tool that could very well be used in other contexts as it includes ingredients that are useful for analysing pop, rock and children songs, but it is not detailed enough for analysing complex musical structures.

Brainstem assessment and FACS have been found appropriate for the RTT population and for comparisons with the non-clinical group. As mentioned earlier, FACS and the combination of brainstem assessment and FACS were new methods and have never been connected before, either in RTT or any other research. This methodology could very well be used in other target groups with or without disabilities.

5.6. Recommendations for further research

The findings from this present study show that music affects brainstem control functions in RTT, which confirms findings from an earlier study (Bergström-Isacsson, et al., 2007), but further research is needed to determine whether these results could be generalised to a wider population. In further research blood gases should be monitored and analysed as continuous variables.

In this current study the mean values from the last minute were used for all musical stimuli. It would have been interesting to include the mean values from the first minute, especially in the comparison between the RTT group and the non-clinical group, but also between the participants. In addition, the facial expressions from the first minute should then have been coded in detail.

FACS itself, and also 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. Such research could also include Baby FACS and comparing both methods when scoring participants with RTT. We know that the RTT population has an immature brain and brainstem (Julu & Witt Engerström, 2005), which might also affect their facial expressions.

Another very interesting area would be to investigate differences in brainstem responses, facial expressions and emotional expressions in music therapy compared with findings from this experimental research study. A wireless version of the NeuroScope must then be developed.

The children in the age span 1-5 years old included in this actual study are the first ones ever to be examined with the NeuroScope. It is necessary to collect more data to find out about normal values for this age group and to be able to draw proper conclusions in comparison with RTT. A recommendation for further research might therefore be to include a larger sample of non-clinical participants. The findings of this research indicated that the RTT population are limited in their responses, but the non-clinical participants varied more.

An incidental finding was that there was a difference in responses to live music vs. recorded music. Live music seemed to create another level of attention and focus, as well as interactions and communication in music. Therefore recommendations for further research could be to look more carefully at the difference between using receptive and active music (in and outside music therapy) and between the two conditions.

This study has given us some new insight into how to understand RTT, but RTT research is an ongoing area for research, and revised diagnostic criteria were formulated and suggested in 2010 (Jeffrey et al., 2010).

5.7. Clinical applicability

To be able to clearly identify responses of RTT participants to music, it would be desirable to first of all identify what kind of breathing phenotype the persons belong to,

according to Julu. There are clear differences between feeble breathers, apneustic breathers and forceful breathers in how they are able to balance their blood gases (see section 2.3.2.) (Julu & Witt Engerström, 2005). The detailed cases described in section 4.7 showed that it is good to observe continuous or categorical brainstem responses, but that is better to also include blood gases, breathing movements, facial activity and emotional changes in the analysis, to be able to understand the participants' state of well-being. Lisa is, as mentioned before, one evident example (4.7.2.). She responded with a parasympathetic increase, she was attentive and concentrated, and she listened to her favourite calming music. She liked the music, but the problem was that she became too relaxed. It was not sufficient to interpret her response by looking at her face. But by observing her breathing in a more detailed way, also knowing she was a feeble breather, it was possible to notice her slower and shallower breathing movements, and thereby a deteriorated balance in blood gases. When Lisa listened to her activating favourite the response was different. She still responded with a parasympathetic increase, but also with a sympathetic increase *and* with an increased (deeper) breathing. This was music that activated her communication, interaction and body movements, and restored more normal blood gas pressures. She liked this activating favourite very much, and she smiled with a true smile and also laughed (AU6+AU12+AU25+AU26). This was live music sung by her carers, and it is impossible to tell whether it was the song in itself, or the fact that the carers sang the song to her in a very interesting and playful way. It should be noted that the carers always used to sing this song to her in this way, so it was not something they did only in the experiment situation. She was responding to her favourite music in, what was for her, a good way. With this knowledge it was possible to recommend to Lisa's parent and carers that they pay more attention to her breathing, changes in facial expressions, and her level of activity. Lisa responded with a parasympathetic increase to all musical stimuli, but the only stimulus that also increased her drive (sympathetic system) was *Activating*. The way she responded to her activating music, is the kind of response worth looking for in *any* activity. Lisa needs help to keep her level of arousal up, she needs activation and she needs a good laugh that would normalise her blood gases. But Lisa's laugh is also highly important, as it is an expression of genuine happiness. She cannot be active and laugh all the time, but this might be a way of regularly giving her body and brain some time to rest and replenish its reserves (Pfaff, 2006).

Felicia sometimes “smiled” to herself (4.7.3.). Her parents and carers could not understand why, but they all assumed that she was alright, and that she was satisfied. All of a sudden she could get upset and nobody could understand why. By combining the results from the brainstem assessment with her facial expressions it was shown that a false smile (AU12+AU25+AU27) was correlated to her ASBAs. She was not at all satisfied, and her ASBAs were most likely the reason why she suddenly got upset. This information made it possible for Felicia’s parents and carers to understand her and her sometimes strange behaviour. They understood why she was upset, and they were also informed about how to distinguish a false smile from a true smile.

5.7.1. *Recommendations*

It is difficult to understand how individuals with RTT really respond to music, VT, or to any stimuli. It is certainly desirable to carry out a detailed brainstem assessment to obtain basic information and to clarify breathing phenotype. By combining the results from the brainstem assessment with observations of facial expressions, identifying individual facial movement patterns, and comparing them with emotional facial expressions, it might be possible to find the key to understanding and interpreting different expressions in people with RTT.

This study indicates that it is crucial to pay attention to all the small details one by one, but also to look at the findings together to gain a better overall understanding. Music is without doubt very important for people with RTT, and a tool well worth using in many situations and activities. Music is a tremendous motivator and sometimes it seems as if it is the only working language. Individuals with RTT are very sensitive to musical input and most likely respond normally to musical input to begin with. However, their immature brainstem makes it difficult for them to control their responses and emotions caused by the music, and they seem to “hang onto” the musical stimulus to a higher degree compared with normally developed children. RTT participants cannot move on to something else, and seem to be unable to ignore the music they are exposed to. However, sometimes people with RTT may *want* to stay with the music and sometimes they may not. It is not realistic to recommend brainstem assessment to *all* individuals with RTT, and it is furthermore impossible to monitor data continuously. But *knowledge* about the importance of detailed observations of dilated pupils, blushing, increased or decreased breathing movements, blue lips, and identifying individual facial movement patterns is one first important step. The next step is to compare these observations with true

emotional facial expressions, body movements, focus and attentiveness. The necessity of these detailed combinations of observations is one of the findings of this present study, and hopefully this knowledge might be something that parents, carers, therapists, teachers and doctors can benefit from when caring for people with RTT.

5.8. Reflections on the doctoral process

Undertaking doctoral research training has been a learning process, and also challenging in many ways. My research area was clear right from the beginning, as I wanted to investigate if it was possible to replicate the findings from my Master's thesis in the same population but in another subject group. I also wanted to investigate whether the group with RTT responded to musical stimuli in the same way as normally developed children. The technique for data collection, the brainstem assessment, was already available at the Swedish Rett Center, and so was the selection of musical stimuli. This made it possible for me to start collecting data more or less immediately.

The Swedish Rett Center had many patients coming from all the Nordic countries during the period for my data collection, which was a gold mine for me. Data collection from the non-clinical participants was carried out in parallel.

Each stage during the process had its challenges but the actual brainstem assessment was the easiest part, as I had previously participated in that procedure as a member of the medical team at the Rett Center.

The next step, identification of the data points (the mean values of continuous brainstem responses from the last minute of all musical stimuli) gave me the opportunity to learn how to use a complex computer program, TONE. During that period, Dr Peter Julu and clinical scientist Stig Hansen PhD helped me a great deal and showed considerable patience.

One of the findings from my Master's study was the difficulty of observing on the outside of the participants what was going on inside. Interpretations of facial expressions by relatives and therapists (myself included) were not always correct. During this doctoral study I wanted to try to find a way to analyse facial expressions and hopefully be able to help parents, carers and therapists to be more precise in interpreting facial expressions that reflect emotions. I began by constructing my own differentiation between facial expressions of e.g. a real smile and a false smile. I tested my formulations and descriptions in the Aalborg PhD group, and found out that this tool was not even close to being good enough. This was frustrating, and it took me some time to find an analytical

method that was useful: FACS, Facial Action Coding System. To be allowed to use FACS in research, I had to learn the method in detail, and also pass the Final Test for FACS coders. This learning process was difficult but at the same time very interesting. The knowledge was invaluable for this research study, but also valuable for my future work, both clinically and in research.

The next thing I had to deal with was finding a way to analyse the facial expressions. All video films were stored in an EEG machine, and unfortunately that format was impossible to transform, which left me with only one solution – I had to find a way to mark and do the analyses in the EEG machine instead of my own computer. I managed to solve that problem together with the clinical scientist, but again, there was new technical equipment which I had to learn how to use, and this took time. It was possible to carry out the final and overall analyses in the EEG machine as the video films were time-synchronised with the recording of the continuous brainstem responses together with music. So in the end the fact that the EEG videos were not transformed into another format proved to be a good thing after all after all.

I was challenged by having to learn and master new skills throughout the research process. Apart from the ones mentioned above, there were skills such as: using a new program for statistical analyses, and improving my general computer knowledge, my English, my writing and my analysis of music.

During the research process I have also been forced, or had the opportunity, to delve deep into areas far from my own basic training such as neurophysiology and medicine. I am, however, fully aware that my knowledge in neurophysiology and medicine is still strictly limited.

Being part of the PhD programme at Aalborg University has been another important factor, which has contributed to my development as a researcher. It has been a great privilege to be in active dialogue with music therapy colleagues from all over the world. Our enriching discussions have definitely broadened my perspectives. Sometimes the process has been frustrating, but good support from supervisors and others involved has made it possible for me to find my way in the end.

5.9. 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. It seemed as if these movement patterns

were elicited by sudden abnormal brainstem activity (ASBAs). These movement patterns occurred spontaneously and may not 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 assessments 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 the RTT participants responded to different kinds of music in a variety of ways, similar to the non-clinical participants with a basically 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 were differences in how they responded to the stimuli over time.

The RTT participants responded with attention. Some of them looked for the musical source, and some of them looked at their parents, but the main difference compared with the non-clinical group was that they generally seemed to “hold onto” the music. The RTT group did not ignore the music to the same extent as the non-clinical participants. Music seemed to be more important to the RTT participants, something to hold onto, or maybe they simply could not stop listening even if they wanted to, due to the poor control function of their brainstems.

The non-clinical participants, on the other hand, listened to the music during the first minute. Their first visible response was to look at their parents and then at the CD recorder or at the music bag. They seemed to want to find out where the music came from, and also check the situation with their parents, as if they wanted to be sure that they had also heard the music and that everything was alright (shared attention). After that, most of the children continued playing with toys or communicating with their parent. The older children in the non-clinical group sometimes smiled because they recognised the music and looked at their parent. This smile was not an emotional smile; it was more like a social and communicative smile, one of mutual understanding. It seemed as if they listened, processed and then ignored the music.

Their different way of responding had an effect on the results, as the measured data were collected during the last minute of the musical stimuli. At that time the non-clinical

participants had already moved on from the music, whereas the RTT participants were still involved in and with the music. This might be worth bearing in mind, as music could be overwhelming in different situations, such as department stores, non-stop music on TV and radio at home or in other contexts. Individuals in the RTT population can generally not tell anyone that they do not want to listen to the music, and as they seem to be unable to ignore it they can easily become overwhelmed.

Almost all the participants in this study used music in one way or another. The importance of music and the response to it indicated that the part of the brain which receives and processes music seems to be intact in RTT, which might explain why music is so important throughout life. However, the control of responses is not intact. Another reason for the importance of music might also be that music seems to serve as the main tool to communicate, to interact with other people, and to understand contexts and situations. Music was also commonly used as a very important tool by other people in their relation to the RTT participants.

Parents and carers were often very clear about what favourite music to play to achieve a calming or an activating response. But their choices of calming music did not always create a calming response, and the activating music was not always as activating as they expected. Neither parents nor carers had thought about the difference between a genuine smile and a false smile elicited by abnormal brainstem activities. Nor did they know about the importance of observing changes in facial expressions over time. This suggests frequent misinterpretation of facial expressions by caregivers and is an important finding for clinical practice.

It seems difficult to gain access to music therapy both within and outside Sweden. The participants of this study were mainly from Sweden, but also from other European countries. Only 38% had access to some kind of music therapy even though 93% of the participants' parents and carers expressed that they deliberately used music in many different situations. One reason for not having music therapy could be that this form of therapy is not yet fully accepted in traditional healthcare. Music is frequently *used* by many professions, but it is perhaps important to differentiate between *listening to music* and *interaction in music*. It is only music therapists who are professionally trained in using music in interaction forms; other professions might not know the difference, and therefore might not refer to music therapists. Earlier it was more common, but today RTT is not a reason in itself to have music therapy. As early as 1966, Dr Rett mentioned the

necessity of music in relation to people with RTT (Rett, 1966). Already at that time, he realised the potential that music and music therapy seemed to have in breaking through barriers of difficulties, and according to parents and carers this is still true. I therefore find it remarkable to find out from parents and carers that it is difficult for them to get access to music therapy for those RTT participants who suffer from anxiety, self-destructiveness, anger and sadness. Why not allow them to use their “main language” in therapy, and why not follow the guidelines issued by the medical authorities?

An additional reason for the difficulty in getting access to music therapy might be that working with this population might be difficult and challenging for therapists in general, including music therapists, and the therapists need to be experienced, sensitive and patient. However, I would like to encourage music therapists, as I personally find it extremely rewarding to work with this population, and I am impressed by their never-ending fighting spirit, and how patient they generally are with me as a clinician. It is not an easy task to interpret the responses from the clients, and sometimes the signals are weak, quick and hard to notice, even for me, despite the fact that I have been working with RTT, music and music therapy for 15 years. I have noticed both happiness as well as frustration provoked by music. I have also noticed changes in breathing, dilated pupils, varied attention, varied facial activity, sudden laughs, varied level of activity, varied motivation and varied communicative ability. I wanted to investigate what was going on inside the participants, and how that knowledge could be used in clinical practice. I hope that the findings in this research will be of help, even though there are still many questions that need to be explored.

5.9.1. Coda

This research study balanced between different research areas, as well as research methods, which means that various angles are included. Measured data, technique and machines have a tendency to present “the truth” – and it is indeed a truth in that specific situation, for that specific participant or group of participants. Personally I cannot relinquish my perspective as a clinician with a holistic perspective. Brainstem assessment is a technique that gives extremely detailed information, creating fantastic possibilities, but these results cannot alone present the only truth. The method also creates difficulties that need to be highlighted, and set in relation to measurable results. The balance between the technical results, the needs of the actual individual, and my knowledge and experience

of RTT in general, is important for epistemological stance, and therefore for my interpretation of the results.

From my perspective, there is a difference between what I can see, based on measured data, and what I know. From my experience and knowledge of RTT, I know that interaction, active music, being in a context, being able to develop new skills and being included is tremendously important for the individuals. As I see it, the balance between recommendations based on measured data and quality in the daily life situation is a relevant topic to discuss. If the favourite music releases a physiologically unhealthy response, does this mean that the music is dangerous? Does this mean that the person is no longer allowed to listen to that specific music even if it is their favourite? What consequence does this have for the quality of life for people with RTT?

I totally agree that it is important to identify and to avoid life-threatening conditions, and some of these conditions can be identified with the help of a brainstem assessment. But the question is more a matter of what kind of recommendations parents and carers are given – and for whom. Is it an acceptable recommendation to avoid everything that releases happiness or to treat abnormal breathing patterns with different methods that make other important activities impossible? What consequences will that have, and whose anxiety are we then treating?

Another question for discussion is our general knowledge about facial expressions. I have met comments such as: *“It is easy to identify and to interpret people’s emotional expressions, as this is something humans have been doing for thousands and thousands of years”*. To a certain extent I agree, but this is also knowledge that we do not “need” to use today. We can all survive without it, and therefore our ability to read faces has diminished. If we read other persons faces, why do we misunderstand each other, and why do we misinterpret people with RTT to such a high degree. What do we *really* know about how people with intellectual disabilities, RTT included, express pain, sadness, anger, disgust and happiness?

This research study has highlighted that we misinterpret expressions of emotions in the RTT population due to lack of knowledge. The combination of a brainstem assessment and FACS has been invaluable for this finding. I think it is most relevant to know about all problems and difficulties related to RTT, but it is also important for me as a clinician

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 of the two might lead us in the right direction. The only truth is that people with RTT have tremendous difficulties, which obviously have to be dealt with, but we must never forget that they also need enrichment in life, for example in the form of music.

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, et al., 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, et al., 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, et al., 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 Eric Christensen, based on Grocke (1999), Hooper, (2003, 2010) and Aare, Grønager & Rønnefelt (2003). 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.

Svensk Sammanfattning

Bakgrund

Rett syndrom (RTT) är en utvecklingsneurologisk sjukdom som påträffas globalt. Tillståndet omfattar grundläggande kroppsliga funktioner inklusive hjärnstammens centrala kontroll av det autonoma nervsystemet. Musik tycks vara oerhört betydelsefullt för nästan varje individ med RTT och används av föräldrar och vårdare i olika situationer till exempel för att lugna ner, aktivera, motivera och för att kommunicera. Betydelsen av musik för personer med RTT finns dokumenterad i litteraturen. Dr Andreas Rett (Rett 1966), som först beskrev syndromet, skrev om musikens betydelse så tidigt som 1966. Ingen studie är däremot gjord för att mer i detalj undersöka varför musiken har så stor betydelse, och hur musiken fysiologiskt påverkar personer med RTT. De har i allmänhet vissa musikstycken som sina stora favoriter, och när de lyssnar till dem kan man observera tydliga effekter. Betydelsen av favoriter och en viss typ av musik hos personer med RTT har undersökts i en svensk och en amerikansk studie (Houtaling, 2003; Merker, et al., 2001). Båda rapporterna slog fast dels att musik är av avgörande betydelse för personer med RTT vad avser deras sätt att reagera på musik och dels att de hade favoritlåtar vilket rapporterades av deras vårdare. Familjemedlemmar till personer med RTT beskrev hur man använde musik som en ”medicin” för att få dem att lugna ner sig och dämpa ångest, otålighet och skrikande, men också för att få bättre kontakt, få dem att somna eller minska ångesten vid ett besök hos doktorn eller tandläkaren – helt enkelt när ingenting annat tycktes hjälpa (Bergström-Isacsson, 2001). Personer med RTT har mycket stora kommunikationssvårigheter (Elefant, 2002; Trevarthen & Burford, 2001). Flertalet saknar tal och tydligt kroppsspråk. Föräldrar och annan vårdpersonal måste i allmänhet lita till sin egen förmåga att tolka individens kommunikativa signaler, mestadels i form av ansiktsuttryck och ögonpekning. Tidigare forskning har framhållit att dessa signaler ibland blir övertolkade (Bergström-Isacsson, et al., 2007). Musikterapeuter och forskare har funnit att vissa musikstycken tycks ha en lugnande effekt medan andra ökar andningsfrekvensen, och att de skilda reaktionerna är svåra att värdera (Bergström-Isacsson, et al., 2007; Mount, et al., 2001).

Medicinsk forskning har pekat på att det är mycket vanligt att personer med RTT har en omogen hjärnstam och ett bristfälligt fungerande autonomt nervsystem (Armstrong & Kinney, 2001; Julu, 2001). Hjärnstammen styr en stor del av det autonoma nervsystemet,

som samordnar och kontrollerar kroppens basala funktioner. Det svarar mycket snabbt på hur vi upplever stimulans från vår omgivning och har stor del i våra känslor samt styr en del av våra ansiktsuttryck. Det autonoma nervsystemet består av två delar, det parasympatiska och det sympatiska systemet. Det senare höjer blodtrycket och ökar pulsen för att möta plötsliga förändringar. När det sympatiska systemet stimuleras blir vi alerta, rodnar och får förhöjd puls och blodtryck. När det parasympatiska systemet aktiveras går hjärtats frekvens och slagvolym ner, blodtrycket sjunker, pupillerna dras samman och salivproduktion och tarmrörelser ökar. Det parasympatiska systemet fungerar som en naturlig broms så att det sympatiska systemet inte ökar okontrollerat. I denna studie var avsikten att komma på ”insidan” av försökspersonerna med hjälp av en hjärnstamsundersökning och mäta det fysiologiska svaret från hjärnstammen på den musik som var försökspersonernas favorit men också på okänd musik. Det fanns dessutom en avsikt att från ”utsidan” identifiera ansiktsuttryck som uppstod i samband med musiken och registrerade hjärnstamsreaktioner. Eftersom musik kan ha både stimulerande och lugnande effekt var det av intresse att relatera olika typer av musik till både ansiktsuttryck och den autonoma reaktionen i hjärnstammen. Känslomässiga reaktioner som framkallas av musik kan avläsas i ansiktsuttryck, och kan skilja sig från dem som uppstår på grund av patologiska spontana hjärnstamsaktiveringar (ASBA). Det är därför viktigt att kombinera fynden från hjärnstamsaktiveringar med ansiktsuttrycken för att om möjligt skilja dessa som uttryck för en äkta känsla från dem som är utlösta av patologisk hjärnstamsaktivitet.

De undersökningar som genomförts i denna studie grundar sig på tidigare presenterad forskning (se kapitel 2). Klinisk erfarenhet och föräldrars berättelser är däremot underlag för mina hypoteser om hur personer med RTT uppfattar musik både psykologiskt och fysiskt (det vill säga stimulerande eller lugnande) och de fördelar musiken innebär. Syftet med denna forskning är att undersöka vilken effekt musikaliska stimuli har på det autonoma nervsystemets kontrollfunktioner och på kortikala emotionella reaktioner hos personer med RTT.

Hypoteser

De följande sex hypoteserna är formulerade med tanke på de förväntade effekterna i det autonoma nervsystemet när personen utsätts för olika typer av musikaliska stimuli.

1. *Ett okänt musikstycke (Horn), särskilt utvalt för detta ändamål*, ger endast upphov till ökad uppmärksamhet (en fysiologisk arousal) utan ökning av sympatisk eller parasympatiska aktivitet.
2. *Aktiverande musik (Activating) vald av föräldrar eller vårdare*, ger upphov till en sympatisk reaktion (ett aktiverande svar).
3. *Lugnande musik (Calming), vald av föräldrar eller vårdare*, ger upphov till en parasympatisk reaktion (ett avslappnings svar).
4. *Vibroakustisk stimulering (VT)*, ger upphov till en parasympatisk reaktion (ett avslappnings svar).
5. *VT kombinerad med ett särskilt utvalt musikstycke (VT+Mu)*, ger upphov till en parasympatisk reaktion (ett avslappnings svar).
6. *Det särskilt utvalda musikstycket från kombinationen med VT men nu framfört utan VT, (Mu)* ger upphov till en parasympatisk reaktion (ett avslappnings svar).

De fysiologiska svaren jämförs med ett utgångsvärde (baslinje) som består av de mest stabila registreringarna av sympatisk och parasympatisk aktivitet under normal andningsverksamhet med blodgaser inom normalområdet, full vakenhet och ingen epileptisk aktivitet (Julu, et al., 2001). Personer med RTT bildar en grupp och ett kliniskt normalmaterial (barn mellan 1 och 5 år) bildar en jämförelsegrupp.

Metod

Design

Denna experimentella studie är genomförd som både en jämförelse av data mellan de två grupperna (a between-groups study) och individuella mätresultat inom respektive grupp (a within-subjects study), även kallad ”a repeated measures design”. Utgångsvärdena för varje individ i bägge grupperna jämfördes med de individuella svaren på de sex olika musikaliska stimuli som användes. Studiens design användes för att öka testresultatens känslighet. ”Repeted measure design” kunde användas eftersom varje individ fungerade som sin egen kontroll och variationen mellan de olika försökspersonerna blev då inget problem. Denna typ av design var möjlig eftersom reaktionerna på de olika stimuli personerna exponerades för förväntades bli relativt kortvariga. Resultaten från gruppen med normala barn användes för att undersöka eventuella skillnader eller likheter i de erhållna värdena. Fysiologiska data registrerades vid en hjärnstamsundersökning. Analysen på gruppnivå kompletterades med fallbeskrivningar som gjorde det möjligt att ta hänsyn till ytterligare en uppsättning fysiologiska parametrar i form av blodgaser. Data

registrerades också med en videoanalys av ansiktsuttryck med hjälp av Facial Action Coding System (FACS). Avsikten med FACS var att identifiera ansiktsuttryck (Action Unit = AU) som utlöstes av patologisk hjärnstamsaktivitet och om möjligt skilja dem från emotionellt orsakade ansiktsuttryck som utlösts från cortex. Dessa ansiktsuttryck indelades i positiva, negativa och obestämda och jämfördes med resultaten av hjärnstamsregistreringen och respektive musikaliska stimuli.

Försökspersoner

I studien deltog 35 personer med RTT som remitterats till Rett Center för rutinmässig hjärnstamsbedömning under en period av två år (2006-2008). Sex personer uteslöts enligt vissa kriterier varför 29 återstod, varav två av manligt kön. Dessa var diagnosticerade med RTT innan de remitterades till Rett Center och hjärnstamsbedömningen. En genetisk undersökning var inget krav eftersom RTT fortfarande betraktas som en klinisk diagnos. En identisk hjärnstamsbedömning förutom EEG gjordes på 11 barn med normal utveckling, i den här studien kallad *the non-clinical group*. Denna grupp bestod av sex flickor och fem pojkar som alla genomgått en normal förlossning och sedan utvecklats normalt både fysiskt och intellektuellt.

Teknisk utrustning

Ett NeuroScope från MediFit Instruments Ltd, London, UK användes för att registrera hjärtverksamheten slag för slag räknat mellan R-R intervallen på EKG. Systoliskt och diastoliskt blodtryck registrerades också per hjärtslag med Portapres modell 2. En fotopletysmografisk fingermanschett användes för att erhålla kontinuerlig information om det arteriella fingerblodtrycket. Andningsrörelserna registrerades med ett piezoelektriskt bälte runt nedre delen av bröstkorgen. I en dator integrerades de registrerade andningsrörelserna med värdena på blodets syre- och koldioxidspänning som registrerats transkutant. Enheten anslöts till ett Medulla Lab som bearbetade alla data och gjorde det möjligt att studera hjärtverksamheten slag för slag. En EEG-hätta med inbyggda elektroder användes för EEG-registreringen. Samtliga data kunde visualiseras samtidigt på en datorskärm som gjorde det möjligt att under pågående hjärnstamsbedömningen diskutera och följa förloppet i realtid. Samtliga undersökningsresultat synkroniserades och processen filmades av två digitala videokameror som gjorde det möjligt att i efterhand analysera resultaten i detalj. Den ena kameran var fokuserad på försökspersonens ansikte medan den andra registrerade uppträdande och kroppsrörelser under registreringen. Videofilmen användes för att i efterhand koda ansiktsuttryck och

analysera deras samband med olika typer av musik och fysiologiska reaktioner från hjärnstammen. Under själva registreringen satt försökspersonen i en saccosäck (Musik-Molly) med inbyggda högtalare. Under *VT* och *VT+Mu* kom de lågfrekventa tonerna från högtalarna i saccosäcken och upplevdes som vibrationer. En CD-spelare kopplad till saccosäcken skapade vibrationerna och ytterligare en CD-spelare framförde musiken under *VT+Mu* liksom den musik som valts av föräldrar eller vårdare.

Genomförandet

Varje förälder eller vårdare intervjuades före hjärnstamsbedömningen. De fick frågor om den favoritmusik man använde både för aktivering och i lugnande syfte. De fick dessutom frågor om försökspersonen haft eller hade pågående musikterapi och i så fall enligt vilken metod, samt om, och i vilket syfte de använde musik i boendet. Före hjärnstamsbedömningen genomgick också försökspersonen en medicinsk undersökning som var ett av syftena med remissen till Rett Center. Försökspersonen och föräldrar eller vårdare visades runt i undersökningsrummet och fick i förväg se all utrustning. Strax innan registreringen började fick försökspersonen ta plats i bönsäcken. Alla elektroder för EKG och transkutan blodgasmätning, andningsbältet, fingermanschetten och EEG huvan fästes vid försökspersonen. Videokamerorna, datorn och EEG-maskinen synkroniserades. I början av hjärnstamsbedömningen registrerades utgångsvärdet enligt ovan.

Datainsamling och analys

De data som samlades in kom från en undersökning av hjärnstammens kontroll av de autonoma funktionerna under cirka en timmes tid. Kontrollvärdena utgjordes av försökspersonens egna utgångsvärden, baslinjen. När baslinjen var säkerställd utsattes försökspersonerna för sex olika musikaliska stimuli: *Horn*, *Activating*, *Calming*, *VT*, *VT+Mu* och *Mu* i slumpartad ordningsföljd. De kontinuerliga beroende variabler som registrerades var: Cardiac Vagal Tone (CVT, styrkan av vagusnervens styrning av hjärtat), Cardiac Sensitivity to Baroreflex (CSB, hjärtats känslighet för baroreflexen), Mean Arterial blood Pressure (MAP, genomsnittligt arteriellt fingerblodtryck) och koefficienten för variationen i MAP (MAP-CV). Dessa parametrar användes för att beskriva hjärnstammens reaktioner på de olika typerna av musikalisk stimulans och karakterisera dem i parasympatiskt, sympatiskt, arousal eller obestämt svar. Dessa fyra kategorier användes i hypoteserna för att beskriva det förväntade svaret på de sex olika musikaliska stimulanserna. Efter varje stimulus följde en viloperiod då försökspersonens

värden återgick till baslinjevärdena eller näst intill. Ingenting annat pågick i undersökningsrummet när försökspersonen utsattes för den musikaliska stimulansen. Transkutana registreringar av partialtryck av syrgas och koldioxid i blod var ett mått på hjärnstammens förmåga att balansera blodgaserna och utgjorde tillsammans med andningsmönstret grunden för att bestämma försökspersonens fenotyp beträffande andningsrörelser (Julu, 2001). Blodgasvärden användes dessutom i fallbeskrivningarna för att få en mer genomgripande förståelse av analysen av de individuella mätvärdena. En analys av videoupptagningarna av ansiktsuttrycken under den sista minuten relaterades till CVT, CSB och MAP från motsvarande tidsperiod. Genom att videokameran synkroniserats med EEG maskinen var det möjligt att i den maskinen markera och koda både frekvens och duration av alla ansiktsuttryck. Detta var viktigt för att särskilja de olika ansiktsuttrycken från specifika individuella ansiktsrörelser orsakade av RTT. Kombinationer av AU:s kodade enligt FACS ("events") kan beskrivas med emotionella termer om undersökaren väljer att göra så, men detta är en följd av ett ytterligare steg inom FACS (Ekman & Rosenberg, 2005). I detta arbete användes sådana termer för att undersöka om FACS kan vara en metod för att identifiera och särskilja ansiktsuttryck kopplade till en känsla från dem orsakade av patologisk hjärnstamsaktivitet. Varje enskilt AU kodades och markerades (start och stopp av AU). Tool for Music Analysis (TMA) användes för att urskilja förändringar i musiken vilket kan ha betydelse för olika emotionella uttryck. TMA är skapat av mig i samarbete med musikvetaren och forskaren Eric Christensen, grundat på Grocke (1999), Hooper (2003, 2010) och Aare, Grønager & Rønnefelt (2003). TMA gjorde det också möjligt att jämföra de val som föräldrar eller vårdare gjorde av försökspersonens favoritlåtar.

Resultat

Kontinuerliga och kategoriska variabler

Baslinjevärdena skiljde sig mellan försökspersonerna i båda grupperna liksom mellan grupperna. CVT och CSB låg högre i gruppen med normala barn och MAP var signifikant lägre. Dessa högre värden bland de normala barnen kan tyda på en mer mogen hjärnstam och därigenom en bättre förmåga att styra det autonoma nervsystemet. I gruppen med RTT registrerades det förväntade kategoriska svaret enligt hypoteserna med 7% för *Horn*, 36% för *Activating*, 39% för *Calming*, 52% för *VT*, 32% för *VT+Mu*, och 28% för *Mu*. Inom de två grupperna sågs det förväntade svaret oftast hos en minoritet av försökspersonerna: förväntad reaktion för de tre stimuli *Activating*, *VT* och *VT+Mu*,

förekom i över 30% och det förväntade svaret för *Calming* var vanligare för personer med RTT (39%) än för de normala barnen (9%). Ett obestämt svar, som innebar att alla registrerade parametrar (CVT, CSB, MAP) ökade förekom i bägge grupperna. Ett obestämt svar kunde också erhållas vid en så kallad hjärnstamsavstängning då värdet för samtliga registrerade variabler gick ner. Denna typ av reaktion ses när en hjärnstam inte kan hantera alltför många signaler eller stimuli. Det är en patologisk reaktion som man framför allt observerar när hjärnstammen är mycket omogen och lätt blir överbelastad. Denna hjärnstamsavstängning sågs endast hos personer med RTT. Resultaten visade också på betydelsen av blodgasvärden och andningsmönster för att korrekt bedöma den fysiologiska reaktionen och ansiktsuttrycken hos personer med RTT som exponerades för musikaliska stimuli.

Tolkning av ansiktsuttryck och känslomässiga uttryck

Analys av ansiktsuttryck hos personer med RTT visade att *Activating* gav upphov till mer leenden än övriga stimuli. *Mu* utlöste mer negativa svar som ilska eller ångest, och *Horn* framkallade flera liknande reaktioner. Ett övergripande chi-två test visade att de känslomässiga svaren inte var slumpmässigt fördelade ($p < .001$) vilket antyder att personer med RTT faktiskt kan uttrycka både avsikt och musikaliska preferenser. Bland de normala barnen var leenden oftast förekommande vid *VT+Mu* och *Calming*, men också relativt vanliga vid *Activating*. I den gruppen förekom nästan inga negativa reaktioner. Falska leenden vid *Activating* förekom i båda grupperna.

Kategoriska hjärnstamsreaktioner i samband med musik och ansiktsuttryck

Vid analys av ansiktsuttrycken visade det sig att flertalet av personer med RTT hade ett unikt och specifikt rörelsemönster relaterat till diagnosen och som tycktes vara utlöst av patologisk hjärnstamsaktivitet. Motsvarande sågs inte hos de normala barnen. De kategoriska reaktionerna från hjärnstammen överensstämde i allmänhet med ansiktsuttrycken, utom vid *VT*. Analysen av ansiktsuttrycken relaterat till hela stycken av favoritmusiken (inte bara den sista minuten) visade också att samtliga deltagare i båda grupperna reagerade när musiken började, men det föreföll finnas skillnader i det sätt försökspersonerna i de två grupperna reagerade över tid. I fallbeskrivningarna användes blodgasvärdena som en ytterligare parameter för att uppnå en mer rikhaltig förståelse av de individuella reaktionerna. När fallbeskrivningarna jämfördes med varandra visade det sig att musiken hade effekt på de fyra försökspersonerna. Det förekom däremot skillnader

i deras förmåga att kontrollera de reaktioner som musiken gav upphov till, att balansera blodgaserna och att förmedla (kommunicera) de känslomässiga reaktionerna.

Diskussion

Erhållna resultat i detta arbete visar att både personer med RTT och de normala barnen hade olika reaktioner från hjärnstammen på musikaliska stimuli (parasympatiska, sympatiska, arousal och obestämda reaktioner), men inte alltid med det förväntade svaret. En omogen hjärnstam, som förekommer vid RTT, har inte förmåga att styra det autonoma nervsystemets funktioner på ett normalt sätt. När försökspersonerna med RTT fick lyssna till musik kunde de till exempel att börja med reagera med en äkta lyckokänsla, men på grund av hjärnstammens bristande kontrollfunktion kunde denna känsla gå över i ett tillstånd av stress. För att uppmärksamma denna övergång är det mycket viktigt att i detalj observera förändringar i ansiktsuttrycken. Resultaten visar också att det är kliniskt möjligt att tolka ansiktsuttryck hos personer med RTT, grundat på sambandet mellan hjärnstamsreaktioner och FACS, och därigenom förhoppningsvis kunna undvika feltolkningar. De detaljerade fallbeskrivningarna visar att det är av värde att följa kontinuerliga eller kategoriska hjärnstamsreaktioner, men för att komma underfund med hur personen verkligen mår är det bättre att även ta med en bedömning av blodgaser, andningsrörelser, ansiktsrörelser och känslouttryck i analysen.

Studiens begränsningar

En grupp på 29 personer med RTT som inte var slumpmässigt sammansatt, kan inte ses som representativ för hela populationen (med RTT). Resultaten hänför sig givetvis endast till denna grupp.

Framtida forskning

Framtida forskning borde om möjligt försöka kombinera ytterligare neurofysiologiska variabler för att undersöka musikens påverkan på både kropp och sinnesstämning. Man bör till exempel registrera blodgaserna och analysera dem som kontinuerliga variabler. Olika typer av musik gav i denna studie skilda resultat vilket är av intresse att följa upp. FACS som enskild metod, och i kombination med en hjärnstamsbedömning hos personer med RTT, är ett nytt och tidigare oprövat angreppssätt. Ytterligare forskning inom området som helhet är nödvändig för att kunna dra generella slutsatser.

Slutsats

Ett av de huvudsakliga fynden i detta arbete var att flertalet personer med RTT hade ett unikt rörelsemönster i sina ansiktsuttryck, kopplat till diagnosen, och som lätt kunde

uppfattas som en känslomässigt grundad mimik. Dessa specifika rörelsemönster visade sig vara utlösta av plötsligt uppträdande patologisk hjärnstamsaktivitet (ASBA:s) som förekom spontant och inte behövde varar uttryck för en känsla. Däremot kunde denna patologiska hjärnstamsaktivering ge upphov till känslor som exempelvis ångest och rädsla vilket grundar sig på sambandet mellan resultaten av hjärnstamsbedömningen och FACS. Analysen visade också att man ur klinisk synpunkt kunde skilja mellan de patologiskt utlösta rörelsemönstren och känslouttryck, men då var en detaljerad observans helt nödvändig.

Föreliggande arbete visade också att personer med RTT reagerade på olika typer av musik på skilda sätt, vilket liknade reaktionerna hos de normala barnen med hjärnstam av ungefär samma mognadsgrad. Detta stod klart både vid bedömning av fysiologiska svar från hjärnstammen och vid analys av ansiktsuttryck. Samtliga deltagare i båda grupperna gav någon form av reaktion när musiken eller vibrationerna började men det föreföll vara en skillnad i hur de reagerade för respektive stimulus över tid. Nästan samtliga deltagare i de båda grupperna använde vanligtvis musik i någon form. Betydelsen av musik, och de reaktioner den utlöste, antyder att den del av hjärnan som tar emot och bearbetar musik förefaller intakt hos personer med RTT, vilket kan förklara varför musik är så viktig del av deras liv. Musik förefaller även vara den mest väsentliga vägen för kommunikation, att samverka med andra och att förstå sammanhang och olika situationer för personer med RTT. Musik användes också som ett mycket viktigt medium av andra människor i deras relation till deltagarna i denna studie.

Denna studie har satt fingret på att man misstolkar uttrycken för känslor hos personer med RTT på grund av bristande kunskaper. Kombinationen av en hjärnstamsbedömning och FACS har varit avgörande för detta resultat. Det är mycket viktigt att känna till alla problem och svårigheter som är förknippade med RTT i all samverkan med dessa personer, och det är väsentligt för kliniker att se hela människan, inte bara svårigheterna, och att vara mycket uppmärksam på ansikts- och känslouttryck.

Var för sig innebär varken resultaten från en hjärnstamsbedömning eller värderingen med FACS någon ”sanning”, men kombinationen leder i rätt riktning. Den enda sanningen är att personer med RTT har enorma svårigheter, som man givetvis måste ta hand om, men vi får aldrig glömma att de också behöver stimulans och en berikande livsmiljö, till exempel i form av musik.

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Appendices

APPENDIX 1 Information document sent to parents and guardians of all RTT patients referred to the Rett Center

Välkommen till bedömning av autonoma

hjärnstamsfunktioner vid Rett Center,

v..., mån....., 200....

Vi har reserverat plats för er på Rett Centers boende mellan och under vecka 37. Behöver ni övernatta ytterligare någon natt går det också bra.

Rett Center ligger i hus A på Frösö Strand, boendet på plan 6 och Rett Centers behandlingslokaler och kontor på plan 7. Kommer ni när entrédörren är låst får ni ringa på en klocka märkt ”Rett Center, plan 6”, så kommer boendevärden och öppnar.

För er som kommer med egen bil finns några olika parkeringsplatser att välja på.

- *I boendet finns* sänglinne och handdukar
 tillgång till kök, matsal, TV-rum mm.
 rum för avslappning med musik, vibroakustik, taktil massage mm.
- *Tag med* egna blöjor och hygienartiklar
 egna mediciner
 badkläder
 inneskor
 varma kläder
 favoritmusik* på CD eller kassettband

Ta gärna kontakt med Rett Centers boendevärd för information om boende, matvanor el. dyl.

Boendevärd: Gun-Marie Nyström, tel. 063-15 48 18

Bedömningen av autonoma hjärnstamsfunktioner görs under den heldag ni finns på plats. Självva mätningen tar en dryg timme i anspråk, men föregås av läkarundersökning samt introduktion för flickan/kvinnan och information till medföljande.

* Vid Rett Center och i samband med hjärnstamsundersökningarna erbjuds ni att delta i ett pågående forskningsarbete kring musik och VT (vibroakustik) eventuella påverkan på det autonoma nervsystemet. Deltagande i projektet är frivilligt. Om ni önskar delta är det viktigt att ni funderar lite extra kring val av musik. Vi vill att ni väljer ett stycke/låt som är av uppiggande och aktiverande karaktär, som gör flickan/ kvinnan alert och uppspelt och ett stycke/låt som hon blir lugn, koncentrerad och ev. känslomässigt berörd av. Förutom dessa stycken kommer vi att spela ett okänt stycke samt använda oss av VT, VT+musik för att göra så noggranna mätningar/jämförelser som möjligt.

Innan mätningen startar kommer ni att få ytterligare information kring ert eventuella deltagande i projektet av musikerapeut Märith Bergström-Isacsson som är den som i samarbete med Dr. Peter Julu genomför forskningsarbetet. Personuppgiftsansvarig är styrelsen i Jämtlands läns landsting, Box 602, 832 23 Frösön (Anette Högstedt, personuppgifts ombudsman, tel. 063-14 76 62). Enligt personuppgiftslagen har du rätt att gratis en gång per år få ta del av de uppgifter om dig som hanteras och vid behov få eventuella fel rättade. Kontaktperson är Märith Bergström-Isacsson, tel.063-15 48 12.

Förutom mätningen och sammanfattningen av den finns det möjlighet under vistelsen vid Rett Center till bl a bassängbad. Det finns även fina promenadvägar i området så ta med kläder för utevistelse.

Bifogar formulär som vi önskar få tillbaka ifyllt så snart som möjligt, dock xxxxxxx !

Välkommen!

/Birgitta Wesslund,

kurator

APPENDIX 2 Consent form

Godkännande

Härmed godkänner undertecknad förälder/god man att:

Namn:

.....

Pers.nr:

Deltar i forskning gällande Märith Bergström-Isacsson's PhD arbete kring vilka effekter musik och vibroakustik har på det autonoma nervsystemets kontrollfunktioner.

Uppgifterna för forskningen inhämtas som en del i samband med hjärnstamsundersökning utförd vid svenskt Rett Center under perioden 2006- 2012.

Östersund 20 - -

Namnteckning:.....

.....

Namnförtydligande:

.....

APPENDIX 3 Questions about the participant's experience of music therapy and comments concerning facial expressions

1. Hasever had music therapy?

Yes No Don't know

2. If yes, what kind?

FMT Analytic Tomatis Behaviouristic Other

3. Has there been much music around her during childhood?

Yes No Don't know

4. In what way do you use music?

Calming Activating As medicine For sleep As a signal

Other Do not use music

Parents'/Carers' comments concerning facial expressions:

Smile:

Grimace:

Frowning:

Blank:

Laugh:

Sudden laugh:

Angry:

Sad:

Other comments:



Musik!

Kära Förälder!

Vill du delta i ett forskningsprojekt med ditt barn?

Jag som frågar är doktorand Märith Bergström-Isacsson vid Aalborgs Universitet och musikerapeut vid Rett Center i Östersund.

Jag söker efter dig som kan tänka dig att låta ditt barn i åldern 1-5 år vara med i en forskningsstudie kring hur olika sorters musik påverkar oss.

Är det här något som du känner att du gärna deltar i är du *mycket* välkommen att kontakta mig för vidare information, muntlig och skriftligt.

Undersökningen tar en dryg timme i anspråk, är helt smärtfri och du som förälder är naturligtvis med hela tiden.

Forskning kring musik är ett angeläget ämne och det vore spännande att få reda på mer om det som händer inom oss när vi exponeras för musik. *Att* vi påverkas vet vi ju alla - det är inget nytt - men vi vet ännu inte riktigt hur. Din medverkan kan hjälpa oss att förstå mer.

Musikerapeut MA, PhD forskare Märith Bergström-Isacsson
Rett Center
Box 601
832 23 Frösön
Tel: 063-15 48 12
E-post: marith.bergstrom-isacsson@jll.se

APPENDIX 5 Second information document, how to contact the researcher



Kort information

En neurofysiologisk studie - Musiks och vibroakustiks inverkan på hjärnstammens förmåga att kontrollera det autonoma nervsystemet gällande personer med Rett syndrom.

Vid Rett Center, Frösö strand och i samband med hjärnstamsundersökningar för personer med Rett syndrom pågår ett forskningsarbete, ett doktorandarbete, kring musik och VT (vibroakustik) eventuella inverkan på hjärnstammens förmåga att kontrollera det autonoma nervsystemet.

Musikterapeut och PhD forskare Märith Bergström-Isacson är ansvarig för projektet i samarbete med neurofysiolog Dr Peter Julu.

Grunden för studien handlar om den stora påverkan musik och VT verkar ha på personer med Rett syndrom. Föräldrar beskriver hur de använder musik ”som medicin” för att lugna oro och ångest, vid insomning, vid tandläkarbesök, i stressiga situationer – när inget annat fungerar.

Något som fascinerar är det starka, till synes normala, musik intresset hos personer med Rett syndrom vilket leder till teorin att en hjärna med Rett syndrom reagerar normalt på musik och vibroakustik. Det skulle i så fall kunna vara en förklaring till musikens stora betydelse genom livet för personer med Rett syndrom och vara värdefull information även när det gäller andra behandlings- och kommunikationssammanhang.

För att kunna bevisa eller motbevisa teorin behövs en grupp normalbarn att jämföra resultaten med.

Jag söker därför kontakt med dig som kan tänka dig att låta ditt barn vara med i en jämförelsegrupp. Barnet ska vara i åldrarna 1-5 år, normalutvecklad för sin ålder, frisk och kry. Undersökningen tar en dryg timme och är en undersökning utan stick eller något som gör ont. Vi

mäter EKG, hjärtfrekvens, syre och koldioxid, blodtryck, puls, och andning under en dryg timme med hjälp av elektroder som klistras fast på kroppen, en fingermanschett och ett ”skärp” runt magen. Barnet kommer att sitta i en ”sacko-säck” med inbyggda högtalare. Via högtalaren kommer ett lågfrekvent ljud, 40Hz, som känns som vibrationer i kroppen. Vibrationerna kommer att spelas två gånger, med och utan musik till. Under mätningen spelas även två okända stycken av olika karaktär. Dessutom ber vi er att ta med två låtar/stycken. Ett som barnet lyssnar lugnt, stilla och koncentrerat till (kan vara ex. vaggvisa) och ett stycke som barnet blir aktiverat av.

Du som förälder är naturligtvis med hela tiden!

Är det här något som du känner att du gärna deltar i är du *mycket* välkommen att kontakta Märith Bergström-Isacsson för vidare information. Forskning kring musik är ett angeläget ämne och det vore spännande att få reda på mer om det som händer inom oss när vi exponeras för musik. Att vi påverkas vet vi ju alla men vi vet ännu inte riktigt hur.

Med vänlig hälsning

Märith Bergström-Isacsson

APPENDIX 6 Facial Action Units (AU)

Facial Action Units (AU)

Upper face AUs

1	Inner brow raise	20	Lip stretch
2	Outer brow raise	22	Lip funneler
4	Brow lowerer	23	Lip tightener
5	Upper lid raise		
6	Cheek raise	24	Lip presser
7	Lids tight	28	Lip suck
43	Eye closure	72	Lower face not visible
45	Blink		
46	Wink		
70	Brows not visible	8	Lips towards each other
71	Eyes not visible	19	Tongue show

Miscellaneous AUs

Lip parting and jaw opening

25	Lips part	29	Jaw thrust
26	Jaw drop	30	Jaw sideways
27	Mouth stretch	31	Jaw clencher
		32	Bite
		33	Blow
		34	Puff
		35	Cheek suck
		36	Tongue bulge
		37	Lip wipe
		38	Nostril dilate
		39	Nostril compress

Lower face AUs

9	Nose wrinkle
10	Upper lip raiser
11	Nasolabial furrow deepener
12	Lip corner puller
13	Sharp lip puller
14	Dimpler
15	Lip corner depressor
16	Lower lip depressor
17	Chin raiser
18	Lip pucker

APPENDIX 7 Facial expressions, emotional events using FACS codes

Facial expressions, emotional events using FACS codes

Smile (happiness) 6 (+7)+12

False smile

12

Variants: 12+5*

Laugh (happiness)

6 (+7)+12

+ a long or short vocal sound/laugh, ex. ha, ha.

Sudden laugh

12

Variants: 12-+5*+ a short vocal sound/laugh.

(False laugh)

+ a short vocal sound as if the person was laughing.

Sadness

1+4+11+15B with or without 54+64

1+4+15* with or without 54+64

6+15* with or without 54+64

(With or without tears)

Variants:

1+4+11 with or without 54+64

1+4+15B with or without 54+64

1+4+17 with or without 54+64

11+15B with or without 54+64

11+17

25 or 26 may occur with all prototypes or major variants

Anger/Anxiety

4+5*+7+10*+22+23+25,26

4+5*+7+10*+23+25,26

4+5*+7+23+25, 26

4+5*+7+17+23

4+5*+7+17+24

4+5*+7+23

4+5*+7+24

Variants: Any of the prototypes without anyone of the following AU:s 4,5,

7 or 10

Surprise

$1+2+5B+26$

$1+2+5B+27$

Variants:

$1+2+5B$

$1+2+26$

$1+2+27$

$5B+26$

$5B+27$

Fear

$1+2+4+5^*+20^*+25, 26, \text{ or } 27$

$1+2+4+5^*+25, 26, \text{ or } 27$

Variants:

$1+2+4+5^*+L \text{ or } R20^*+25, 26, \text{ or } 27$

$1+2+4+5^*$

$1+2+5Z, \text{ with or without } 25, 26, 27$

$5^*+20^* \text{ with or without } 25, 26, 27$

Disgust

9

9+16+15, 26

9+17

10*

10*+16+25, 26

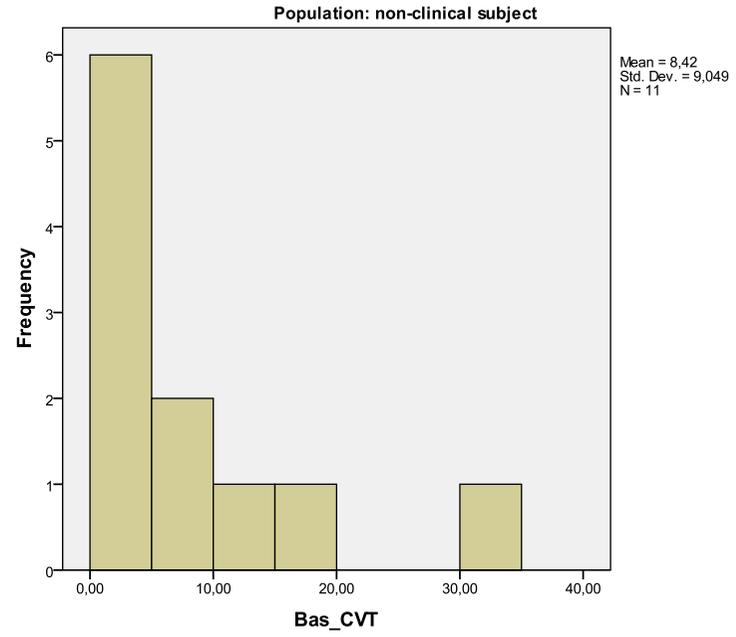
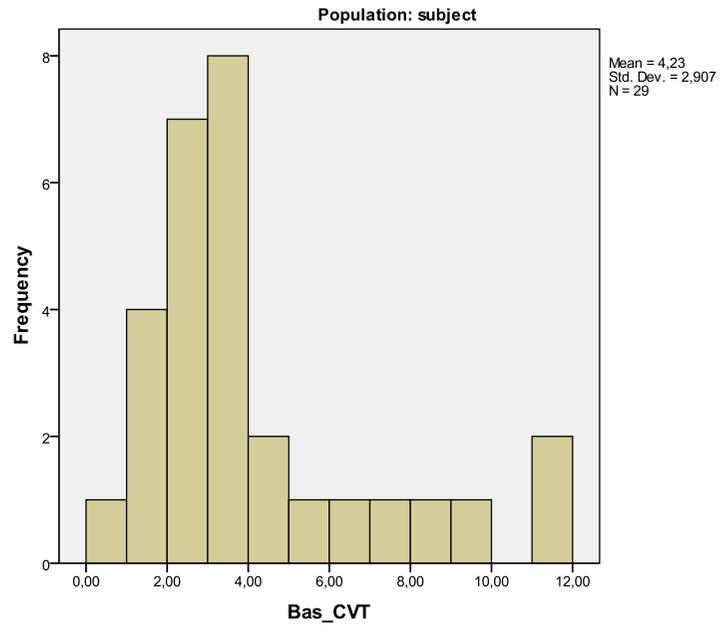
10+17

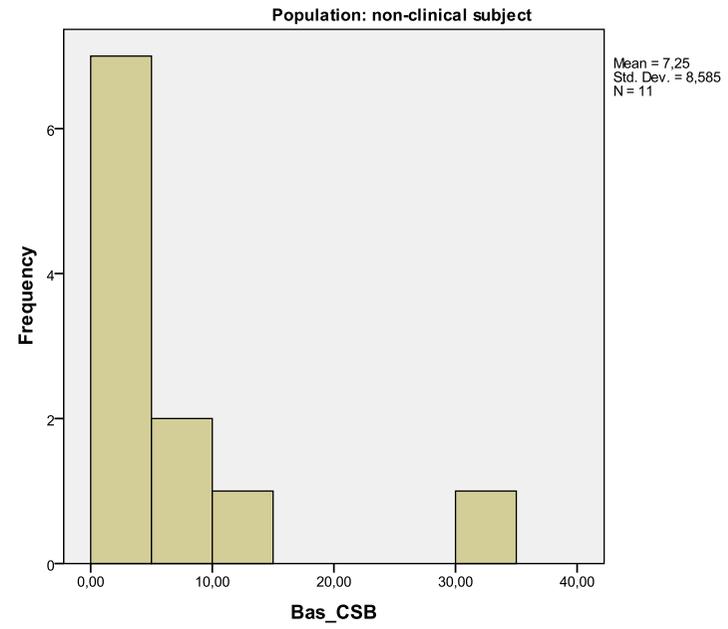
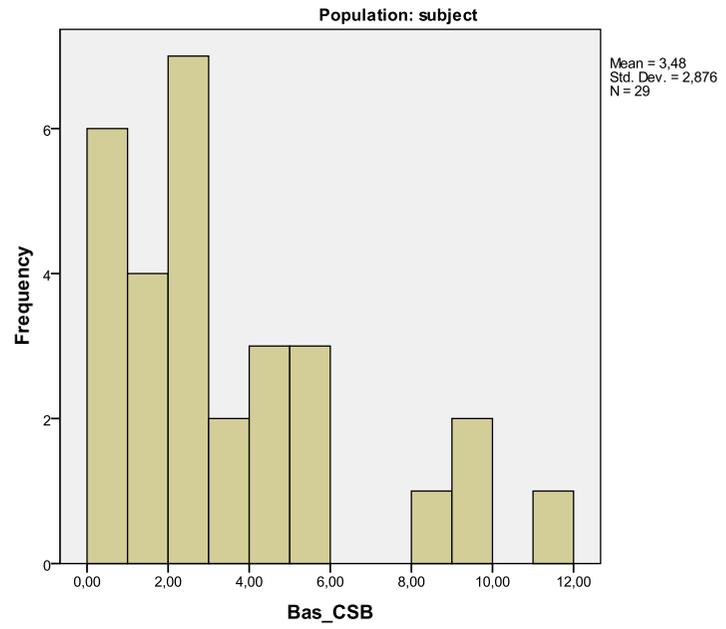
Blank

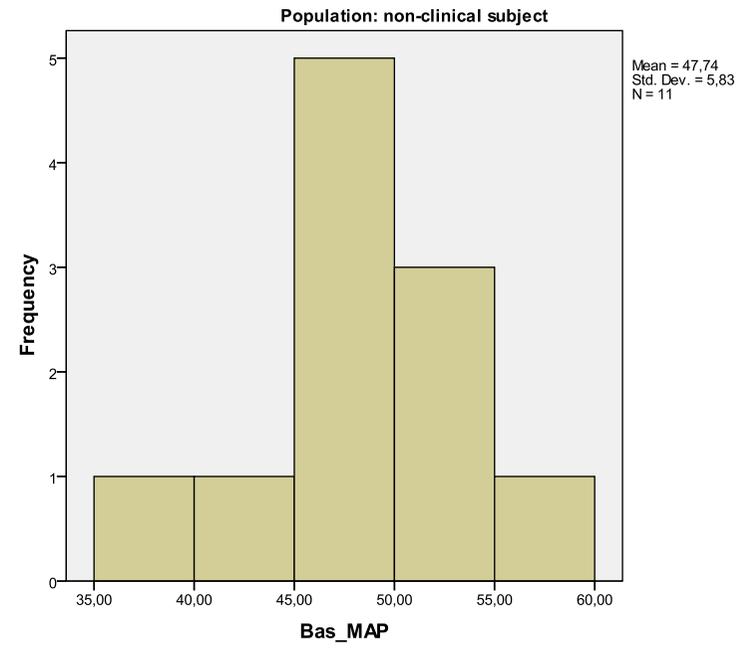
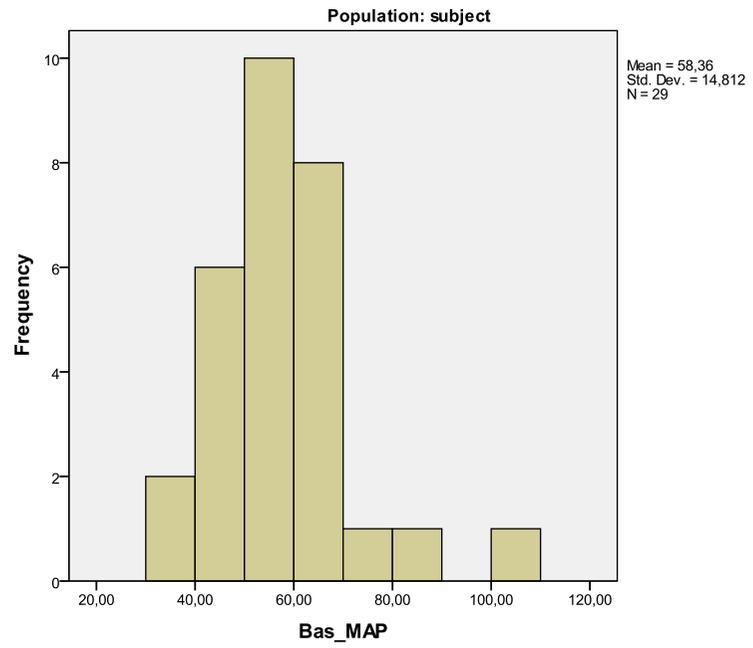
Transfixed and very still for a long time, code the changes

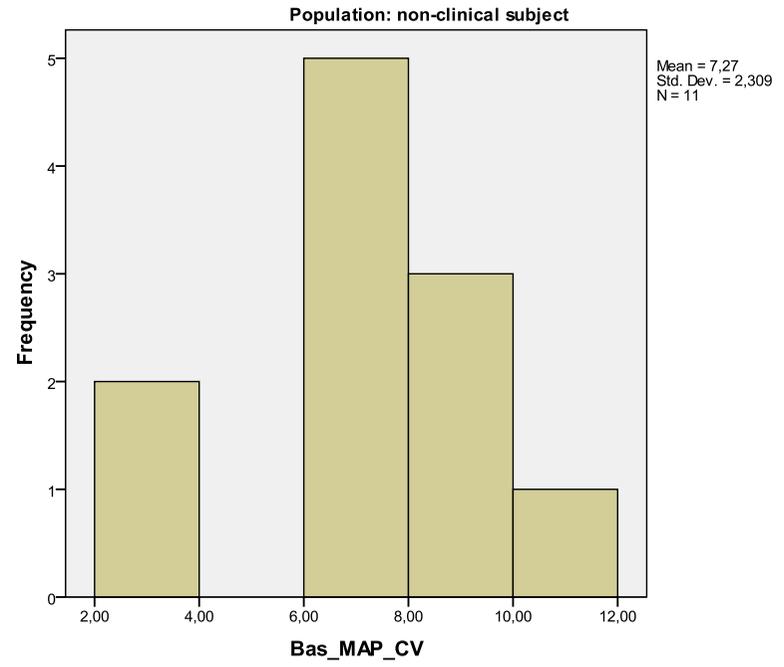
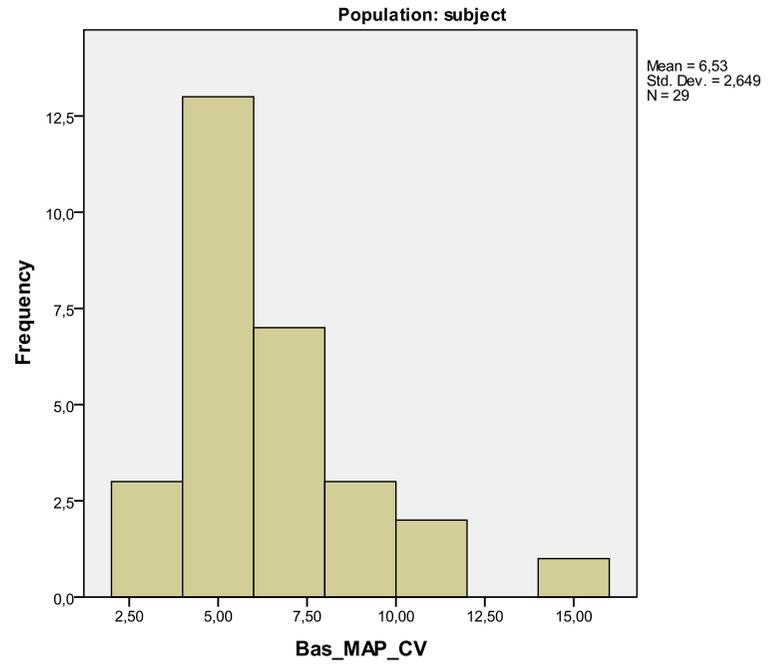
Table note: * means in this combination the AU may be at any level of intensity

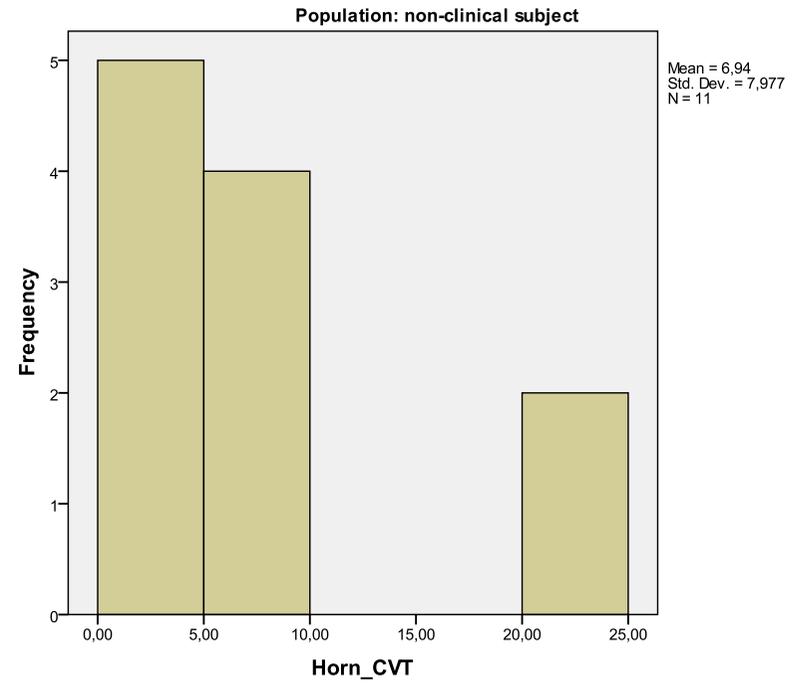
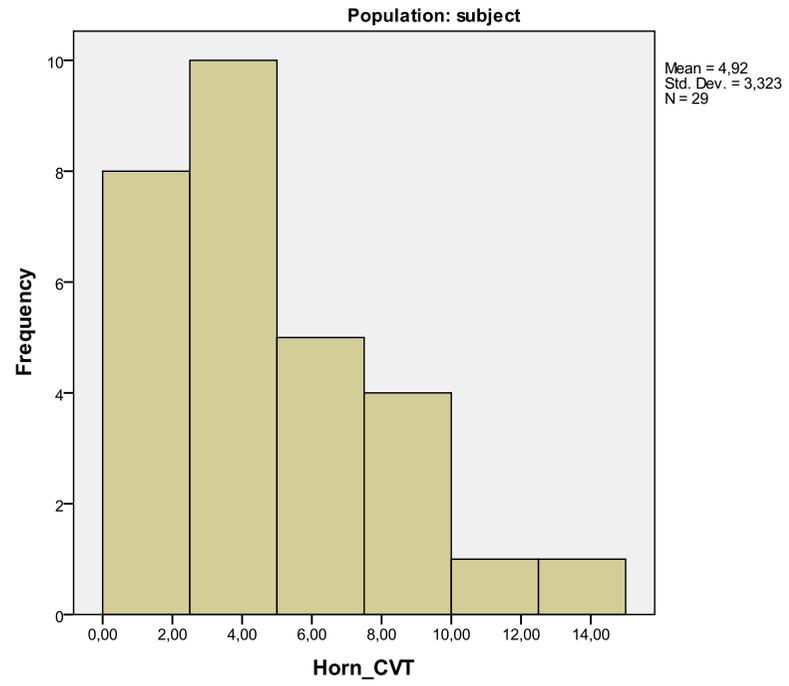
APPENDIX 8 Histograms, distribution of data

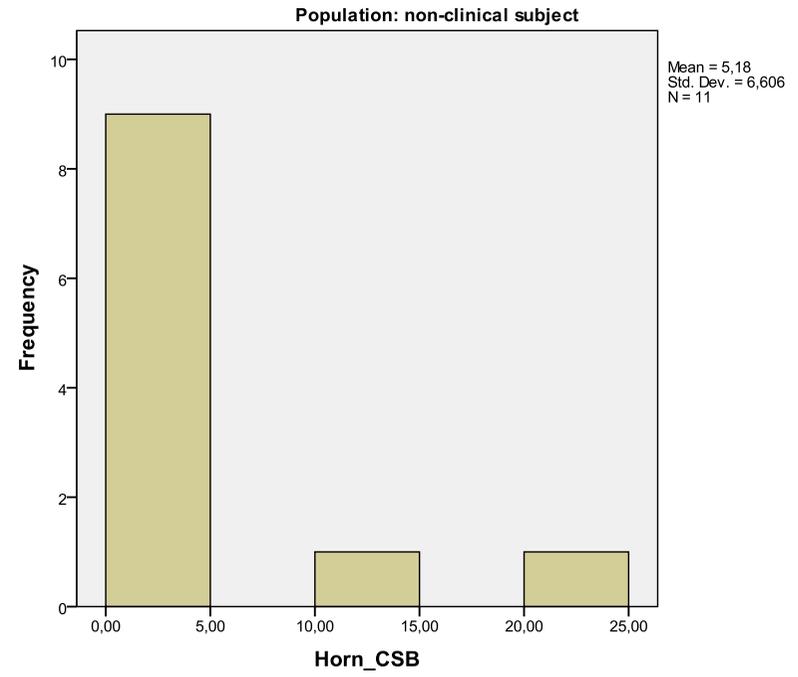
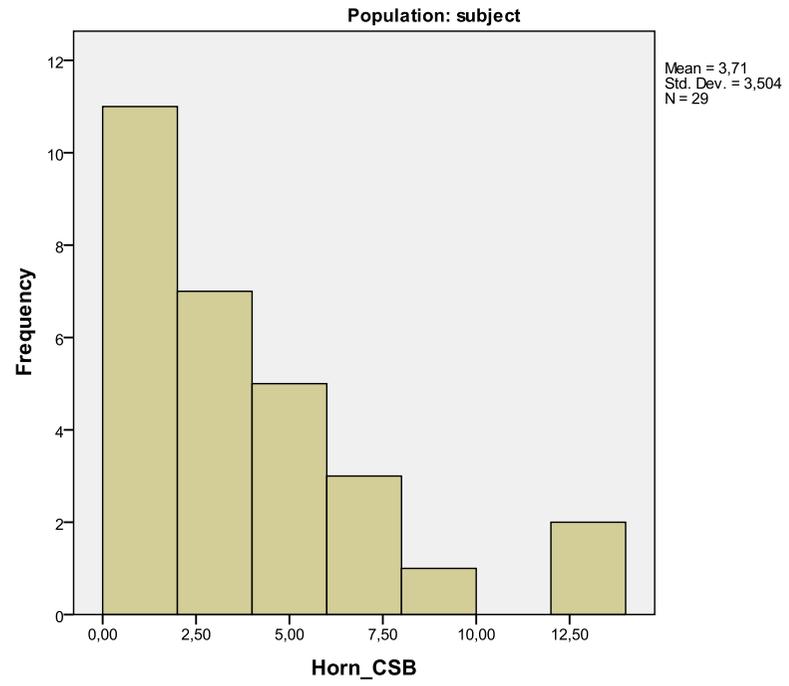


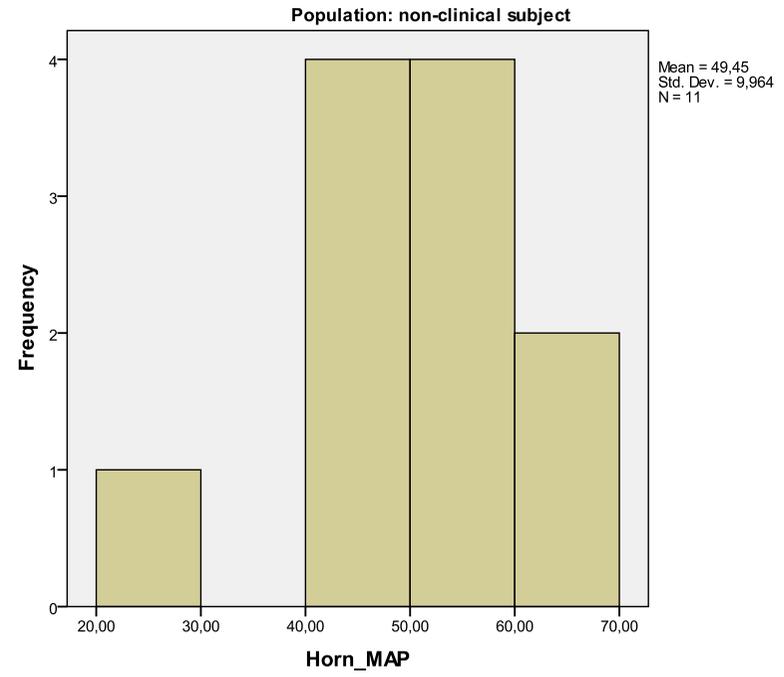
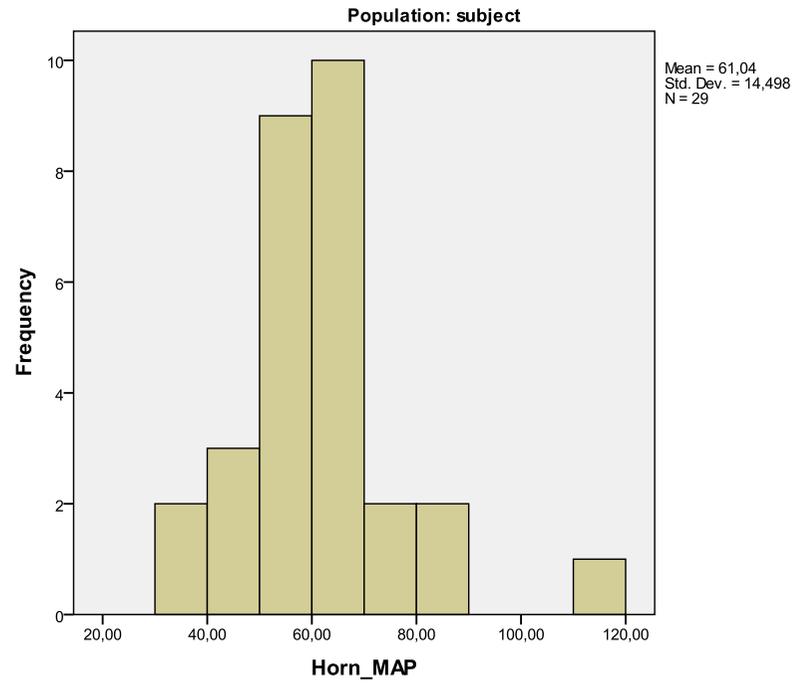


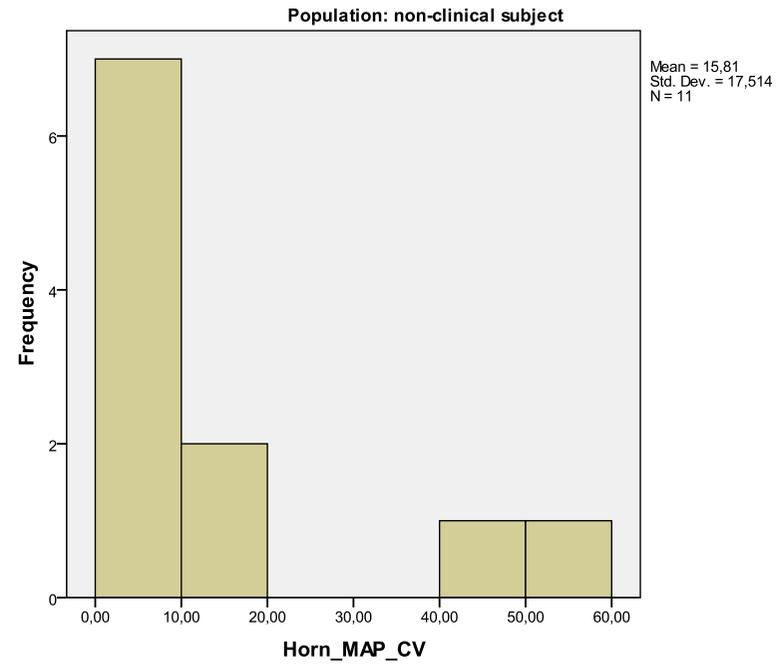
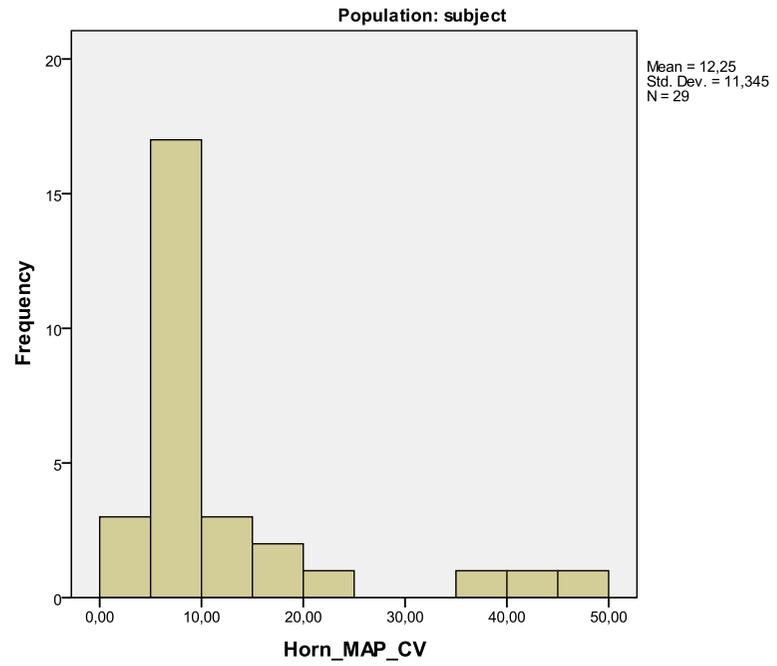












APPENDIX 9 Record of all music used

Title	Track	Artist	Category	CD title	CD number	Published by	Act/calm
Kom och ta mig		Bransta City Släckers	pop	cd-copy			Act
Caroline		Status Quo	pop	cd-copy			Act
Hejsan	1	Märith Bergström-Isacsson	children	Musik från topp till tå	SSMDC 20599	Svensk Skolmusik AB	Act
Kaj & Andrea	1	Kaj & Andrea	children	Bom-Tjickabom		CMC Records	Act
Wannabe		Spice Girls	pop	cd-copy			Act
Kajs sang		Kaj & Andrea	children	Kaj & Andrea	4549CL	ELAP music	Act
Maria Terese		Robban Broberg	ballads & trad songs	cd-copy			Act
My number one		Helena Paparitsou	pop	cd-copy			Act
	1	B-Boys	pop	cd-copy			Act
Pienen Pieni Veturi	3		children	Anni tammim leikkilaulut 2	04-00037-00163	Sympaali	Act
Prinsesse	4	Kaj & Andrea	children	Bom-Tjickabom	CMC 5249922	CMC Records	Act
Παισιόκό κοτί	1		story	Α Μπε μπα μπου	1653	FM Records	Act
Jag hade en älskling en gång	1	Ulf Lundell	ballads & trad songs	Öppna landskap	724347516320	EMI	Act
Mamma Mia		ABBA	pop	ABBA	549952-2	Polar Music	Act
Katariina			folk	Värttina aaitara	MIPUCD 302	MIPU MUSIC	Act
	1	Annti Kppale	children	cd-copy			Act
What can I do	1		ballads & trad songs	Hallelujah Live	82876865672	Playroom management	Act
Lille Katt, G Riedel	sång	Carers	children				Act
Heartbreak Hotel	1	Elvis Presley	pop	Tiger Man	LC0316	RCA Records	Act

Turbo	1	Nicke & Nilla	children	Tjaba Tjena Igen	016581-2	Sprinkler production	Act
Les Champs-Élysées	4		folk		COL481116 2	Columbia	Act
Step up to the right			pop	cd-copy			Act
	7		children	Hits for kids 14 (hembränd skiva)			Act
Alle Klauren	1	K3	children	Wivani entertainment	74321846602	BGM/Ariola	Act
	1		children	Hugo børnehits	LC00309	Polydor	Act
Hakkebakke skogen	1		children	cd-copy			Act
Ooa hela natten	2		pop	cd-copy			Act
Medley	3	Glada Hudik teatern	pop	Elvis live och glada Hudikteatern	SKRCD119	Start klart records	Act
Nalle Puh			children	cd-copy			Calm
Långsamt farväl		Lisa Nilsson	pop	cd-copy			Calm
Morgenmad til Kirsten	1		story	En dag med Anna og Lotte	24033-2	ELAP music	Calm
Swear it again		Westlife	pop	Unbreakable, The greatest hits vol.1		BGM UK&Ireland Ltd.	Calm
Vindens farver		Simone	pop	Simone	C00130-2	CMC Records	Calm
I want tomorrow		Enya	relaxation	cd-copy			Calm
Earth spirit		Terry Oldfield	relaxation	cd-copy			Calm
The journey	1		relaxation	Music Cure	GFO 20132	Gefion Records	Calm
Sonata Nr 14, C sharp Minor op 27			classical	Lapselleni Iltahetki	8.5503104/2 FIN	Naxos	Calm
Namnsang	2	Kaj & Andrea	childen	Bom-Tjickabom	CMC 5249922	CMC Records	Calm
Mother's song	sång	Mother	childen				Calm
The magic of Mozart	1		classical	Music for relaxation	440083-2	London	Calm
The forest			relaxation	Alpina Spirit	55776-Z	Natures Harmony	Calm
Elk river morning		B. J:son Lind &	relaxation	Inner Beauty	FMF-CD 1177	Fønix Musik	Calm

		T.Carlsson					
Arrival of spring	1		relaxtion	Quiet moments	PSP9809C	Bombardier Aerospace	Calm
Ti-Ti Nalle - Yön värit	24	Riitta Korpela	children	Parhaat	TNCD010	Ti-Ti Tuotanto Oy	Calm
Nine million bicycles		Katie Melua	pop	Piece by piece (från I-pod)			Calm
Yesterday, Lennon/McCartney	1		pop	In a pan pipe mood	FMC111		Calm
I feel the earth move	1	Carole King, Tapestry	pop		CDEPC 32110	Epic	Calm
Stilla natt	12		ballads & trad songs	Unique tracks world wide	DPD-SE5		Calm
Nine million bicycles	1	Katie Melua	pop	Nine million bicycles	DRAMCDS0012	Dramatica Records	Calm
Rain forest			relaxation	cd-copy			Calm
Pippi Långstrump	1		children	cd-copy			Calm
	1	Il Divo	children	cd-copy			Calm
Eine kleine Nachtmusik	1		classical	Posthorn serenade	LC0173	Deuche Grammophon	Calm
Vargsången	12		children	Hujedamej och andra visor	GRAMMCD254	Grammofon barnmedia	Calm
Mandy	1	Westlife	pop	Absolut Lugna Favoriter	EVACD4041	Eva records	Calm
Good night baby	sång	Father	pop				Calm
Mulan	DVD		children	Filmmusik, Mulan (cd-copy)			Calm
NON-CLINICAL PARTICIPANTS							Act/calm
Crazy			pop	cd-copy			Act
Krokodilen i bilen	1		children	Älskade barnvisor från Barnkammarboken	33421823	Bonnier Carlsson	Act
Dämpa basen	9		pop	Lilla melodifestivalen 2006 (cd- copy)			Act
Här ska byggas			children	Byggare Bob		Universal Music TV	Act
We're from Barcelona	1		pop	I'm from Barcelona	94635486223	Virgin	Act
Headless cross	1	Black Sabbath	pop	The sabbat stone		Bel Biem	Act
Krokodilen i bilen	1		children	Älskade barnvisor från	33421823	Bonnier Carlsson	Act

				Barnkammarboken			
Far & flyg	19		children	Astrid Lindgrens stora samlingsskiva			Act
Jag hamrar och spikar	3		children	Barnkammarboken vol.2	33423663	Bonnier Carlsson	Act
Jag hamrar och spikar	3		children	Barnkammarboken vol.2	33423663	Bonnier Carlsson	Act
Hjulen på bussen	1		children	Barnkammarboken vol.2	33423663	Bonnier Carlsson	Act
Imse vimse spindel Wow!	5		children	Älskade barnvisor från Barnkammarboken	33421823	Bonnier Carlsson	Calm
Rumpringen	10	Märith Bergström-Isacsson	children	Musik från Topp till tå	SSMDC20599	Svensk skolmusik AB	Calm
Imse vimse spindel	3	Märith Bergström-Isacsson	children	Musik från topp till tå	SSMDC20599	Svensk Skolmusik AB	Calm
Trollmors vagsång	sång	Mother	children				Calm
Trollmors vagsång	4		children	cd-copy			Calm
Trollmors vagsång	15		children	Älskade barnvisor från Barnkammarboken	33421823	Bonnier Carlsson	Calm
Trollmors vagsång	15		children	Älskade barnvisor från Barnkammarboken	33421823	Bonnier Carlsson	Calm
Idas sommarvisa	3		children	Astrid Lindgrens stora samlingsskiva			Calm
Trollmors vagsång	11	Dunsö Kapell	children	Imse Vimse med Dunsö Kapell	GAMMCD691	Grammofon	Calm
Trollmors vagsång	11	Dunsö Kapell	children	Imse Vimse med Dunsö Kapell	GAMMCD691	Grammofon	Calm
Trollmors vagsång	11	Dunsö Kapell	children	Imse Vimse med Dunsö Kapell	GAMMCD691	Grammofon	Calm

APPENDIX 10 Tool for Music Analysis (TMA)

Tool for Music Analysis (TMA)

Developed by Erik Christensen and Märith Bergström-Isacsson 2009, inspired by Grocke (1999), Hooper (2003) and Aare, Grønager & Rønnefelt (2003)

Surface, Energy, Mood

Volume		loud	medium	quiet
Tempo	(beats per minute)	fast	medium	slow
Pulse		regular pulse / free flow		
Timing		pushing	on the beat	laid back
Sound - Timbre	cutting through	rough	medium	blending in
		accented	medium	smooth
		staccato	medium	not accented
				legato

Presence, Attention

Effects		hook, break, gimmick		
Voice	male / female	solo / group	lyric	
Time and space	non-directed (space)	forward-directed (time)		

Coherence, Memory

Melody		scale: major short phrases	minor long phrases	modal
Harmony	short/predictable	varied / unpredictable		
Structural form		predictable	medium	unpredictable
Features	repetitions, sequencing, call-and-response, ready-steady-go			