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AUTONOMIC CORRELATES AT REST AND DURING EVOKED ATTENTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EFFECTS OF SYMPATHOMIMETIC MEDICATION

by

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Man's mind stretched to a new idea never goes back to its original dimensions

~Oliver Wendell Holmes~

SUMMARY

Title: Autonomic correlates at rest and during evoked attention in children with attention-deficit/hyperactivity disorder and effects of sympathomimetic medication
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Indications are that autonomic under-arousal exists in children with ADHD. Published results are, however, controversial and few studies examine the relationship between the autonomic nervous system and focussed attention. In line with the indications of sympathetic under-arousal, patients with the disorder are treated with sympathomimetic stimulants such as Ritalin (methylphenidate). Since these medications stimulate the sympathetic nervous system, they possess the potential to influence cardiac function. The aims of this study were a) to assess autonomic nervous system functioning in 20 children with ADHD, as compared to controls, and to examine the effects of focussed attention and sympathomimetic medication on this system, b) to investigate cardiac functioning in 20 children with ADHD, as compared to controls, and to examine the effects of sympathomimetic medication on this system and c) to assess EEG functioning in children with ADHD, as compared to controls, and to examine the effects of sympathomimetic medication on this functioning. Children with ADHD were tested while they were stimulant-free and during a period in which they were on stimulant medication, while controls were tested once. Autonomic nervous system activity of the children was assessed at baseline and during focussed attention by means of heart rate variability (HRV) and skin conductivity. Attention was evoked by means of a program on the BioGraph Infiniti biofeedback apparatus, which is used specifically to train ADHD individuals to increase their attentive abilities. HRV was determined by time-domain, frequency-domain and Poincaré analysis of RR interval data. Skin conductivity was determined by BioGraph Infiniti biofeedback apparatus. Cardiac functioning of the children was assessed at baseline by means of blood pressure recordings and electrocardiograms (ECGs). Blood pressure was measured by means of a stethoscope and mercurial sphygmomanometer. ECGs were obtained by means of a Schiller CardioLaptop AT-110 ECG recorder using the standard 12-lead cable positioning for a resting ECG and parameters measured included HR, RR, QT, JT, QTc, JTc, QTd, JTd, QTcd and JTcd. EEG values were determined at baseline and during focussed attention by means of BioGraph Infiniti biofeedback apparatus. EEG values measured in this study included theta/beta ratios, theta/SMR ratios and thalpha, low alpha and high alpha power.

The main findings of this study are that:

- Stimulant-free ADHD children show a parasympathetic dominance of the sympathovagal balance relative to controls.
- Methylphenidate usage shifts the autonomic balance of children with ADHD towards normal levels; however a normal autonomic balance is not reached.

- Stimulant-free ADHD children exhibit a shift in the sympathovagal balance towards the sympathetic nervous system from baseline to focussed attention; however, methylphenidate abolishes this shift.
- Methylphenidate usage does not, in general, cause QTc or JTc prolongation but it may cause QTc or JTc prolongation in susceptible individuals.
- Children with ADHD can not be differentiated from normal children on the basis of theta/beta ratios, theta/SMR ratios or alpha power.
- Methylphenidate increases the level of centering in children with ADHD.
- Stimulant-free ADHD children display an alpha block from baseline to focussed attention; however, methylphenidate abolishes this alpha block.

Keywords: ADHD, methylphenidate, Ritalin, autonomic nervous system, sympathovagal balance, heart rate variability, skin conductivity, cardiac function, blood pressure, electrocardiograms, theta/beta ratios, theta/SMR ratios, alpha waves, focussed attention.

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Chapter 1

Theoretical background and aim

1.1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a developmental disorder (1) characterized by inattention, hyperactivity and impulsivity (2). The inattention found in ADHD individuals commonly manifests itself as forgetfulness, messy, careless work performance and sudden shifts in attention, while hyperactivity and impulsivity most commonly manifest as fidgetiness and impatience respectively (2). Opinions on the intellectual ability of individuals with ADHD vary from below normal to normal intellectual ability. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (2), intellectual development of children with ADHD seems to be lower than that of children of a comparable age and developmental level, with ADHD children scoring, on average, nine points lower than controls on individual IQ tests (3). It has been suggested that the co-occurrence of ADHD and lower IQ scores may have genetic origins, with candidate genes for ADHD also contributing to IQ variation (3). A meta-analytic review found that adults with ADHD scored lower than non-ADHD adults on Wechsler Adult Intelligence Scales; however, the difference was small (4). The authors of the latter study suggest that only ADHD adults with co-morbid disorders may experience lower intellectual ability than non-ADHD individuals (4). Moreover, some studies have indicated comparable IQ scores between ADHD children and controls (5). The lower IQ scores experienced by ADHD individuals in some studies may, therefore, be due to the impairment of the application of skills and efficient test

taking strategies necessary to perform well on intelligence tests. This may be caused by the poor impulse control and attentional problems of ADHD (6), and not due to lower intellectual ability itself. ADHD is found in every ethnic and socio-economic group and is not limited to children (7). Childhood ADHD persists into adulthood in 58-70 % of cases, with an adult ADHD prevalence rate of 4% (8).

ADHD is classified into three subtypes, namely the predominately inattentive subtype, the predominately hyperactive-impulsive subtype and the most common subtype found in children and adolescents, i.e. the combined subtype (2). However, an individual diagnosed with any one ADHD subtype is not restricted to that subtype and can progress onto either of the other two subtypes respectively (2). ADHD is found more commonly in males with a male-to-female ratio ranging from 4:1 to 9:1 and a prevalence of 3-5% of school-age children, according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (2). This makes ADHD the most prevalent childhood disorder (9). It has been suggested that the difference in the prevalence of ADHD in males and females may merely be due to selective referral, with males exhibiting more aggressive and anti-social behaviours, and therefore being referred more often than females, who commonly exhibit problems in mood, affect and emotion (10). When controlling for differences in expression, it has been suggested that the occurrence of ADHD may be equal in males and females (10). Interestingly, in adults, the reported ratio of ADHD males to females becomes almost even (11). Moreover, it has been found that dopamine release in the ventral striatum, anterior putamen and anterior and posterior caudate nuclei is higher in adult males following amphetamine administration (12). This

sex difference in dopamine release is believed to be caused by the influence of the sex hormones on the dopaminergic system, with oestrogen decreasing dopamine release, while testosterone is believed to have no effect (12). Should a gender difference in ADHD expression occur in adulthood, it would not be unreasonable to assume that it may be due to this modulatory effect of oestrogen on the dopaminergic system.

1.1.1 Aetiology of ADHD

Although the cause of ADHD is not completely understood, research into the condition has identified various possible contributing factors such as nutrition, socio-surroundings (including early problems in parental attachment, prenatal alcohol or tobacco exposure and premature delivery), toxic chemicals (such as lead) and pharmaceuticals (such as anticonvulsants), as well as possible inherent physical deficiencies such as metabolic, neuroanatomical and neurochemical deficits. It is, however, believed that the greatest contributors to the development of ADHD are neurological and genetic factors (13). It is feasible to assume that the aetiology of ADHD is not one dimensional, but instead involves various neuroanatomical and neurochemical systems (8), with the main abnormalities believed to be catecholaminergic, specifically dopaminergic, and fronto-striatal dysfunction (14). Dopamine is believed to be responsible for the integrative properties and synaptic plasticity of the frontal-striatal circuits (15), causing us to assume that dopaminergic abnormalities may lead to fronto-striatal dysfunction. This highlights the potential role of dopaminergic dysfunction as the central ADHD abnormality. Studies of cerebral spinal fluid in ADHD children have indeed shown decreased dopamine levels in children with ADHD, as compared to controls (13).

1.1.2 Theories on ADHD

Central to the understanding of the theories on ADHD discussed below, is the distinction between peripheral and central autonomic nervous systems. The peripheral autonomic nervous system consists of the thoracolumbar sympathetic branch and craniosacral parasympathetic branch, which regulate the activity of the heart, smooth muscle fibres, exocrine glands and some endocrine glands (16). The brainstem consists of various neuromodulatory systems which are responsible for the regulation and modulation of the activity of various central nervous system structures (17). These neuromodulatory systems project diffusely to a number of cerebral structures and are also capable of propagating impulses *via* volume transmission, whereby neurotransmitters are released into the extracellular fluid (17). The central noradrenergic neuromodulatory system consists of cell bodies in the locus coeruleus and lateral parts of the medullary reticular formation such as the lateral tegmentum (18). This system is responsible for cortical activation, an increase in cerebral responsiveness to stimuli, an increase in the rate at which the brain processes information and the ability of an individual to focus attention on the relevant and ignore irrelevant incoming information (17). Ascending and descending fibres from the central noradrenergic cell bodies innervate the entire cerebral cortex, the brainstem, thalamus and hypothalamus, limbic forebrain, cerebellum and spinal cord (17). However, the central noradrenergic pathway of most interest in ADHD is the lateral tegmental noradrenergic circuit, which involves the innervation of the orbitofrontal cortex by A2 noradrenergic neurons of the solitary nucleus in the medullary reticular formation (19) (see Fig 1-1). These noradrenergic neurons of the solitary nucleus receive vagal afferents and project to the orbitofrontal cortex via the medial

forebrain bundle (19). The central dopaminergic neuromodulatory system, on the other hand, consists of cell bodies in the substantia nigra and ventral tegmentum and is believed to be responsible for attention, alerting, motivation and asymmetric motor behaviour (18). The dopaminergic ventral tegmental forebrain-midbrain circuit, also important in ADHD, involves the dense ipsilateral innervation of the orbitofrontal cortex by A10 dopaminergic neurons in the ventral tegmentum of the midbrain (19) (see Fig 1-1). The orbitofrontal cortex, in turn, controls the sympathetic and parasympathetic nervous systems via its influence on the medullary and hypothalamic autonomic control areas and is described as the apex of the hierarchy of control over autonomic functions (20) (see Fig 1-1). The noradrenergic lateral tegmental forebrain-midbrain pathway is believed to activate the parasympathetic nervous system via outputs from the orbitofrontal cortex to the parasympathetic autonomic areas of the hypothalamus such as the lateral hypothalamus, whose activation results in bradycardia and quiet inactivity (21); and to noradrenergic neurons in the medullary solitary nucleus, which sends noradrenergic outputs to the paraventricular nuclei, resulting in decreased energy expenditure and motor activity (20). This circuit is therefore responsible for passive coping and withdrawal, as well as inhibitory states (18) and can be described as the central parasympathetic nervous system pathway. The dopaminergic ventral tegmental forebrain-midbrain pathway, on the other hand, is responsible for the activation of the sympathetic nervous system *via*, for example, the activation of the hypothalamic ventromedial nucleus, which is involved in cardiac acceleration and vagal suppression (20); activation of the hypothalamic paraventricular nucleus, which is responsible for the inhibition of medullary cardio-inhibitory neurons (20); and activation of ventral

tegmental dopaminergic neurons which innervate the hypothalamic paraventricular nuclei causing the production of corticotrophin releasing hormone (CRH), which can lead to, amongst other functions, an activation of the peripheral sympathetic nervous system (20). The ventral tegmental limbic system is therefore responsible for high levels of positive affect and exploratory behaviour, behavioural hyperactivity and hyperarousal (19), and can be described as the central sympathetic nervous system pathway. The reciprocal connections of the orbitofrontal cortex and the autonomic nervous system areas allow for the essential control of the orbitofrontal cortex over emotional behaviour, allowing for emotional self-regulation (18). The orbitofrontal cortex therefore regulates autonomic responses to affective cues (19).

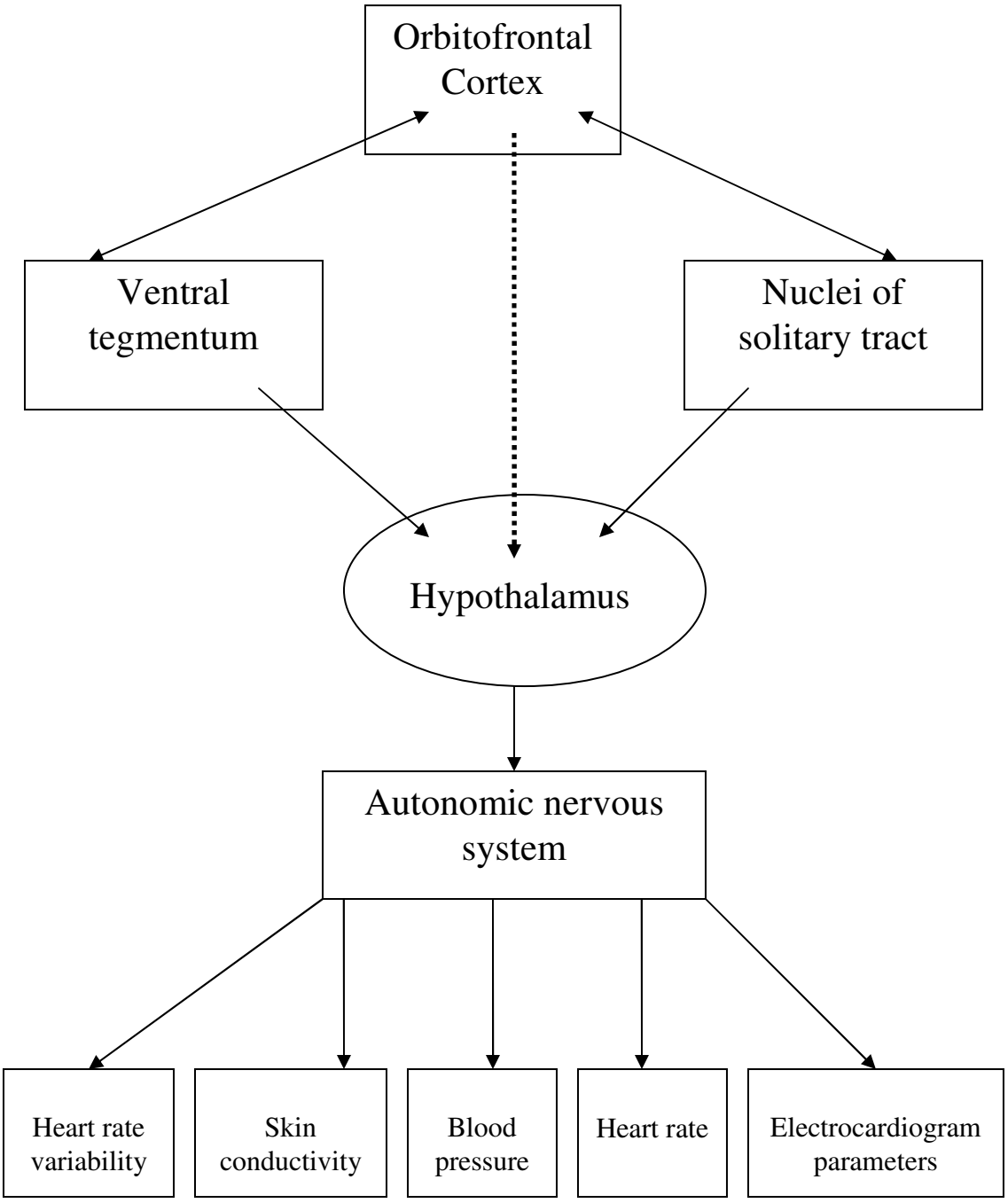

Figure 1-1: Central autonomic pathways. The ventral tegmental dopaminergic pathway and lateral tegmental noradrenergic pathway both innervate the orbitofrontal cortex. These pathways are reciprocal, with the orbitofrontal cortex sending cholinergic impulses back to the ventral tegmentum and the nucleus of the solitary tract. These areas both influence the autonomic nervous system via their activity on the hypothalamus. The orbitofrontal cortex also sends direct impulses to the hypothalamus. The action of the autonomic nervous system can then be picked up in peripheral indices of autonomic function such as heart rate variability, skin conductivity, blood pressure, heart rate and electrocardiogram parameters.

1.1.2.1 Gray's Motivational Theory

Gray's Motivational Theory describes a Behavioural Activation System (BAS), consisting of the central dopaminergic pathway encompassing the ventral tegmentum and nucleus accumbens, as well as a Behavioural Inhibition System (BIS), consisting of the septo-hippocampal system innervated by the serotonergic raphe nuclei and noradrenergic locus coeruleus (22). The BAS is believed to be responsible for approach and active avoidance (23), with the BIS being sensitive to signals of conditioned punishment and resulting in an inhibitory effect on behaviour (13). Under this theory, the impulsivity of ADHD can therefore be ascribed to an excessive BAS, attenuated BIS, or both (23). It is believed that a deficit of behavioural inhibition impairs the development of executive functioning such as working memory, self-regulation of affect, motivation and arousal (8). It is interesting to note that the serotonergic median raphe nuclei are believed to be responsible for the desynchronization of the hippocampal electroencephalography (EEG), causing a block of hippocampal theta activity (24). Attenuation of the BIS, which is believed to contribute to the manifestation of ADHD, may be caused by an attenuation of the serotonergic raphe nuclei. This would, in turn, remove the inhibitory effect of the raphe nuclei on theta activity, resulting in the characteristic excess theta activity seen in individuals with ADHD, discussed later.

1.1.2.2 Panzer and Viljoen's neurodevelopmental theory

Similar to Gray's Motivational Theory is the theory by Panzer and Viljoen which states that ADHD is a developmental abnormality. It is known that the early practising period (12-14 months) of a child's development is dominated by the ventral tegmental

dopaminergic limbic system which stimulates the sympathetic nervous system and is therefore responsible for hyperactivity and distractibility (19). The late practising period (14-18 months) involves the inhibition of the sympathetic ventral limbic system and the innervation of the right orbitofrontal cortex by the parasympathetic lateral tegmental noradrenergic limbic system (19). Both ventral and lateral tegmental circuits are believed to activate the frontal lobes and thereby enhance focus, attention, concentration and alertness (25). It is suggested that disapproval from a caregiver plunges a child into a parasympathetic-dominant "shame state" characterized by withdrawal, whereas consolation allows the child to regain sympathetic dominance and continue playing (20). The theory by Panzer and Viljoen therefore hypothesizes that children with ADHD remain stuck in the early practising period and do not develop their lateral tegmental noradrenergic forebrain-midbrain system (1).

1.1.2.3 Porge's Polyvagal theory

Porge's Polyvagal theory advocates that the vagal efferents terminating on the sinoatrial node of the heart originate in the dorsal motor nucleus, which mediates reflexive cardiac activity, and the nucleus ambiguus of the medulla, which is described as the "smart" vagus and mediates respiratory sinus arrhythmia (RSA) (26). RSA is described as the parasympathetic influence on cardiac function found during respiration, namely a decrease in vagal tone and an associated increase in heart rate during inhalation and *vice versa* (23). Under this Polyvagal theory it is believed that sustained attention is associated with a parasympathetic nervous system mediated decrease in heart rate (27).

ADHD individuals, with their attenuation of sustained attention, would therefore exhibit an attenuation of the parasympathetic nervous system response.

1.1.2.4 Vakalopoulos' Pre-motor Theory

Another theory, presented by Vakalopoulos, is that the core symptoms of ADHD are due to an imbalance between the neuromodulatory effects of acetylcholine and the monoamines (28). Under this theory, a dual process model of cognition, which consists of parallel neural networks, is proposed (28). These parallel neural networks are categorized by complex or stereotypical motor behaviours respectively, such that the monoaminergic system facilitates conscious, complex, voluntary pre-motor activity and inhibits unconscious, simple, automated pre-motor activity (28). This system will therefore permit the reversal of learning by triggering synaptic plasticity (28). The cholinergic system, on the other hand, will facilitate unconscious and inhibit conscious networks (28). This theory suggests that the hyperactivity and impulsivity characteristic of ADHD is due to the failure of the voluntary suppression of previously learned automatic behaviours (i.e. cognitive inhibition) due to a deficit in monoaminergic antagonism of cholinergic facilitated responses (28).

Despite several theories on the aetiology of ADHD, the picture, both at baseline level and with stimulation, is not completely clear. It would appear that the catecholaminergic systems play a role, but confusion still exists. This is further confounded by the presence of co-morbidities such as that of oppositionality and conduct disorder and to the type of assessment techniques employed, as well as the specific patients being studied.

1.1.3 Treatment of ADHD

1.1.3.1 Stimulants

Treatment of ADHD is often highly controversial, with various methods being advocated. In line with the indications of sympathetic under-arousal found in individuals with ADHD, several pharmaceuticals are used to treat the disorder, with most of these drugs having mild to moderate stimulatory effects on the sympathetic nervous system, resulting in sympathomimetic effects such as increases in blood pressure and heart rate (29). Interestingly, in 2006, five million individuals in the U.S were taking stimulants, with 3.5 million of these between the ages of three and nineteen (30). Stimulants such as methylphenidate (Ritalin) and the amphetamines, which are structurally similar to the catecholamines (13), are believed to increase the concentration of dopamine and noradrenaline in the synaptic cleft by, for example, inhibiting their pre-synaptic transporters and thereby blocking their re-uptake (31). The central nervous system areas predominantly affected include the limbic system, prefrontal cortex and ascending reticular activating system (ARAS) (31), with Ritalin specifically shown by functional magnetic resonance imaging (fMRI) to alter the frontal-striatal circuitry by increasing the activation of the prefrontal cortex and striatum (8). The prefrontal cortex and striatum commonly show under-activity in ADHD individuals; therefore the normalization of the activity of these areas may possibly account for the improvements in symptoms of ADHD, seen with stimulant usage. Stimulants have, furthermore, been shown to cause an increase in the activity of bilateral orbitofrontal areas and the left sensorimotor and parietal areas, together with a decrease in the activity of the left temporal region (13).

Although these sympathomimetic drugs could potentially increase the risk for sudden cardiac death, the necessary statistics to assess such a possibility are not available (29). Furthermore, the consequences of long-term exposure to stimulants such as methylphenidate remain unclear (32). Recent concerns over the United States Food and Drug Administration (FDA) warnings on stimulants have, however, increased, with one ADHD medication, i.e. Strattera, being associated with potential liver damage (33). Concerns are that stimulants may cause excessive neural plasticity, resulting in irreversible damage to developing brains. Rats treated with methylphenidate have presented with dysfunctional brain reward systems (32,34) and the development of depressive-like behaviours during adulthood (32). Furthermore, it has been shown that, when treated with methylphenidate, rats become less responsive to natural rewards and more sensitive to stressful situations with increased anxiety-like behaviours and increased plasma levels of corticosterone (35). In 2005 it was found that Ritalin usage at therapeutic dosages resulted in the induction of cytogenetic abnormalities in peripheral blood lymphocytes of paediatric patients (36). These cytogenetic abnormalities included chromosome aberrations, micronuclei, sister chromatid exchanges and chromosome rearrangements such as nucleoplasmic bridges (36). Interestingly, in every individual examined in this study there was a statistically significant increase in every genotoxic endpoint analyzed with p-values equal to zero (36). However, a follow-up study by Walitza *et al* (37) found that methylphenidate usage was not associated with any alterations in the number of micronucleated cells. Furthermore, a study by Suter *et al* (38) concluded that methylphenidate usage was associated with negative genotoxicity findings in the *in vitro* human lymphocyte chromosomal aberration assay.

The use of methylphenidate together with an α-2 adrenergic receptor agonist sometimes used to treat ADHD, has resulted in several reports of unexplained deaths in children (8), while adverse events such as syncope, chest pain, myocardial infarction, stroke and arrhythmias due to stimulant treatment have been reported (29). Other potential side-effects of these medications include appetite suppression, headaches, stomach aches, irritability, nausea, sleep disturbances, depression, growth suppression, anaemia, and the appearance of tics and gross brain malfunction in children, to name a few (25). Rebound also occurs in individuals on these stimulants, in which the worsening of ADHD symptoms beyond baseline conditions and the appearance of irritability and rage occur as the blood level of the stimulant decreases (30).

It is believed that the wide range of clinical problems associated with ADHD cannot be treated effectively by medication alone (39), with these drugs being highly criticised to cause no improvement in reading, athletic or gaming skills, pro-active social skills or learning (40). However, some studies have shown that the number of errors made by ADHD children in a continuous performance task decreases significantly with the administration of stimulants (41). Similarly, certain studies have shown that these stimulants improve attention, school behaviour and social and family functioning in 75-80% of ADHD children (8). It is, however, estimated that 20-30% of children taking these stimulants experience no positive response or, even worse, further deterioration of symptoms (13). Furthermore, of the percentage of ADHD individuals who do respond, a fraction of these are incomplete responders, whereby the improvements noted only occur in some domains (42). Moreover, these stimulants are believed to cause no long-term

adjustment in academic achievement and anti-social behaviours (40) and are believed to be effective for only a limited duration of time (43), after which tolerance occurs, in which the efficacy of the drug decreases with prolonged use (30). This is believed to be due to compensatory decreases in the number of receptor sites available for the stimulants to act on (13). Some studies even suggest that the effectiveness of stimulants cannot be demonstrated beyond four weeks (44). Furthermore, stimulants, especially amphetamines, have high addiction potentials (30) and relatively low compliance, with 20% of individuals terminating use within four months (44). Stimulants, moreover, display a wide inter-individual variability in dose response (45), instigating the need for titration to determine the correct dosage for specific individuals (13). Furthermore, high stimulant doses have been associated with cognitively toxic effects in some children, characterised by over-focussing, constriction of attention and diminished flexibility in problem solving (13). These stimulants have no lasting effects on the underlying neuropathy of ADHD, even with long-term use (40), and are therefore described as merely a prophylactic intervention (39). Other medications used to treat ADHD include the tricyclic antidepressants, which block noradrenaline and serotonin re-uptake and downregulate β-adrenergic receptors, and atomoxetine (Strattera), which inhibits the noradrenaline transporter in the prefrontal cortex and thus inhibits noradrenaline re-uptake (30). Interestingly, the prefrontal noradrenaline transporter is believed to play a prominent role in regulating the levels of dopamine in the prefrontal cortex (14) and, furthermore, it is believed that serotonin receptors on endorphin-releasing neurons in the hypothalamus increase the activity of dopamine pathways by inhibiting the release of γ-aminobutyric acid (GABA) in the ventral tegmentum (11). Therefore, an increase in

either noradrenaline or serotonin has the ability to affect dopamine transmission, thereby supporting the previously mentioned possibility of dopaminergic dysregulation as the major abnormality in ADHD. The use of tricyclic antidepressants has been criticized in children due to adverse cardiac events (46). Tricyclic antidepressants are believed to block the potassium channel responsible for rapid cardiac repolarization and therefore result in prolongation of the QT interval (47). Therefore, tricyclic antidepressants are associated with an increased risk for lethal cardiac arrhythmias (48).

1.1.3.2 Neurofeedback

Neurofeedback is described as an operant conditioning procedure whereby an individual can learn to self-regulate the electrical activity of their brain (49). The use of neurofeedback to treat ADHD dates back to the 1970's; while only in the 1990's did it become widely available (44). The intended goal of this treatment is to train subjects to maintain a calm, relaxed, alert and focussed mental state while carrying out cognitive tasks (50). The results of several studies have indicated that neurofeedback is efficacious in treating children with ADHD (15), with significant clinical improvements being noted in 75% of patients according to published research studies (42). This, together with the fact that non-drug alternatives for ADHD have become more viable and sought-after (33), has resulted in a recent increase in the use of neurofeedback treatment. Studies have shown that the improvements seen with neurofeedback training are equivalent to those seen on stimulants (44). However, according to the efficacy guidelines jointly established by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neuronal Regulation, neurofeedback is described as "probably

efficacious" in the treatment of ADHD (42). On the downside, literature supporting the use of neurofeedback treatment has, on occasion, been criticised as being methodologically flawed and unconvincing (51). Some believe that data from studies that randomly assign participants to neurofeedback or comparison groups is needed, in order to clarify the response of patients to neurofeedback (42). However, others argue that randomized control designs almost never enrol patient samples that are representative of the specific patient population with the disorder in question and the studies conducted so far have been effectiveness studies which evaluate the treatment as it is provided in clinical practise (51).

Nevertheless, in contrast to stimulant therapy, neurofeedback training has been associated with long-term sustained benefits with significant improvements in behavioural and neuropsychological measures (40). One case-study has shown that a child suffering from ADHD who was treated with neurofeedback training in the 4th grade was able to maintain sustained control over their hyperactive symptoms for ten years (52). Neurofeedback is, furthermore, believed to affect a wider area of functioning and to generalise to other areas, such as sport and social functioning, better than other interventions (50). Neurologically, neurofeedback training has been shown to cause an increased activation of the right anterior cingulate cortex, left caudate nucleus, right ventrolateral prefrontal cortex, left thalamus and left substantia nigra during attentional tasks (15). Normalization of the activity in the caudate nuclei and substantia nigra is believed to be mediated by dopamine (49). The activation of these brain areas, associated with behavioural inhibition and decision making and monitoring, was found to be absent in

controls not treated with neurofeedback (15). Neurofeedback would thus appear to have the potential to normalize the deficit in anterior cingulate cortex activity, which is believed to be central to the deficit in attention associated with ADHD (49), discussed later.

Neurofeedback training is moreover associated with a decrease in commission and omission errors as well as decreases in response time and response time variability in tests such as the GO/NOGO test (53). Errors of commission and errors of omission are believed to represent impulsivity and inattentiveness respectively (54), with response time and response time variability representing processing speed or sustained attention abilities and variability in attention respectively (51). Furthermore, neurofeedback training is believed to cause an increase in the late components of evoked response potentials, such as P300 (53), which is believed to represent an increase in the integration of stimuli in working memory (54). A marked increase in the contingent negative variation, which is a slow negative wave occurring during the fore-period of a reaction time task that is related to expectancy, mental priming, association and attention (55), has been shown to occur with neurofeedback training specifically directed at event-related potentials (56). This increase has been shown to be stable six months after treatment (56). Furthermore, an increase in IQ tests scores has been shown to occur in children with ADHD, suggesting that neurofeedback training is associated with intellectual improvements (40,56,57). It has, furthermore, been shown to increase levels of cortical activation and behavioural and attention ratings, with these improvements being maintained throughout a three year period (58). Moreover, it is associated with an

increase in behavioural and emotional adjustment of ADHD individuals (51); an increase in academic performance, specifically arithmetic, word recognition and spelling scores (50); improvements in sport (50); and a decrease in externalizing and internalizing problems (44). In adults specifically, it is associated with improvements in organizational and time management skills and memory (50). Moreover, it has been shown that a large percentage of ADHD patients are able to decrease their dose of stimulants or discontinue stimulant treatment completely due to the effects of neurofeedback training (56,58). Although quantitative electroencephalography (QEEG) variables of interest such as beta, SMR and delta-theta amplitude have shown no consistent pattern of improvement with neurofeedback treatment (42), a decrease in mean theta/beta microvolt ratios has been shown to occur (39,50).

The most commonly used types of neurofeedback training for ADHD include SMR and beta training. SMR neurofeedback training involves an enhancement of SMR activity, together with a suppression of theta activity. SMR training specifically is associated with a decrease in impulsivity and hyperactivity; an increase in attention processing, due to a decrease in somatosensory and motor interference in attentive cognitive processing; and an improvement in semantic memory performance (54,59). It has, based on such results, been suggested that SMR may aid in the maintenance of memory representations used in semantic working memory (59). SMR is further believed to be associated with an increase in awareness and preparation to engage in a planned and purposeful action (58). Beta neurofeedback training, on the other hand, involves an enhancement of beta activity, together with a suppression of theta activity. Beta activity is associated with sustained

mental effort (58) and beta neurofeedback training is believed to help alleviate inattention due to its activation of the noradrenergic alertness/vigilance attentional network (54). Therefore, SMR and beta training are described as attention-enhancing and arousal-enhancing respectively (54).

It is believed that the positive effects of neurofeedback are due to modulation of the neural activity in the fronto-striatal circuits by dopamine (15), with dopamine receptors 4 and 5 (DRD4 and DRD5) and long-term potentiation (LTP) believed to be involved (49).

Some believe that the excessive use of certain types of attention results in an attentional rigidity, causing neurotransmitter and chemical-nutritional deficits due to the chronic exhaustion of underlying systems (33). Under this view, the target of neurofeedback training is to increase EEG flexibility by learning to control brain synchrony and thereby gaining volitional attentional flexibility (33). Synchrony and asynchrony can be trained at any frequency, with synchrony described as any in-phase activity between waves of an identical frequency and asynchrony occurring in many forms, such as out-of-phase activity or a change in frequency (33).

It is important to note here that it is possible for deterioration and relapse to occur with neurofeedback training; however, this is believed to be due to the discontinuation of treatment before its necessary completion (58). Neurofeedback treatment courses range from 20 to 50 or more sessions, with 40 sessions believed to be necessary for the training to hold longitudinally (33). However, the presence of multiple co-morbidities together

with the related higher level of medication usage, generally results in a need for more than 40 sessions of treatment (33). Adverse events such as increased moodiness, hyperactivity, irritability, anxiety and impaired anger control have been shown to occur mid-phase in individuals treated with stimulants and neurofeedback simultaneously; however, a decrease in the medication dosage has been shown to resolve these symptoms (58). Similarly, headaches and dizziness associated with neurofeedback have been shown to occur, with these symptoms being resolved with a short resting period or food consumption (58). Neurofeedback training has not been shown to be beneficial in children under 6, mentally retarded individuals, individuals suffering from bipolar disorder, depression, seizure disorder, traumatic brain injury, psychosis or alcohol or drug abuse (58), individuals with a history of neurological disease or individuals with family dysfunction which is likely to interfere with their participation in the treatment process (33). It is important to note here that some clinicians have, however, reported positive neurofeedback outcomes with clients with the above-mentioned exclusionary criteria (33). As with stimulant treatment, a certain percentage of ADHD individuals will not be able to learn to regulate their cortical activity and are therefore described as neurofeedback non-responders (58). This percentage is, however, comparable to the rate of stimulant non-responders, which is described as 20-30% (13).

1.1.3.3 Other treatments

Other treatments that are advocated in their own right include dietary changes such as the elimination diet, which advocates the avoidance of artificial ingredients and preservatives such as monosodium glutamate (MSG), a restriction in the amount of refined

carbohydrates, replacing refined carbohydrates with protein and complex carbohydrates, and the supplementation of co-factors and essential fatty acids (7). Furthermore, two-thirds of ADHD children are said to be deficient in zinc, magnesium and Vitamin B6, which is involved in neurotransmitter synthesis, advocating the inclusion of vitamin supplementation in their diet (7).

Also similarly promoted is behavioural training, which teaches ADHD children how to correctly adjust to their environment (60). This treatment has, however, been criticised as it is believed that cessation of training results in the rapid return of symptoms and dysfunction (60) and the procedure itself is believed to be complicated and time-consuming (57). Interestingly, it has been shown that parenting style has an effect on ADHD symptom presentation, with systematic parenting, described as a consistent use of rewards and response cost strategies, being associated with a significant reduction in ADHD symptoms (39). Therefore, it is feasible to assume that parent counselling may yield beneficial results. Other treatments include relaxation, massage, meditation, laser acupuncture and mirror feedback, all with varying results (61). It is argued that the effectiveness of treatment depends on the specific ADHD patient being treated (61).

Success has been claimed with a variety of unorthodox treatments. For instance, a five year old patient with ADHD treated unsuccessfully with stimulants for three years was treated by a chiropractor for a period of eight weeks, during which the child's cervical kyphosis was said to be corrected (62). After this eight week period the child's behaviour

is said to have improved, facial tics resolved and ADHD symptoms improved sufficiently for medication to be discontinued (62).

Therefore, the best approach currently available for the management of ADHD is a multimodal approach encompassing various treatments (43).

1.1.4 Clinical findings of ADHD

1.1.4.1 Neuroimaging

Although the disorder was initially referred to as "Minimal Brain Damage Syndrome" and subsequently as "Minimal Brain Dysfunction" (8), no distinct neural profile has, as yet, been established for ADHD. Several neural abnormalities have, however, been described. The neural attention network is believed to consist of the noradrenergic system in the locus coeruleus (63), responsible for achieving and maintaining an alert state (59); the cholinergic system in the basal forebrain (63), which is responsible for orienting by selecting the required information from sensory input (59); and the anterior cingulate and lateral prefrontal cortices, which are target areas for the dopaminergic system, and are believed to be responsible for executive attention (63), which, amongst other functions, is involved in working memory and is responsible for resolving any conflict among responses (59). Interestingly, all these areas have, by means of neuroimaging, been shown to be affected in individuals with ADHD.

It has, amongst others, been shown that ADHD individuals display an under-activity in the dopaminergic-rich striatum and frontal projections, which are associated with reward

processing (64) and response inhibition (15); abnormal volume and reversed asymmetry of the basal ganglia, where dopamine is significantly produced (65); a decrease in activity of the anterior cingulate cortex, thalamus and hippocampus; and a decrease in the size of the corpus callosum and prefrontal cortex (8). It has, however, been suggested that the decreases in corpus callosal volume may be more related to learning disabilities than ADHD itself (13). In addition to the decrease in the size of the prefrontal cortex, it has been shown that ADHD children lack the normal right-greater-than left asymmetry in the mass of the frontal lobes, with a hyper-coherence between left and right frontal recordings (60). Studies have shown that ADHD adults cannot generate an anterior cingulate response during a response task (8), with the anterior cingulate cortex believe to play an important role in the frontal attention network, as previously mentioned. The anterior cingulate is furthermore believed to be involved in functions such as selective attention, response inhibition, allocation of attentional resources and response selection (15), providing a basis for the impairment of these functions in individuals with ADHD. Furthermore, neuroimaging studies into ADHD have documented a decreased size and under-activity of the globus pallidus and caudate nucleus (8) and magnetic resonance imaging (MRI) studies on twins discordant for ADHD have indicated smaller caudate volumes in the affected twin (66), thus supporting the hypothesis of striatal under-activity in ADHD. Attention deficits have indeed been associated with a decrease in the activation of both the right and left caudate nuclei (8). Interestingly, it is believed that the ability to interrupt an about-to-be-executed response requires the activation of the right inferior frontal cortex and the caudate region (67). Therefore, the under-activity of the caudate region in ADHD individuals could possibly explain their inability to react

appropriately to a situation since the system which would inhibit inappropriate responses in these individuals does not function adequately. The impulsivity associated with ADHD has recently been hypothesized to be related to problems in time perception or timing, with the noradrenergic-rich (16) cerebellum playing an important role in processing temporal information in order to elicit an appropriate behavioural response (67). Interestingly, neuroimaging studies have recently indicated a decrease in the size of the cerebellum in ADHD individuals (8). This decrease in cerebellar volume may localize to the vermis, which is believed to be involved in maintaining attention (8). Furthermore, fMRI has indicated that task impairment is associated with a decrease in cerebellar activation in individuals with ADHD (8). Interestingly, unaffected siblings of ADHD children have been shown to display reduced cortical volume but normal cerebellar functioning (8). Therefore the reduced size and activation of the cerebellum in individuals with ADHD could potentially account for both impairments in timing and time perception, as well as the inattention experienced by these individuals.

An interesting suggestion by Casey and Durston (68) is that there exist basic learning systems in the brain which signal the top-down cortical control systems, such as the prefrontal cortex, to adjust behaviour according to changes in the environment. These systems include the basal ganglia, cerebellum and posterior parietal region (68). Therefore, ineffective signalling by any of these regions will result in poor behaviour regulation, with differences depending on the specific system impacted (68). Similarly, inefficient regulation by the top-down control systems would result in a more general form of dysregulated behaviour (68). This theory would, according to Casey and Durston

(68), account for the wide variability in cognitive performance reported in individuals with ADHD. It is interesting to note that all the above-mentioned regions have been shown to be affected, to varying degrees, in individuals with ADHD, providing preliminary support for this theory.

Further discoveries, made by ^{123}I-labelled single photon emission computed tomography (SPECT) and ^{11}C Altropane positron emission tomography (PET), indicate that individuals with ADHD exhibit higher dopamine transporter binding potentials in striatal regions, due to either an increase in the density of transporter sites or an increase in the affinity of the transporters for the ligands (14). These dopamine transporters are responsible for the uptake of dopamine into neurons (9). Therefore, an increase in the binding potential of these dopamine transporters in individuals with ADHD would account for increased dopamine re-uptake into neurons and a decrease in the extracellular dopamine available to act on receptors. This appears to be one of the potential problems accounting for the catecholaminergic dysfunction found in ADHD. Furthermore, it has been shown that treatment with methylphenidate causes a decrease in dopamine transporter binding (14). This would intuitively cause an increase in extracellular dopamine concentration which could potentially explain the improvement in ADHD symptoms seen with methylphenidate treatment.

1.1.4.2 Metabolic findings

Ten thousand SPECT studies and 15 000 patient evaluations conducted by Dr. Amen (69) have demonstrated characteristic metabolic patterns in ADHD individuals (25). These

studies have led to the classification of ADHD into 6 subtypes, based on metabolic characteristics.

i) Type 1 or "classic" ADHD: characterized by a normal resting brain but decreases in the metabolic activity of the orbitofrontal and dorsolateral prefrontal cortices during concentration (25). The main symptoms of this subtype include inattention, distractibility, disorganization, hyperactivity, restlessness and impulsiveness (25). This subtype is believed to suffer from a dopamine deficiency and subsequently responds best to stimulant treatment (33).

ii) Type 2 or "inattentive" ADHD: characterized by a normal resting brain but decreased metabolic activity in the dorsolateral prefrontal cortex during concentration (25). The primary symptoms of this subtype include inattentiveness, sluggishness, low-motivation and frequent boredom (25). These individuals are often described as day-dreamers, space cadets or couch potatoes (25). Once again, this subtype is believed to experience a deficiency in dopamine and subsequently responds best to stimulant therapy (33).

iii) Type 3 or "over-focussed" ADHD: characterized by increased metabolic activity in the anterior cingulate gyrus at rest and during concentration, as well as a decrease in the activity of the orbitofrontal and dorsolateral prefrontal cortices during concentration (25). These individuals appear to be inflexible, obsessive, argumentative, and have trouble shifting attention (25). The finding of an increase in the activity of the anterior cingulate cortex, specific to this subtype, is contradictory to previous findings. Since the anterior

cingulate cortex is believed to be an important component of the frontal attention network, an over-activity of this region would explain the extreme level of attention, which borders on obsession, found specifically in these individuals and no other subtype. These individuals are believed to be characterized by both a dopamine and serotonin deficiency and therefore respond best to stimulant therapy together with a selective serotonin re-uptake inhibitor (SSRI) (33). If neurofeedback is administered, it should specifically target an increase in alpha activity over the anterior cingulate cortex (33).

iv) Type 4 or "temporal lobe" ADHD: characterized by a decrease (or occasional increase) in the activity of the temporal lobe at rest and during concentration (25). Furthermore, concentration is once again associated with a decrease in the activity of the orbitofrontal and dorsolateral prefrontal cortices (25). Primary symptoms include inattentiveness, impulsiveness, learning difficulties, unstable moods and aggressiveness (25). The temporal lobes are believed to play an important role in memory, emotional stability, learning and socialization (70). Their dysregulation could, therefore, potentially account for some of the characteristic symptoms found in this ADHD subtype. The dominant temporal lobe is, furthermore, believed to be involved in understanding and processing of language, retrieval of words and auditory processing (70). Temporal lobe dysregulation would therefore explain the miscommunication, language difficulties and reading disabilities often found in individuals with ADHD. It has furthermore been shown that ADHD individuals have smaller right plana temporale, which is the region of the right temporal lobe that is associated with auditory detection and analysis (13). This could possibly also account for the language difficulties experienced by those with

ADHD. Interestingly ADHD has been shown to have a 78% co-morbidity with speech and language disorders (10). This subtype is best treated with anti-convulsant medication and neurofeedback therapy should target an increase in SMR and decrease in theta activity over the temporal lobe specifically (33).

v) Type 5 or "limbic" ADHD: characterized by an increase in the activity of the deep limbic system (thalamus and hypothalamus) at rest and during concentration and, once again, a decrease in the activity of the dorsolateral and orbitofrontal prefrontal cortices during concentration (25). Primary symptoms of this subtype include inattentiveness, low-grade depression, feelings of hopelessness and chronic negativity (25). The limbic system is intimately involved in the regulation of behaviour, emotion and motivation (16). The dysregulation of this system could therefore potentially account for the negative emotions experienced by this subtype. Interestingly, evidence has shown that individuals with depression exhibit higher levels of the enzyme monoamine oxidase, which is responsible for the breakdown of the monoamines (65). Therefore a link is suggested between the decreased availability of monoamines such as dopamine and noradrenaline in ADHD individuals and depression, which is commonly co-morbid (33,65). This subtype is believed to suffer from both a dopamine and noradrenaline deficiency and is therefore best treated with amino acid supplementation or stimulating antidepressants (33). Furthermore, neurofeedback therapy should target an increase in beta and a decrease in theta activity over the left prefrontal cortex specifically (33).

vi) Type 6 or "ring of fire" ADHD: characterized by a patchy increase in activity across the cerebral cortex with focal areas of increased activity in the cingulate gyrus (33), prefrontal cortex and parietal and temporal lobes, both at rest and during concentration (25). In other words, this subtype is characterised by a global cortical disinhibition (33). Primary symptoms of this subtype include inattentiveness, extreme distractibility, anger, moodiness, irritability and oppositionality (25). This subtype has been shown to respond best to anti-psychotic or anti-convulsant medication together with a psychostimulant or stimulating antidepressant (33). Although not cited by Dr. Amen, it is believed that neurofeedback does work for this subtype, resulting in an increase in psychophysiological calm and a decrease in impulsivity and oppositional behaviour (33).

It is important to note that the above-mentioned metabolic changes do not occur in all ADHD individuals. In other words, it is possible that an ADHD individual may not fit into any one group. The commonality experienced by five of the six ADHD subtypes is a decrease in the activity of the orbitofrontal and dorsolateral prefrontal cortices. The orbitofrontal cortex is believed to play a role in behavioural inhibition (13), the selection of appropriate actions, problem solving, contemplation of actions before their execution and learning from mistakes (70). Dysfunction in the orbitofrontal cortex is therefore associated with poor impulse control, decreased social skills, mood control problems and decreased control of behaviour (70), all characteristic of ADHD. The dorsolateral cortex, on the other hand, is believed to be involved in focussing and sustaining attention, with its dysfunction being associated with distraction and loss of concentration (70), both characteristic of ADHD. Moreover, the dorsolateral prefrontal cortex is also believed to

play a role in working memory (13), which is commonly impaired in ADHD individuals. Further difficulties sometimes experienced by individuals with ADHD include disinhibition of behavioural responses and difficulties in planning, verbal fluency and motor sequencing, which are all believed to be functions of the frontal lobes (13). Therefore, it is feasible to assume that the frontal lobe dysfunction seen in patients with ADHD is responsible for the deficits in inhibition and executive function characteristic of this disorder (13).

1.1.4.3 Electroencephalography findings

The normal paediatric resting EEG is characterised by a small amount of 4-8 Hz theta, significant 8-13 Hz alpha activity and scattered 14 Hz and above beta activity (71). EEG studies have shown that ADHD children, on the other hand, produce excessive theta activity, characteristic of sedated states; a deficiency in beta activity, which is required for concentration and focussed attention (25); and reduced alpha activity, characteristic of alert, relaxed states (42). The most consistent finding, however, is that of an increase in theta activity, characteristic of cortical hypo-arousal (72). The electrophysiological hypo-arousal described above has been shown to occur in 80-90% of patients, over frontal and central midline cortical regions and, furthermore, has not been shown to occur in oppositional defiant disorder, anxiety disorder and mood disorders, which are all common co-morbidities of ADHD (58).

Current research has advocated the use of QEEG in the diagnosis of ADHD patients (73). This technique involves the determination of the electrophysiological power in both the

theta and beta frequency bands and the calculation of a theta/beta power ratio, defined as the attentional index (73). This attentional index is calculated as an average across baseline, reading, listening and drawing tasks (73). The ratio of theta to beta is used in order to control for the gradual difference in theta and beta values found between different age groups (57). An individual's theta and beta values decrease with age, however, the ratio remains more constant (57). This attentional index is described as a "biological" measure of attention (39) and its determination is said to allow for the assessment of the presence and severity of ADHD, by comparison to that of a normative sample (73). This normative database, established by Monastra *et al* (74), classifies the attentional index of individuals as positive for ADHD if an individual's score is more than 1.5 standard deviations (SD) above the average obtained by same-age non-ADHD peers (74). These critical values for the attentional index are 5.03 (ages 6-11), 3.31 (ages 12-15) and 2.36 (ages 16-20) (74). Although a decrease in theta activity normally occurs with age, ADHD individuals have been shown to exhibit high theta and theta/beta ratios into adulthood (72). Previous studies have indicated a sensitivity of 90% and a specificity of 94% of the QEEG attentional index in identifying ADHD individuals (74). Sensitivity is described as the percentage of ADHD individuals that display abnormal attentional indices and specificity is described as the percentage of non-ADHD individuals that display normal attentional indices (72). Furthermore, the attentional index has been shown to yield test results consistent with those obtained from other assessment procedures, with an 83% classification agreement between attentional index and the Attention Deficit Disorders Evaluation Scale (ADDES) and 70% classification agreement between the attentional index and Test Of Variables of Attention (TOVA)

continuous performance test (74). In other words, the results of the QEEG method are consistent with those of two instruments commonly used in the assessment of ADHD patients (74). Furthermore, the QEEG attentional index has been shown to yield results which are stable across time, as shown by a re-test done thirty days later (74). More work is, however, necessary to confirm these assumptions. Furthermore, the decreased availability of the QEEG limits its usage as a diagnostic tool.

Three subtypes have been identified on the basis of characteristic brainwaves determined by QEEG (33).

- "Hypo-aroused" ADHD individuals experience a surplus of theta activity, a deficiency of beta and delta activity and elevated theta/beta ratios (33). These individuals are more likely to respond to stimulant treatment (40).
- "Hyper-aroused" ADHD individuals experience a surplus of beta activity, specifically in frontal and posterior regions (33), a decrease in theta activity and decreased theta/beta ratios (42). These "hyper-aroused" individuals constitute a small group of about 15% of ADHD children, with the only difference in symptom expression being a slight increase in temper tantrums and moodiness (72). These individuals are described as stimulant non-responders (58). However, neurofeedback protocols have been developed for both hypo- and hyper-arousal subtypes respectively (42).
- "Maturational lag" ADHD individuals are characterized by a surplus of delta and theta and a deficiency of alpha and beta activity (33).

No studies have, however, been conducted to examine whether EEG can differentiate between DSM-IV defined subtypes (72).

1.1.4.4 Event-related potentials

Event-related potentials are believed to be the summation of post-synaptic potentials of a large number of neurons that occurs in preparation for, or in response to, specific events (55). It has been shown that ADHD individuals experience smaller amplitudes and longer latencies for N1, N2, mismatch negativity, readiness potential and P3b, which indicates attentional and information processing deficits (75). The attenuation of late positive components such as P300, which is believed to be a function of prefrontal regions (13), has also been shown to occur in ADHD individuals and is corrected by the usage of stimulants (13) and neurofeedback (53). P300 is elicited by oddball stimuli and is believed to represent stimulus evaluation and the updating of models of the environment in working memory (55).

1.1.4.5 Genetic findings

Family, twin and adoption studies have indicated a significant genetic role in ADHD (9), with the disorder being more prevalent in first-degree biological relatives of ADHD individuals (2). It is likely that susceptibility to ADHD is mediated by the interaction of numerous genes and their subsequent interaction with the environment (9). This is highlighted by the fact that ADHD is a highly heterogenous disorder, with affected individuals showing a wide variation in clinical features and differences in intellect, co-morbidity, response to stimulants and prognosis (9). The candidate gene approach in

rodents has allowed the discovery of various genes believed to be associated with the disorder, including genes for neurotransmitter receptors, metabolic enzymes and synaptosomal proteins (9). The focus of these studies has, however, been on dopaminergic alleles with abnormalities in dopamine receptors 2 and 4 (DRD2 and DRD4) and dopamine transporter 1 (DAT1) occurring frequently in individuals with ADHD (42). These anomalies are believed to limit the number of dopamine receptors and the amount of available dopamine, thereby decreasing the size of dopaminergic-rich areas in the brain (42).

Interestingly, the frequency of ADHD is strongly associated with generalized resistance to thyroid hormone, caused by mutations in the thyroid receptor β gene (76). Thyroid hormone resistance is an autosomal dominant genetic disorder characterised by a hyposensitivity of the tissues to thyroid hormone (13). In one study it was found that 70% of individuals with thyroid hormone resistance suffered from ADHD (13). However, given that thyroid hormone resistance is extremely rare in children with ADHD, it is unlikely that resistance to thyroid hormone is a major cause of ADHD (13).

1.1.4.6 Autonomic correlates of ADHD individuals at baseline

Various tests are used for the identification of ADHD, however no standardized, established, diagnostic laboratory test exists (2). Currently ADHD diagnosis involves behavioural descriptors that inevitably overlap with a range of other disorders (67). Furthermore, these interview and rating scales are often confounded by rater bias (74). Although neuropsychological attention measures, such as continuous performance tests

administered and scored by computers, are considered more objective measures of inattention and impulsivity, they tend to yield a high rate of false negatives (74). Furthermore, ADHD diagnosis is complicated by the fact that none of the core symptoms are exclusive to the disorder and that the majority of sufferers have additional psychiatric disorders (44).

There are, however, indications that autonomic under-arousal exists in ADHD individuals. Some believe that it is this physiological under-activity which causes ADHD individuals to seek out further stimulation (77), resulting in inattention, impulsivity and hyperactivity. Various methods have been used in an effort to assess the autonomic nervous system level of activity in attention-deficit and disruptive behaviour disorders. In ADHD autonomic dysregulation has been indicated by abnormal responses in adrenomedullary functioning, heart rate responses, respiratory sinus arrhythmia as an indicator of parasympathetic nervous system functioning and both electrodermal responses and cardiac pre-ejection period as indicators of sympathetic nervous system functioning. Table 1-1 lists selected published autonomic nervous system findings in ADHD individuals.

Table 1-1: Studies on autonomic correlates of Attention-Deficit/Hyperactivity Disorder (ADHD) and control subjects

Study	Finding	Methodology	Sample	Mean age (years)	Gender	Diagnosis of ADHD	Comorbidity	Treatment
Crowell *et al* 2006 (64)	Attenuated EDR Lengthened cardiac PEP at baseline and reward No difference in baseline RSA	EDR: Physiodata amplifier system PEP: Impedance cardiograph RSA: Spectral analysis	ADHD: n=18 Controls: n=20	ADHD: 4.78 years Controls: 4.55 years	ADHD: 11/18 male Controls: 11/20 male	DSM-IV criteria CBCL	Oppositional defiant disorder (ODD)	None on stimulants
Beauchaine *et al* 2001 (23)	Attenuated EDR ADHD/CD: longer cardiac PEP ADHD/CD: lower RSA	EDR: Polygraph PEP: Impedance cardiograph RSA: Spectral analysis	ADHD: n=17 ADHD/CD: n=20 Controls: n = 22	ADHD: 13.1 years ADHD/CD: 14.0 years Controls: 13.2 years	All male	ASI CBCL DSM-IV	Conduct disorder (CD)	Discontinued stimulant use 48 hours prior

Oades *et al* 1998 (78)	Plasma adrenaline and noradrenaline levels elevated Urinary levels of noradrenaline markedly increased	Blood and urine samples	ADHD: n = 14 Controls: n = 9	ADHD: 9.8 years Controls: 10.6 years	ADHD: 93% male Control: 56% male	DSM-III-R ICD CPTQ	None	All ADHD patients were naïve to medication
Ernst *et al* 1997 (79)	Higher plasma noradrenaline levels Lower nor-metanephrine at baseline	Blood samples	ADHD: n = 15 No controls			DSM-III-R Conners ATRS		Selegiline
Broyd *et al* 2004 (31)	Decreased skin conductance pre-medication Difference not found after medication	UFI Bioderm model	ADHD: n= 18 Controls: n = 18	ADHD: 11.4 years	All male	DSM-IV		Stopped taking Ritalin 24 hours before testing

EDR, electrodermal response; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; CBCL, Child Behaviour Checklist; ASI, Adolescent Symptom Inventory; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders 3rd edition revised; ICD, International Statistical Classification of Diseases; CPTQ, Conners short parent-teacher scale; Conners ATRS, Conners Abbreviated Teacher Rating Scale.

1.1.4.6.1 Electrodermal response

The electrodermal response assesses the output of the sweat glands and is therefore a measure of the level of sympathetic nervous system activity (23). Studies have repeatedly shown an attenuated electrodermal response (EDR) in ADHD individuals (23,64,80), indicating a hypo-activation of the sympathetic nervous system specifically. O'Connell *et al* (81) have discovered an attenuated EDR specifically during error-making, emphasizing hypo-activation of the sympathetic nervous system response to errors (81). These findings correspond to the theory by Vakalopoulos in which monoaminergic hypo-function is emphasized as the central underlying dysfunction in ADHD. The findings, however, contradict the neurodevelopmental theory of Panzer and Viljoen (1) and Gray's Motivational Theory (22). Panzer and Viljoen (1) state that ADHD children are stuck in the early practising period in which the ventral tegmental dopaminergic limbic system, which stimulates the peripheral sympathetic nervous system, dominates. Gray's Motivational Theory (22) argues that the ventral tegmental dopaminergic system, which is responsible for behavioural activation, may be hyper-active in ADHD individuals. According to these theories, one would expect the sympathetic nervous system to dominate, however, according to electrodermal responses, this is not the case.

1.1.4.6.2 Respiratory Sinus Arrhythmia

An attenuated respiratory sinus arrhythmia in ADHD individuals has been described, indicating an attenuation of the parasympathetic nervous system response in these individuals (82). This finding corresponds to that of both Porge's Polyvagal Theory (26)

and the neurodevelopmental theory of Panzer and Viljoen (1). Porge's Polyvagal Theory (26) states that sustained attention is associated with parasympathetic-mediated reactions. Therefore, one would expect ADHD individuals to exhibit an attenuated parasympathetic nervous system response, accounting for their inattention. Panzer and Viljoen's neurodevelopmental theory (1) advocates the under-development of the central parasympathetic noradrenergic system in individuals with ADHD. It is feasible to assume that the attenuation of the central parasympathetic system would reflect in peripheral parasympathetic indices such as respiratory sinus arrhythmia.

1.1.4.6.3 Heart rate

An attenuated resting heart rate, indicative of a parasympathetic dominant sympathovagal balance, has been cited as the best replicated physiological correlate of antisocial behaviour in both children and adolescents (83). Previous findings of EDR attenuation suggest that the attenuated heart rate is due to sympathetic nervous system under-arousal.

1.1.4.6.4 Adrenomedullary function

Studies into adrenomedullary function in ADHD individuals have yielded conflicting results. Since adrenaline is known to increase the blood glucose level and blood flow to the brain, it is not surprising that a positive correlation has been shown to exist between the level of adrenaline in the body and classroom performance (84). However, in contradiction to this, studies have indicated that ADHD individuals display slightly elevated plasma levels of adrenaline (78). This increase in adrenaline levels could, however, be explained by the possibility that the ADHD individuals found the

experimental conditions stressful or frightening. It has, furthermore, been found that ADHD children have higher baseline plasma levels of noradrenaline (78,79,85); with these higher baseline levels predicting worse performances on continuous performance tests (79). Furthermore, it has been found that ADHD individuals display markedly increased urinary levels of noradrenaline (78). An explanation of this phenomenon was attempted by Oades *et al* (78) who stated that the increased urinary levels of noradrenaline could possibly indicate a decrease in noradrenaline metabolism and utilization in individuals with ADHD. However, this does not appear to be justified since an increase in the excretion and hence filtration of noradrenaline would intuitively lead one to assume that there are increased levels of noradrenaline available for use in the body. A potential explanation for the increased levels of noradrenaline yet noradrenergic hypo-functioning characteristic of ADHD may be the phenomenon of receptor down-regulation whereby the decreased number of noradrenergic receptors leads to their rapid saturation and would therefore account for the increase in noradrenaline excretion. It is important to note that Anderson *et al* (84), however, found no difference in urinary noradrenaline excretion between ADHD individuals and controls. Studies into noradrenaline metabolites have also yielded contradictory results with both lower and higher than normal baseline normetanephrine plasma and urinary levels being found in ADHD individuals (79,85).

A review of a significant number of studies involving plasma and urinary levels of adrenaline and noradrenaline has concluded that children with ADHD display higher levels of noradrenaline activity and lower levels of adrenaline activity in the body (8).

The conclusion of an increase in the level of noradrenaline activity in ADHD individuals does, however, seem counter-intuitive, since we know that noradrenaline plays an important role in the frontal attention network and commonly used stimulants, such as methylphenidate and the amphetamines, exert their effects by increasing the level of catecholamines in the brain.

1.1.4.7 Autonomic correlates of ADHD individuals after physiological stimulation

The previously mentioned studies have dealt with differences in physiological parameters of ADHD individuals and controls at baseline. Very little is known about the autonomic response with stimulation, whether physical or mental. A study where the adrenomedullary response was assessed is described. ADHD children were found to experience a blunted increase in both adrenaline and noradrenaline during exercise when compared to age- and gender-matched controls, indicative of catecholamine dysfunction (86). Furthermore, these ADHD children did not experience an increase in dopamine levels during exercise, although the dopamine levels did increase significantly in controls (86).

More studies in which the autonomic response to stimulation is assessed are therefore needed.

1.1.4.8 Autonomic correlates and sympathomimetic medications

Only a small number of studies have investigated the effect of sympathomimetic medication on the autonomic nervous system, with controversial results (31). Some studies have indicated an increase in the usually attenuated EDR, whilst others showed no difference in EDR pre- and post-medication (31). This highlights the need for further investigations into the electrodermal response in ADHD individuals, both at baseline and with stimulant use. It is interesting to note that neurofeedback therapy is believed to normalize the usually attenuated EDR response in ADHD individuals (57). A study into the autonomic nervous system function by means of heart rate variability in ADHD adults taking stimulants versus age- and gender-matched controls uncovered autonomic nervous system abnormalities in 24% of the ADHD group as compared to 4% in the control group (87). However, these results are not completely substantiated since the control group did display a higher fitness level and the findings in the ADHD group were comparable to that of the general population (87). Moreover, this study did not determine the autonomic nervous system functioning of ADHD individuals that were not being treated with stimulants, deterring the determination of whether autonomic nervous system abnormalities are influenced by stimulant use or whether they are present in all ADHD individuals in the unstimulated condition (87).

1.1.4.9 Cardiac function and sympathomimetic medications

The sympathetic branch of the autonomic nervous system supplies the cardiovascular system via preganglionic fibres of the intermediolateral grey column of the spinal cord, which synapse in the paravertebral ganglia (16). From here, postganglionic sympathetic

fibres travel to the heart and innervate the sinoatrial (SA) and atrioventricular (AV) nodes, the conducting system and the atrial and ventricular muscle (16). The parasympathetic branch of the autonomic nervous system supplies the cardiovascular system through the vagus nerve, with vagal efferent fibres innervating the SA and AV nodes and the atrial muscle (16). Depolarization of the pacemaker cells of the heart determines the rate at which the heart contracts (88). The permeability of the pacemaker cells to different ions can be modified in order to alter the intervals between action potentials (88). The sympathetic nervous system releases noradrenaline which reacts with β_1 adrenoreceptors in the SA node to increase the permeability of calcium channels (88) and decrease the permeability of potassium channels, thereby speeding up the rate of depolarization (16). The conducting system of the heart is similarly affected (16), with noradrenaline increasing conduction of action potentials through the AV node (88). Therefore, sympathetic discharge results in an increase in impulse discharge and conduction rate (16). Since the pacemaker cells are now firing action potentials more rapidly, the heart rate increases (88). Furthermore, the sympathetic nervous system causes the force of ventricular contraction to be stronger and more rapid due to the increased availability of calcium for muscle contraction (88). This causes the ventricles to empty more completely and results in a larger cardiac output (16). The parasympathetic nervous system, on the other hand, releases acetylcholine, which increases the permeability of the potassium channels and decreases the permeability of the calcium channels of the SA node via M2 muscarinic cholinergic receptors (16,88). This combination causes a delay in the onset of the pacemaker cell's action potentials and therefore slows the heart rate (88). Similarly, impulse transmission through the AV node

is slowed, resulting in a decrease in the speed of impulse conduction (16). Vagal stimulation also diminishes atrial contractility by decreasing the amount of calcium available for muscle contraction, resulting in a decrease in cardiac output (16).

Blood pressure is another cardiovascular factor influenced by the autonomic nervous system. Most systemic arterioles are innervated by sympathetic neurons, with tonic noradrenaline discharge maintaining myogenic tone (88). Noradrenaline binds to α-1 receptors on the smooth muscle causing vasoconstriction (88). If sympathetic tone increases, arterioles constrict, resulting in an increase in blood pressure. On the other hand, if sympathetic tone decreases, the arterioles will dilate, causing blood pressure to decrease. The direct effect of the parasympathetic nervous system on the blood vessels is small (16).

There are indications that the cardiovascular side-effects of medications commonly used to treat ADHD include an average increase of 1-2 beats per minute (bpm) in heart rate and increases of 3-4 mmHg in both systolic and diastolic blood pressure (89). Although these side-effects are believed to be insignificant for most children, they could potentially result in cardiovascular incidences in children with structural heart abnormalities, such as congenital heart disease or arrhythmias (89). Worryingly, indications are that ADHD may be more prevalent in children with heart disease (89). Studies have reported that 33% to 42% of paediatric cardiac patients also suffer from ADHD (90). It is tempting to ask whether cardiac abnormalities are more frequent in ADHD children or whether the co-existence of ADHD and cardiac abnormalities is epiphenomenological.

Cardiac channelopathies are described as primary ion channel abnormalities based on mutations in genes encoding subunits of ion channels, which underlie inherited cardiac arrhythmia syndromes (91). Clinical presentations of channelopathies include abrupt-onset syncope, seizures or sudden death (91). These channelopathies may lie dormant for decades, however, when properly diagnosed they are treatable (91). One such cardiac channelopathy is the long QT syndrome (LQTS), which occurs both in congenital and acquired forms. LQTS is characterised by repolarization abnormalities which present as prolongation of the QT interval (91), T wave abnormalities (92) and increased QT dispersion (93) on the electrocardiogram (ECG). Furthermore, average resting heart rate and heart rate during moderate or maximal exercise is believed to be lower in individuals with the disorder (93). The characteristic ECG findings are, however, intermittently and transiently absent (91). The presence of LQTS predisposes patients to torsades de pointes (91), which is described as a polymorphic ventricular tachycardia which may degenerate into ventricular fibrillation (93). In the United States LQTS is responsible for 3000-4000 sudden deaths in children and young adults each year (93). Furthermore, LQTS has a high mortality rate, possibly as high as 70% in untreated subjects (93).

Congenital long QT syndrome is caused by mutations in genes affecting cardiac potassium and sodium channels, as well as rare disturbances in channel-interacting proteins such as ankyrin-B (91). Hundreds of mutations in nine distinct LQTS susceptibility genes have so far been identified (91). Over 70% of these mutations are missense mutations, which lead to a single amino acid substitution in the protein of interest (93). Mutations associated with the potassium channel are loss-of-function

mutations, which may be due to a decrease in channel expression, increase in channel turnover, impaired channel maturation or impaired channel trafficking (91). These loss-of-function mutations lead to a decrease in the repolarizing efflux of potassium ions from cardiac cells, and therefore retard repolarization, causing a longer action potential and prolongation of the QT interval (94). Mutations associated with the sodium channel are gain-of-function mutations which lead to incomplete activation of the sodium channel (91). This incomplete inactivation of the sodium channel adds a sustained depolarizing force which retards repolarization (94). This, once again, results in a longer cardiac action potential and QT interval prolongation. Ankyrin-B is responsible for recognizing the sodium/calcium exchanger, sodium pump and inositol-1,4,5-triphosphate (IP3) receptors and ensuring they are inserted into appropriate domains of the cell membrane (93). Loss-of-function mutations in the ankyrin-B gene are therefore responsible for abnormal calcium homeostasis and signalling, once again resulting in repolarization abnormalities (93). Different forms of congenital LQTS have been identified based on the origin and number of mutations. Romano-Ward LQTS is an autosomal dominant form of the disorder with variable penetrance (92), which affects 1 in 3000 individuals (91). The majority of Romano-Ward cases are due to mutations in the KCNQ1-encoded slow component of the delayed rectifier potassium current (I_{KS}) channel (30-35%), the KCNH2-encoded rapid component of the delayed rectifier potassium current (I_{KR}) channel (25-30%) and the SCN5A-encoded sodium channel (I_{NA}) channel (5-10%) (91). These disorders are referred to as LQT1, LQT2 and LQT3 respectively (91). Jervell and Lange-Nielsen LQTS is an extremely rare autosomal recessive form of the disorder which affects 1 in a million individuals and is associated with a more severe cardiac

phenotype together with profound bilateral sensorineural hearing loss present at birth (91,92). It is due to homozygous or compound heterozygous mutations of the I_{KS} channel, such that one subtype of the disorder (JLN1) is due to double mutations in the alpha subunit of the I_{KS} channel and another (JLN2) is due to double mutations in the beta subunit of the I_{KS} channel (91). Mutations are therefore inherited from both parents, who are usually asymptomatic (93). The potassium concentration of the endolymph is very high, with the movement of potassium ions into hair cells being essential for the transduction of sound into neural signals (92). Potassium recycling into the endolymph is therefore crucial to ensure adequate functioning of the inner ear (92). The potassium ions are believed to be secreted by the stria vascularis of the cochlea and the vestibular dark cells (92). Interestingly, both KCNQ1 and KCNE1 genes are expressed in the marginal cells of the stria vascularis and, furthermore, the vestibular dark cells produce an I_{KS} current at their apical membranes (92). Therefore, the I_{KS} channel is also critical for potassium homeostasis of the endolymph of the inner ear, with mutations in this channel resulting in the deafness characteristic of this disorder (91). LQTS can also occur as a spontaneous germline mutation as in 5-10 % of LQTS cases (91). Furthermore, multisystem or complex LQTS has also been identified, such as in Andersen-Tawil syndrome and Timothy syndrome, where abnormal repolarization occurs simultaneously with other symptoms (91). It is interesting to note that the repolarization abnormalities associated with Timothy syndrome are due to mutations in the alpha subunit of calcium channels, resulting in a loss of calcium channel inactivation and therefore a QT prolongation due to an increase in calcium influx (91).

Acquired LQTS can be due to medical conditions, such as pheochromocytoma, anorexia, diabetes and hypertrophic cardiomyopathy; electrolyte derangements, such as hypokalaemia; and QT-prolonging antiarrhythmic and noncardiovascular medications (91). It has been suggested that phenotypically mild or subclinical mutations in the LQTS genes may be present in the general population and could dispose these individuals to drug-induced ventricular arrhythmias when in conjunction with other risk factors (93). The repolarization reserve of an individual is described as the excess capacity of the myocardium, which will compensate for the underlying channelopathy by increasing the function of other channels (93). However, it is believed that the repolarization reserve of an individual can be exhausted by drugs that affect cardiac channels, thereby unmasking silent carriers of mutant genes (93). The common mechanism of QT-prolonging medications is believed to be the inhibition of the KCNH2-encoded human ether-a-go-go related (HERG) gene, which leads to an inhibition of the I_{KR} channel (91). The I_{KR} channel is especially susceptible to drug-induced inhibition since the inner cavity of the channel is much larger than that of other channels and may trap large drug molecules (93). Furthermore, the S6 domain of the channel has two aromatic residues that face the inner cavity and may bind large aromatic drugs (93).

Interestingly, recent research is uncovering evidence which suggests that hypokalaemic sensory overstimulation may underlie a form of ADHD caused by an undefined channelopathy (65,95). These individuals display a decreased sensitivity to the anaesthetic lidocaine, a sodium channel blocker which acts in peripheral sensory pathways (65,95). Therefore, the underlying dysfunction is believed to be a

channelopathy of peripheral sensory pathways (95). The sensory overload of these individuals causes a difficulty in filtering out background noise, impingement by visual input, a decreased ability to receive non-verbal signals and an increased tendency to respond in an irritable fashion (95). This overload may cause individuals to appear very distractible, have difficulty completing work and display increased impulsivity, all characteristic of ADHD (95). Interestingly a dose of oral potassium makes the sensory overload disappear in about 20 minutes, providing a tentative form of treatment for individuals affected by this potential ADHD subtype (95). It is important to note that the potassium levels of these individuals are not lower than normal; however, symptoms occur during normal physiological potassium fluctuations that do not affect the average person, such as during exercise, large carbohydrate meals, salt intake (65), diarrhoea or menstruation (95). Although ECG parameters have not been assessed in individuals with hypokalaemic sensory overstimulation, it is feasible to assume that these individuals may have subclinical LQTS gene mutations which are unmasked during hypokalaemia. It would therefore be very interesting to determine whether or not they display the QT prolongation characteristic of LQTS. A tentative link may therefore be suggested between a potential form of ADHD and the long QT syndrome, since both are believed to be caused by channelopathies.

It is believed that 5-10% of long QT syndrome gene carriers manifest a normal QT baseline interval, with long QT syndrome gene defects displaying variable penetrance (47). These individuals may, as previously mentioned, be exposed to agents that block cardiac potassium channels and therefore unmask their genetic predisposition to fatal

arrhythmias (47). It is known that an increase in heart rate, as caused by some medications, without compensation for the increase by the QT interval, can provoke life-threatening arrhythmias (96). A recent statement by the American Heart Association (AHA) dated May 6, 2008 maintains that children with ADHD should receive an electrocardiogram before starting stimulant treatment (89). This recommendation was based on the increased number of deaths due to heart failure associated with stimulants commonly used to treat ADHD (89). Hopes are that a pre-treatment ECG could uncover any structural cardiac abnormalities which may be worsened by stimulant treatment. Furthermore, the AHA states that during stimulant treatment, patients' cardiac health should periodically be monitored (89).

An ECG is described as a recording of the underlying electrical activity of the heart (88). A normal ECG shows five deflections designated by the letters P, Q, R, S and T (16). Sometimes a U wave will be present, which represents the repolarization of the papillary muscles of the ventricles (16). Autonomic nervous system activity can be represented in ECG parameters such as heart rate, duration of the QRS complex, QT intervals and JT intervals. Heart rate on an ECG is timed from one R wave peak to the next (88). An increase in the distance between consecutive R peaks (i.e. an increase in the RR value) indicates a decrease in heart rate and therefore a parasympathetic dominant sympathovagal balance and *vice versa*. The QRS complex represents ventricular depolarization with the incorporation of atrial repolarization (88). An increase in the duration of the QRS complex represents a prolonged depolarization of the ventricles, which can be brought about by a parasympathetic dominant sympathovagal balance and

vice versa. The T wave of the ECG represents ventricular repolarization (88). Therefore the QT interval is a measure of both ventricular depolarization and repolarization. An increase in the length of the QT interval represents a decrease in the rate of depolarization and repolarization (i.e. decreased conduction), which can be brought about by a parasympathetic dominant sympathovagal balance and *vice versa*. The JT interval, on the other hand, is a measure of ventricular repolarization exclusively. Therefore an increase in the length of the JT interval represents a delay in conduction which can be brought about by a parasympathetic dominant sympathovagal balance and *vice versa*. QT and JT intervals are, however, corrected for heart rate in order to compensate for the differences in heart rate of different individuals. Prolongation of QTc or JTc values is therefore usually associated with underlying conduction defects or arrhythmias.

The QTc interval is commonly used as a measure of the depolarization and repolarization of the ventricles of the heart and, as such, a surrogate marker for the risk of adverse cardiac events, and in severe cases, sudden death (46). Invasive studies have discovered a correlation between the QTc interval of an ECG and repolarization durations measured by monophasic action potential recordings obtained directly from the myocardium (97). Since cardiac intervals have an inverse relationship to heart rate, intervals are corrected for heart rate in order to determine whether they are prolonged relative to baseline (46). Therefore, one talks of heart-rate corrected QT intervals or QTc. A prolonged QTc interval, indicative of a prolonged cardiac repolarization, has indeed been associated with cardiac arrhythmias (46,98) and an increased risk of morbidity and mortality (99). Furthermore, an increase in the QTc interval is believed to be a surrogate marker for the

risk of a potentially fatal polymorphic ventricular tachycardia known as torsades de pointes (100). During normal conduction, the QT interval is mainly determined by the duration of cardiac repolarization. However, since the QT interval includes both depolarization and repolarization, it is said to have limited value in the case of an increase in QRS duration (101). Indeed some long QT syndrome patients exhibit normal QTc values, emphasizing the perception that QTc is not always a sensitive indicator of cardiac repolarization abnormalities (99). Clinicians usually do not assess QTc if the duration of QRS is equal to or greater than 120 msec (102). A more generally accepted absolute index of cardiac repolarization which is believed to be depolarization-independent is the JT interval. This interval is believed by some to eliminate QRS duration variability, while others argue that JT is not independent of QRS and that the relationship between the two varies according to the presence of conduction abnormalities (102). It has, however, been shown that JTc values do not change when depolarization abnormalities develop in individuals suffering from long QT syndrome (103). Once again, these intervals are corrected for heart rate to produce heart rate corrected JT or JTc intervals. Formulas used to correct QT and JT intervals include linear, logarithmic, square root and exponential equations (99). Correction methods such as Bazett's formula (102,103,104), Fridericia's formula (105) and Rautaharju algorithms (106) are commonly used. However, no universally accepted method exists. Bazett's formula is believed to work well at heart rates between 50 and 90 bpm, but overcorrects for heart rate at slow rates and undercorrects at high rates (105). This undercorrection at high rates may lead to QTc intervals which appear to be prolonged (105). Fridericia's formula, on the other hand, undercorrects at slow heart rates and overcorrects at high hearts rates, such that the

overcorrection at high heart rates may lead to QTc values which are artificially low (105). A study by Wernicke *et al* (105) has indicated that QT correction methods developed specifically for adults do not apply to children, since it is known that QT intervals increase with age. A meta-analysis involving 2288 ADHD children and adolescents found the most appropriate QT correction formula for children and adolescents to be $QTc=QT/RR^{0.38}$ (105), where RR represents the length of the entire cardiac cycle in seconds. This data-derived method is based on linear regression techniques where the optimum correction factor determined was that value which resulted in zero correlation between the QTc and RR values (105). According to Moss and Robinson (107), a Bazett-corrected QTc greater than 460 ms is considered prolonged for women and children, since this value represents the top 1% of the current normal QTc distribution in this population. A regulatory definition of QTc prolongation is a within-patient medication-related change in the Bazett-corrected QTc of more than 30 ms (46). According to the study by Berul *et al* (99), a Bazett-corrected JTc value greater than 340 ms is believed to be prolonged.

Another value commonly used in this type of assessment is QT dispersion (QTd), which is a measure of inter-lead variations in QT interval length of the surface 12-lead ECG (48). QTd is therefore a non-invasive marker of the underlying inhomogeneity of myocardial repolarization (108). Experimental studies have shown that significant correlation between QT and JT dispersion and dispersion of the monophasic action potential duration recorded directly from the myocardium exists (100). Although the methodology for assessing QTd is far from established, it is believed that reporting heart-

rate corrected QTd without uncorrected values is dubious (97). No evidence exists to suggest that QTd values require heart rate correction, with QTd believed to be independent of heart rate (97). Furthermore, sinus arrhythmia is believed to affect the heart-rate corrected QT dispersion values and since sinus arrhythmia is commonly found in children, it is believed that QTd should not be corrected for heart rate (109). An increased QTd reflects cardiac instability and risk for cardiac arrhythmias (48) and sudden death. Increased QTd values have been found in cardiac disorders such as long QT syndrome, drug toxicity and dilated and hypertrophic cardiomyopathies (110). Interestingly, Glancy *et al* (111) discovered that an increase in QTd values measured four weeks after a myocardial infarction, is associated with an increased rate of mortality in the next five years. JT dispersion is a measure of inter-lead variations in JT interval length of the surface 12-lead ECG and is also commonly used to detect repolarization abnormalities and cardiac instability (101). A study conducted by Shah *et al* (100) on 50 healthy children aged 7 to 15 years has found that a QTd or JTd value equal to or greater than 55 msec is associated with an increased risk of critical ventricular arrhythmias such as ventricular tachycardia, torsades de pointes and cardiac arrest (100). Using QTd or JTd equal to or more than 55 msec as a single predictor for critical ventricular arrhythmias yielded a sensitivity of 95% and a specificity of 69% (100).

In summary, prolonged QTc and JTc intervals and increases in dispersion values are all associated with an increased potential for ventricular arrhythmias (101).

It is important to note than an increase in the QTc of 10 msec is treated as a warning signal for a new drug (98). Patients with a history of stimulant exposure have been shown to display a significantly greater heart rate and slightly higher QTc intervals (46). Studies into ADHD individuals taking amphetamines have indicated a small increase in both QT and QTc intervals, however, these increases were not clinically significant (112). Desiprame-treated ADHD children and adolescents have been shown to experience statistically significant increases in diastolic blood pressure and heart rate, a higher incidence of sinus tachycardia, as well as evidence of intraventricular conduction defects of the right bundle branch block type, with two of these patients developing complete intraventricular conduction defects (113). Desiprame has, furthermore, been associated with lower rates of sinus pauses and junctional rhythm, significantly higher rates of single or paired premature atrial contraction and runs of supraventricular tachycardia (114). Extended release dexmethylphenidate, which specifically inhibits dopamine transporters in the basal ganglia, have been associated with no clinically meaningful changes in ECG (45). However, individuals taking dexmethylphenidate have been shown to experience increases in heart rate, palpitations and tachycardia in 2.4 %, 2.4% and 1.2% of cases respectively (45). Although adverse effects on the cardiovascular system have been associated with noradrenergic medications, atomoxetine, which is a selective noradrenergic re-uptake inhibitor commonly used in the treatment of ADHD, has been found to cause no change in QT interval duration (115,116,117) or dispersion (115). However, atomoxetine treatment is associated with an increased pulse rate and small but significant increases in mean systolic blood pressure in adults and mean diastolic blood pressure in children and adolescents (115). These

changes were reported to stabilise with therapy and returned to baseline upon discontinuation of the stimulant treatment (115,117). Clonidine, although associated with an increased rate of bradycardia, is believed to cause no significant cardiovascular or ECG effects (118). ADHD adults taking oral osmotic release system (OROS) methylphenidate have been shown to exhibit statistically significant increases in systolic and diastolic blood pressure and heart rate, together with subjective cardiovascular complaints (119). Eight percent of the individuals taking OROS methylphenidate displayed a systolic blood pressure above 140mmHg and nine percent displayed increases in heart rate above 100 bpm (119). Contradictory to expectation, these individuals displayed a decrease in the QT interval (119). Ballard *et al* (120) concluded that methylphenidate usage results in an increase in heart rate and systolic and diastolic blood pressure, but no meaningful ECG changes. A study into the effect of methylphenidate on QT dispersion has, contrary to predictions, indicated a significant decrease in QTd after medication administration (121).

Further clinical studies are thus needed to better understand the influence of these stimulants, not only on the overall arousal of the autonomic nervous system, but also on the balance between the sympathetic and parasympathetic nervous systems. The effect of these stimulants on the heart specifically should also be investigated.

1.1.4.10 Autonomic nervous system and iron deficiency

Interestingly, iron deficiency is believed to contribute to ADHD via its impact on the metabolism of dopamine and the catecholamines (122). Iron is believed to be a co-factor

for the enzyme tyrosine hydroxylase, which catalyzes the rate-limiting step of catecholamine synthesis (122). Therefore, a decrease in the amount of available iron would result in a decrease in catecholamine production and potentially result in the catecholaminergic hypo-activity found in ADHD. Human studies have indeed indicated lower serum ferritin levels (the storage form of iron) in ADHD patients, with ferritin levels correlating with ADHD symptom severity (122).

1.1.4.11 Summary

In general, views on autonomic under-arousal in ADHD seem to vary between a deficiency in both sympathetic and parasympathetic responses, to intact parasympathetic withdrawal accompanied by a defect in sympathetic reactivity (23,64,84,123,124). Although not firmly established yet, there are indications that specific contributions of the branches of the autonomic nervous system may have specific implications for temperament (23,125), e.g. that parasympathetic nervous system cardiac-linked activity could perhaps be associated with emotional regulatory abilities (23) and subnormal sympathetic nervous system cardiac-linked activity found during rewards linked to reward insensitivity (64).

There is a dire need to investigate autonomic balance in ADHD patients on stimulants and stimulant-free ADHD patients, by techniques that can clearly differentiate between the sympathetic and parasympathetic contributions of the autonomic nervous system, respectively. It is also necessary to know what the autonomic shift during forced attention entails and whether it follows the expected autonomic shift (i.e. a shift in the

sympathovagal balance towards the sympathetic nervous system) or if it is reversed as found in a number of psychiatric conditions. If the normal physiological autonomic profile, coupled with neurological and psychiatric indices, of an ADHD individual can be established, it could help to pave the way for the development of a diagnostic test for one of the most easily misdiagnosed diseases. It has indeed been shown that long-term changes in biological systems can be brought about through early intervention (64), highlighting the importance of accurate and early diagnosis.

1.2 Aims

The aims of this study were:

- To assess baseline autonomic nervous system functioning in 20 children with ADHD, as compared to age- and gender-matched control subjects, and to determine the effects of focussed attention and sympathomimetic stimulants on this system. The methods used to do this include heart rate variability and skin conductivity.
- To assess baseline cardiac functioning in 20 children with ADHD, as compared to age- and gender-matched control subjects, and to determine the effects of sympathomimetic medications on this system. This will be done by means of ECGs.
- To compare the theta/beta and theta/SMR ratios of ADHD children and controls, in order to determine whether these ratios can distinguish ADHD children from controls.

- To compare alpha values of ADHD children and controls, in order to determine whether these values can distinguish ADHD children from controls.

1.3 Objectives

To assess:

- Baseline cardiac and autonomic nervous system functioning in 20 stimulant-free ADHD children
- Autonomic nervous system functioning in 20 stimulant-free ADHD children during a period of focussed attention
- Baseline cardiac and autonomic nervous system functioning in 20 ADHD children on stimulant medication
- Autonomic nervous system functioning 20 ADHD children on stimulant medication during a period of focussed attention
- Baseline cardiac and autonomic nervous system functioning in 20 gender- and age-matched controls
- Autonomic nervous system functioning in 20 gender- and age-matched controls during a period of focussed attention
- Theta/beta ratios, theta/SMR ratios and alpha power at baseline and during focussed attention in 20 stimulant-free ADHD children
- Theta/beta ratios, theta/SMR ratios and alpha power at baseline and during focussed attention in 20 ADHD children on stimulant medication

- Theta/beta ratios, theta/SMR ratios and alpha power at baseline and during focussed attention in 20 gender- and age-matched controls

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Chapter 2

Materials and methods

2.1 Nature of study

This study is an observational, case-control study with no intervention in the treatment regime of the patients. This study protocol was submitted to and approved by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, clearance number S30/2007. The protocol was, furthermore, submitted to and approved by the Department of Health, DOH trial number DOH-27-0808-1816.

2.2 Patient recruitment

Patient recruitment and supervision was conducted by a registered psychiatrist involved in the study. ADHD children were recruited by the registered psychiatrist from Sonitus School, while controls were recruited from Laerskool Fleur based on the underlying criteria. Only children from whom and from whose guardians/parents voluntary informed consent could be obtained were included in the study. Two informed consent forms were used: one for parents/guardians completed by the parents/guardians of all participants and one for children able to understand and sign free informed assent.

2.2.1 ADHD Inclusion criteria

- Children between the ages of 6 and 15 constituting both genders

- Children diagnosed by a registered psychiatrist according to the text revised

Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria from the following sources:

- Developmental history
- Conners' Teacher Rating Scale

- The experimental group constituting 19 ADHD children on stimulant medication consisted of children that were taking long-acting Ritalin (methylphenidate) consistently at the dosage prescribed specifically for them by their psychiatrist. Eighteen of the children with ADHD tested in our study were taking long-acting Ritalin at a dosage of 10 mg, while one child was on long-acting Ritalin at a dosage of 20 mg. The 20th child arrived at the testing venue and, although he was quite happy to be there, refused to take part in any test procedures.

- The group constituting stimulant-free ADHD children consisted of the same ADHD children who refrained from taking Ritalin for a period of about three weeks during their school holiday.* Since the half-life for long-acting Ritalin is about 2.5 hours in children (1), a wash-out period of three weeks was considered more than sufficient.

*This is normal practice and was not introduced into the treatment regime as part of the study.

2.2.2 ADHD Exclusion criteria

- Children with co-morbidities such as: Anxiety
  Depression

Epilepsy

Bipolar disorder

Conduct Disorder

Oppositional Defiant Disorder and

Pervasive Developmental Disorders not

otherwise specified

- Children on medications other than the stimulant prescribed for ADHD
- Overtly malnutritioned children
- Mentally retarded children
- Children with the inability to understand and give informed assent
- Children who abuse drugs and/or alcohol

2.2.3 Controls

Controls included 18 age- and gender-matched children who:

- Could understand and give informed assent
- Did not have any psychiatric illnesses
- Were not overtly malnutritioned
- Were not mentally retarded
- Were not on any medications
- Did not abuse drugs and/or alcohol

2.3 Procedures

2.3.1 Phase A: Data collection

Informed consent was obtained from all the participants and their parents by the respective school principals. Patients were allowed to have breakfast on the morning of testing as it is known that oral administration of Ritalin with a meal does not impede the rate of absorption or metabolism of the drug (2). However, no caffeine was permitted. To ensure confidentiality of all participants, each participant was assigned a unique study number by which records and recordings were marked and identified. Transport expenditure to the university testing facilities, where applicable, was covered by the researchers.

2.3.1.1 Demographic data

Demographic data was collected for both ADHD children and controls using the appropriate forms (see forms 2.1 and 2.2). The children were familiarised with their new environment as soon as they arrived and care was taken to keep them as relaxed as possible. They arrived at the university testing facilities in groups of four children, accompanied by their day care mother. For the children that were tested twice, each child was tested at the same time of day on both of the two days. No child was tested after 11:00. Height, weight, waist-to-hip ratio and blood pressure were assessed shortly after arrival at the testing venue.

Form 2.1 Demographic data of children with ADHD

Patient Demographic Data
Pasientbesonderhede

Patient name/*Naam van Pasiënt:*_____

Date of first visit to BMW/*Datum van eerste besoek*:_____

Date of second visit to BMW/*Datum van tweede besoek*:_____

Time of day of visit/*tyd van dag (hoelaat)*:_____

Unique study number by which records and recordings will be marked and identified/ *Unieke nommer wat gebruik sal word om die opnames en inligting oor die pasiënt te merk* :_____
(This will be filled in by Bianca Negrao)

Height/*lengte*:_____

Weight/*gewig*:_____

Waist-to-hip ratio/*middel-tot-heup verhouding*:_____

Blood Pressure/*bloeddruk:*_____
(This will be filled in by Bianca Negrao)

Contact number/*Kontaknommer (telefoon)*:_____
Address/*Adres*:_____
_____
_____

Age/Ouderdom:_____
School level/*Skoolgraad*:_____
Gender/*Geslag*:_____
Race/Ras:_____

Date of diagnosis/*Datum waarop u vir die eerste keer gediagnoseer is met ADHD*:_____

Specific diagnosis used/*Spesifieke diagnose* **(to be filled in by Doctor)**:_____
_____

Other disorders/*Ander mediese probleme wat die pasient het*:
_____

Name of stimulant (medication)/*Naam van stimulant (medikasie)*:_____
Dose/*Dosis*:_____

Date when the medication for ADHD was first started/*Datum waarop daar vir die eerste keer met die medikasie begin is*:_____

First visit/*eerste besoek*:
Time and date of last administration of medication/*Tyd en datum wanneer u die laaste dosis van medikasie geneem het*:_____

Other medication/*Ander medikasies*:_____
_____
_____

Side-effects experienced on ADHD medication (please tick)/*Newe effekte wat ondervind is as gevolg van die medikasie (maak asb 'n merkie langs hulle):*

Appetite suppression/*Eetlusonderdrukking* □
Increased heart rate/*Vinniger hartklop* □
Headaches/*Hoofpyn* □
Heart palpitations/*Hartkloppings* □
Stomach aches/*Maagpyn* □
Increased blood pressure/*Verhoogde bloeddruk* □
Irritability/*Irriteerdheid* □
Convulsions/*Konvulsies* □
Nausea/*Naarheid* □
Dizziness/*Duiseligheid* □
Sleep disturbances/*Slaapversteurings* □
Vomiting/*Braking* □
Depression/Depressie *(Teneergedruktheid)* □
Blurred vision/*Dowwe visie* □
Growth suppression/*Onderdrukte groei* □
Hypersensitivity reactions/*Hipersensitiwiteitsreaksies soos allergië* □
Anaemia/*Bloedarmoede* □
Tics/*Senuweetrekking/spiertrekking* □
Syncope/*Sinkopie (val om as opstaan*) □
Chest pain/*Borskaspyn* □
Stroke/*Beroerte* □
Heart attack/*Hartaanval* □
Arrythmias/*Onreëlmatige hart* □
Rebound/*Herhaling* □

Special remarks (if necessary)/*Spesiale aanmerkings wat u wil maak (indien so verlang*):
_____

Form 2.2 Demographic data of control subjects

Patient Demographic Data
Pasientbesonderhede

Patient name*/Naam van Pasiënt:*_____

Date of visit to BMW/*Datum van besoek*:_____

Time of day of visit/*tyd van dag (hoelaat)*:_____

Unique study number by which records and recordings will be marked and identified/ *Unieke nommer wat gebruik sal word om die opnames en inligting oor die pasiënt te merk* :_____
(This will be filled in by Bianca Negrao)

Height/*lengte*:_____

Weight/*gewig*:_____

Waist-to-hip ratio/*middel-tot-heup verhouding*:_____

Blood Pressure/*bloeddruk*:_____
(This will be filled in by Bianca Negrao)

Contact number/*Kontaknommer (telefoon)*:_____
Address/*Adres*:_____
_____
_____

Age/Ouderdom:_____
School level/*Skoolgraad*:_____
Gender/*Geslag*:_____
Race/Ras:_____

Disorders/*Mediese probleme wat die pasient het*:
_____
_____

Medication/*Medikasies waarop u is*:_____
_____
_____

Special remarks (if necessary)/*Spesiale aanmerkings wat u wil maak (indien so verlang)*
_____

Height, weight, waist-to-hip ratios and blood pressure were measured by the investigators before the start of the procedures.

2.3.1.2 Weight

Weight of all children was measured using a Safeway EB9271 electronic scale.

2.3.1.3 Height

Height of all children was measured using a standard height wall chart.

2.3.1.4 Waist-to-hip ratio

The waist-to-hip ratio was calculated for all children by dividing the circumference of the waist in centimetres by the circumference of the hips in centimetres. The circumference of the waist was measured with a tape measure at the smallest part of the waist, just above the bellybutton. The circumference of the hips was measured with a tape measure at the largest part of the hips.

2.3.1.5 Blood pressure

Blood pressure of all children was measured with a stethoscope and a mercurial sphygmomanometer. An average of three readings was obtained for each child. To prevent any inter-individual bias, the blood pressure of all children was measured by the same individual.

Following the collection of demographic data, we began testing. Heart rate variability (HRV), skin conductivity (SC) and electroencephalography (EEG) recordings were conducted simultaneously, while electrocardiograms (ECGs) were conducted afterwards, according to the schematic representations below. HRV, SC and EEG data were sampled while the children were sitting in a quiet environment at a constant room temperature. Baseline recordings were made over a period of 5 minutes. The 5 minute baseline recordings were directly followed by 10 minute recordings during focussed attention. Attention was evoked by means of a program on the BioGraph Infiniti biofeedback apparatus. This program has been developed specifically as a mechanism to train ADHD individuals to increase their attentive abilities. After the 10 minute recording during focussed attention, ECGs were conducted while the children were lying down in a quiet environment at a constant room temperature.

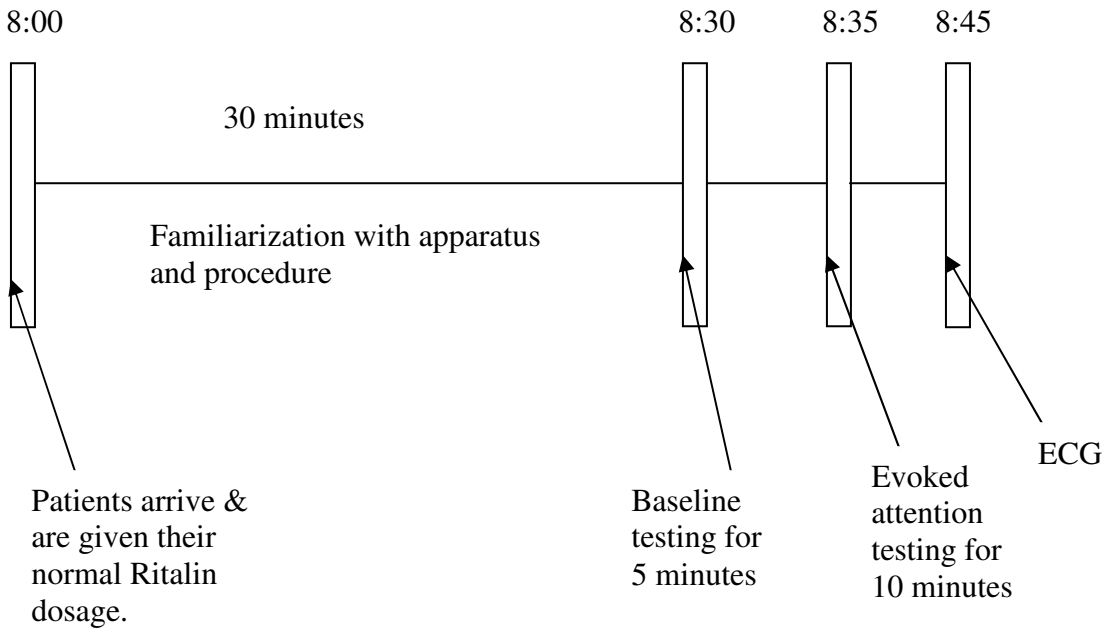

Figure 2.1: Procedure for testing ADHD children on stimulant medication

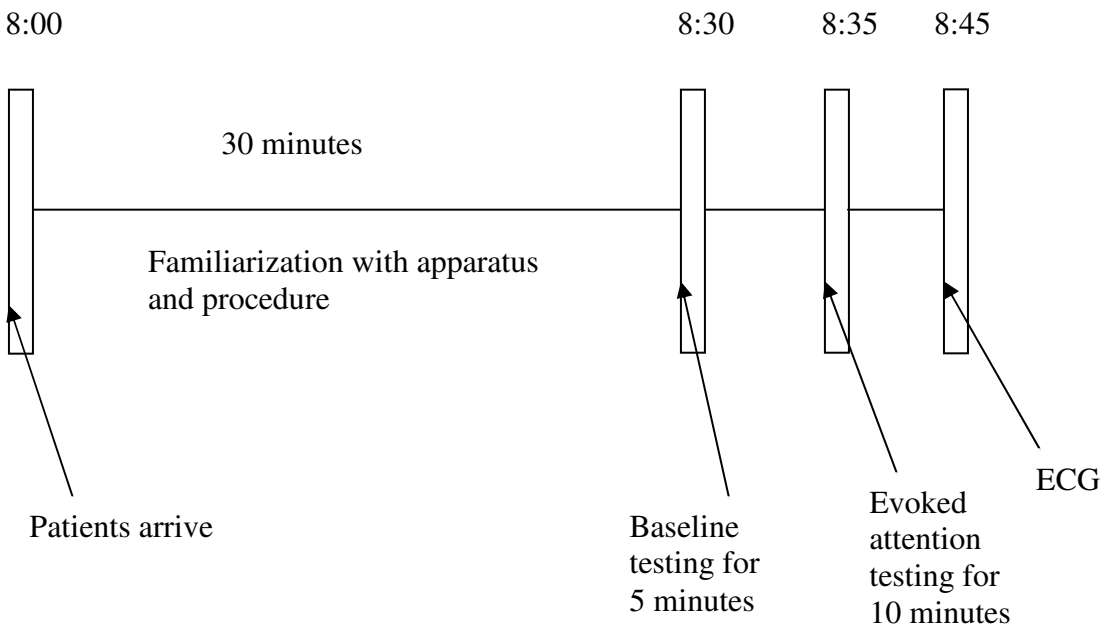

Figure 2.2: Procedure for testing stimulant-free ADHD children and controls

2.3.1.6 Heart Rate Variability

Heart rate variability (HRV) was determined by analysis of the RR interval data sets (tachograms), which were obtained by POLAR NV heart rate monitors. Five minute recordings were analysed since this is considered to be standard in clinical studies (3). The full five minute baseline HRV recording and the middle five minutes of the ten minute HRV recording during focussed attention were analysed for this study.

2.3.1.7 Skin conductivity

Skin conductivity was determined by means of a program on the BioGraph Infiniti biofeedback apparatus. The SC signal was collected through two silver-silver chloride electrodes attached by adhesive collars to the palmar surface of the middle and index

fingers on the child's left hand. Subjects were asked to wash their hands with soap and dry them prior to sampling to ensure the removal of surface salt.

2.3.1.8 EEG theta/beta and theta/SMR ratios and alpha values

EEG values were measured by means of a BioGraph Infiniti biofeedback program designed specifically to increase attentive abilities in individuals with ADHD. This program extracts EEG frequency components and feeds them back in the form of a game, using an audio-visual loop. The specific biofeedback program that was used was a bowling EEG speed game. This program allows subjects to move a bowling ball down an alley as long as two essential criteria are met, i.e. SMR enhancement and theta suppression. In other words, the bowling ball only moved down the alley when the children were able to keep their SMR 13-15 Hz activity above a pre-determined threshold and their theta 3-7 Hz activity below a pre-determined threshold. The pre-determined thresholds used were those pre-set on the program which is, as previously mentioned, used specifically to train individuals with ADHD. SMR activity is associated with the suppression of excitation in the sensorimotor area (4). It is therefore increased with the inhibition of movement and a decrease in muscle tone and is, furthermore, believed to play a role in attention (5). Therefore an increase in SMR indicates a decrease in impulsivity and fidgetiness and an increase in relaxed focus and attention. Theta is usually associated with drowsiness and the withdrawal of vigilance. Therefore a decrease in theta activity indicates an increase in external focus. ADHD individuals typically display low SMR and high theta activity due to a lack of focussed concentration. Although another protocol used to train ADHD individuals does exist, namely a beta

enhancement/theta suppression protocol, it has been shown that there are no differential effects between SMR and beta training (6).

The EEG signal was collected through silver-silver chloride electrodes. Electrode positioning was monopolar with the active electrode at C4 according to the commonly used methods for the SMR enhancement/theta suppression neurofeedback protocol (7). Mastoid reference electrodes were placed on both of the subject's earlobes. Electrode positioning sites were first rubbed with an alcohol swab in order to clean the surface. A small drop of abrasive gel was then applied in order to remove dead skin cells at the surface. Finally, a small amount of conductive paste was applied to the site in order to ensure the electrode stayed firmly in place and to provide a conductive medium for the electrical signal. Electrode skin contact was checked and all impedances were kept below 10 kΩ.

2.3.1.9 Electrocardiograms

ECGs were obtained by a 12-lead Schiller CardioLaptop AT-110 ECG recorder while the children were warm and relaxed in a supine position in a quiet environment at a constant room temperature. All children were instructed to lie quietly for five minutes before the ECGs were recorded to allow stabilization of ECG parameters. To minimize diurnal variations in ECG parameters all ECGs were performed in the morning. Electrode positioning followed the standard 12-lead cable positioning for a resting ECG. The speed of the ECG trace was set at 25 mm/s while the sensitivity of the ECG trace was set at 10 mm/mV. A general filter was set at 50 Hz to suppress AC interference without distorting

the ECG. Both myogram and baseline filters were used to reduce muscle induced noise and baseline fluctuations respectively. A ten second printout was obtained for each subject.

2.3.2 Phase B: Data Analysis

2.3.2.1 Weight, height and waist-to-hip ratios

The values obtained for weight, height and waist-to-hip ratios for the ADHD children were compared to the values obtained for the controls in order to uncover any statistically significant differences.

2.3.2.2 Heart Rate Variability

HRV is a non-invasive measurement of the autonomic nervous system influence on the cardiovascular system, with a decreased HRV believed to be a marker of both physiological and psychological distress (8). A decreased HRV has been found to be associated with pathological conditions such as haemorrhagic and septic shock, hypertension (9) and fatal ventricular arrhythmias (10), and is believed to predict sudden death in patients with myocardial infarction (10). Furthermore, a decreased HRV has been shown to be associated with negative emotions such as anxiety and hostility (10).

The data (RR interval sets) were analysed using HRV Analysis Software 1.1 for Windows, developed by The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland. Smoothness priors for Trend and Model Eye program settings were used for de-trending, with an Alpha value of 500. The auto

regressive model order value used was 16 and the interpolation rate 4 Hz. Error correction of a moderate filter power and minimum protection zone of 6 beats per minute was applied to the raw tachogram. In four of the HRV recordings, extreme outliers had to be removed manually before the error correction could be performed. The techniques used for the evaluation of HRV from the RR interval data sets in this study, were grouped into three categories: time domain, frequency domain and non-linear analysis. Time domain values calculate either the heart rate at a certain point in time or the intervals between successive RR complexes (11). In this study we used both statistical and geometric methods to determine time-domain values. Heart rate variability has the propensity to aggregate into different frequency bands, which are associated with underlying rhythms involved in heart rate regulation (12). Frequency domain analyses delineate the heart signal into its frequency components and quantify the frequency components in terms of their relative intensity (8). Two types of frequency domain analyses exist, namely the parametric or auto-regressive model and non-parametric or Fast Fourier transformation. Non-parametric Fourier analysis is able to decompose a complex time series with cyclical components into underlying sinusoidal functions of particular wavelengths (13). With Fourier analysis the spectrum computed is derived from all recorded data, regardless of how well it fits into a model, while auto-regressive models use the time-domain data to identify a best-fit model (3). In this study frequency components were calculated using Fast Fourier transformation, since it is suggested that this method be used with short-term recordings such as those used in this study (14). Non-linear analyses quantify the complexity and self-similarity of heart rates by

describing the relationship between successive samples of a time series (12). The type of non-linear analysis used in this study was the Poincaré plot.

Time domain values recommended for use by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology include SDNN, HRV triangular index, SDANN and RMSSD (11). These time domain values, together with mean heart rate, were therefore used in our study. Mean heart rate gives us an indication of the sympathovagal balance of an individual. An increase in heart rate is caused by a shift in the autonomic balance towards the sympathetic nervous system and *vice versa*. SDNN or SDRR, measured in seconds, represents the standard deviation of all the NN or RR intervals over the recorded time interval and is therefore used as an estimate for overall or global heart rate variability (11,13). HRV triangular index is described as the base of the triangular area under the main peak of the RR interval frequency distribution diagram (12), and is believed to estimate overall HRV (11). SDANN is the standard deviation of the averages of NN intervals calculated over short periods and is an estimate of the changes in heart rate (11). Therefore SDANN is believed to estimate long-term components of HRV (11). This is considered the same as STDHR, which is the standard deviation of the selected heart rate series in beats per minute (12), which will be measured in our study. RMSSD, measured in milliseconds, is a measure of the square root of the mean squared differences of successive NN intervals, which estimates the short-term components of heart rate variability (11). RMSSD is therefore a measure of parasympathetic nervous system activity (14) and is believed to be highly correlated to the high frequency component (11).

Frequency domain values that were used in this study include high frequency (HF), low frequency (LF) and the LF/HF ratio. High frequency components are found at respiratory frequencies of 0.15 to 0.40 Hz and are believed to reflect the quantity of parasympathetic efferent modulation of the heart via respiratory sinus arrhythmia (3,13,14,15,16,17). It is believed that the sympathetic nervous system is too slow to respond at this frequency, therefore the HF component solely represents parasympathetic outflow (18,19,20,21). Low frequency components are found at 0.04 to 0.15 Hz (12). The autonomic contributions to this frequency component are still being investigated and no consensus currently exists. This frequency component is believed to have a complex association with blood pressure regulation via the arterial baroreceptor reflex (13,14,16) and therefore provides information regarding the sympathetic nervous system activity but with notable contribution from the parasympathetic nervous system (12,13,14,15,16,17, 19,20,21). The arterial baroreceptor reflex is a homeostatic mechanism mediated by the autonomic nervous system and medullary controls (16), which is responsible for the homeostatic control of blood pressure (22). It is, however, believed that in most instances, with the exception of conditions such as heart failure and strenuous exercise, the LF component is indeed an indicator of predominantly sympathetic activity (13,23). Furthermore, the LF component is considered by some a definite marker of sympathetic activity when expressed in normalized units (11,17). LF and HF components were therefore reported in both absolute power (ms^2) and normalized units (nu) in this study. Normalized units are calculated by dividing the power of the LF or HF components by the total power minus the power in the very low frequency component (VLF). This is then multiplied by 100 in order to get a percentage. Normalization minimizes the effects

of changes in total power on LF and HF values, but should always be quoted with absolute values in order to describe the distribution of power in spectral components (11). Furthermore, normalized units are believed to permit the comparison of individuals with different absolute values (13). The VLF is believed to be influenced by temperature, hormonal influences and circadian rhythms and cannot be quantified by the traditional spectral analysis methods performed on short HRV recordings (3). For this reason, the VLF component was not included in our study. The LF/HF ratio provides a measure of sympathovagal balance (12,13,15,18,19,20,21), whereby an increase in the LF/HF ratio indicates a predominance of sympathetic activity and a decrease in the LF/HF ratio indicates parasympathetic predominance (14). It is important to note that due to the lack of complete understanding of the autonomic contributions to the low frequency component, the use of this ratio as an index of sympathovagal balance remains controversial (12).

Non-linear analyses used in this study included the SD1 and SD2 values of the Poincaré plot, which is described by graphing each RR interval against the next (12). SD1 represents the standard deviation of instantaneous beat-to-beat variability data and is therefore an indicator of short term variability in heart rate, representing parasympathetic nervous system activity on the sinus node (3). SD2 is believed to represent the standard deviation of continuous long-term variability and therefore reflects global variability (3). However, SD2 is less well defined and is believed to include both parasympathetic and sympathetic modulations to the sinus node (3).

2.3.2.3 Skin conductivity

The BioGraph Infiniti biofeedback program used to measure skin conductivity contains an assessment program which automatically provided us with the skin conductivity values of the patients in µMhos. Skin conductivity or electrodermal response (EDR) varies with sympathetic nervous system activity, which may be influenced by, amongst other factors, emotions.

2.3.2.4 EEG theta/beta and theta/SMR ratios and alpha values

The specific biofeedback program that was used in order to evoke attention contains an assessment program which uses an analog-to-digital converter to sample the unfiltered analog EEG signal in order to alter it to a digitised signal. This assessment program then filters the signal with a Fast Fourier Transformation in order to produce a digitally filtered signal. This signal is then sampled by a digital-to-analog converter in order to produce the final product, a filtered analog signal. The assessment program used automatically provided us with the theta/beta and theta/SMR ratios by calculating the ratio of the electrophysiological power recorded within the theta band by that recorded within the beta and SMR bands respectively. Furthermore, the assessment program used automatically provided us with the power in µV within the thalpha (6-10 Hz), low alpha (8-10 Hz) and high alpha (11-12 Hz) frequency ranges.

2.3.2.5 Electrocardiograms

All ECG analysis was done manually. The QT interval was measured from the Q wave initiation to the terminal inscription of the T wave, i.e. the intersection of the T wave with

the isoelectric line. If the Q wave was absent the QT interval was measured from the beginning of the R wave. Extrapolation with a tangent was used if the end of the T wave was not clear. Furthermore, if the T wave was followed by a U wave, the QT interval was measured to the nadir between the T and U waves. The average of the QT intervals from three consecutive complexes from both leads II and V6 were used for the analyses. QTc was calculated by using both the previously-mentioned formula for QT correction in children and adolescents, namely $QTc = QT \div RR^{0.38}$, as well as Bazett's formula for heart rate correction, i.e. $QTc = QT \div RR^{0.5}$. In both instances the RR interval in seconds was used. The RR interval was measured manually from the R wave of one QRS complex to the R wave of the successive QRS complex. The average RR interval from three successive complexes from both leads II and V6 was used for the analysis. QT dispersion was determined by calculating the difference between QT intervals of leads II and V6, while QTc dispersion was determined by calculating the difference between corrected QT intervals of leads II and V6, with QT intervals corrected for heart rate using Wernicke's formula of $QTc = QT \div RR^{0.38}$.

The JT interval was measured from the J point, which is found at the intersection of the QRS and ST waves, to the terminal inscription of the T wave. As with the QT interval, extrapolation with a tangent was used if the end of the T wave was not clear and if the T wave was followed by a U wave the QT interval was measured to the nadir between the T and U waves. Three consecutive JT intervals from both leads II and V6 were used for the analyses. JTc was calculated using the formula $JTc = JT \div RR^{0.38}$, as well as Bazett's formula of $JTc = JT \div RR^{0.5}$, with RR measured in seconds. RR was once again

measured manually and the average from three successive complexes from both leads II and V6 was used for the analysis. JT dispersion was determined by calculating the difference between JT intervals of leads II and V6, while JTc dispersion was determined by calculating the difference between heart rate corrected JT intervals of leads II and V6, with JT intervals corrected for heart rate using Wernicke's formula of $JTc = JT \div RR^{0.38}$.

The Bazett-corrected QTc interval was characterised as being prolonged based on the Moss and Robinson (24) criteria for children and females of QTc > 460 ms. Bazett-corrected QTc intervals measured while the children were stimulant-free were compared to those measured while the children were on stimulant medication, in order to determine if a within-patient difference of 30 msec or more was found. As previously mentioned, a within-patient increase of 30 msec or more is defined as a prolongation of the Bazett-corrected QTc interval by the drug under question. The Bazett-corrected JTc value was characterised as being prolonged based on the criteria established in the study by Berul *et al* (25), i.e. a Bazett-corrected JTc > 340 msec. QTd and JTd values equal to or more than 55 msec were highlighted as an increased risk for critical ventricular arrhythmias.

2.3.3 Phase C: Statistical Analysis

All data were statistically analysed in consultation with Prof PJ Becker (MRC). A two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test were used when comparing values obtained for the ADHD children to those obtained for the controls. When comparing values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, a paired t-test and

the Wilcoxon signed-rank test were used. A paired t-test and the Wilcoxon signed-rank test were furthermore used when comparing values at baseline and values during focussed attention for the same participant. To determine whether a relationship between two values existed, a correlation analysis was conducted.

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Chapter 3

Results

The study started out with twenty children with ADHD. However, subject number 02 arrived at the university testing facilities and did not want to participate in the study. As per the informed consent and assent forms, any participant was allowed to withdrawal from the study at any time without stating any reasons. Our results therefore include nineteen children with ADHD. In order to allow for a control group that was completely age- and gender-matched, we did not include a control subject matched for participant 02. Furthermore, the primary school from which we obtained our controls did not have a student enrolled in their school that was a match for participant number 12; therefore we could not include a matched control for this participant. Our results therefore include eighteen age- and gender-matched control subjects. All children were tested both at baseline and during focussed attention. Children with ADHD were tested while they were stimulant-free and during a period in which they were on stimulant medication, while controls were tested once. This provided us with three groups, i.e.

i) stimulant-free ADHD children

ii) ADHD children on stimulant medication and

iii) controls

In this chapter the results are presented in the following order:

- Comparison of the physical characteristics of children with ADHD and age- and gender-matched controls

- Comparison of baseline autonomic nervous system functioning, as derived from analyses of heart rate variability and skin conductivity, between:
    - ❖ Stimulant-free ADHD children and controls
    - ❖ ADHD children on stimulant medication and controls
    - ❖ ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of autonomic nervous system functioning during focussed attention, as derived from analyses of heart rate variability and skin conductivity, between:
    - ❖ Stimulant-free ADHD children and controls
    - ❖ ADHD children on stimulant medication and controls
    - ❖ ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of the effect of focussed attention on the autonomic nervous system in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of autonomic nervous system delta values of focussed attention minus baseline between:
    - ❖ Stimulant-free ADHD children and controls
    - ❖ ADHD children on stimulant medication and controls
    - ❖ ADHD children on stimulant medication and stimulant-free ADHD children

- Comparison of blood pressure and ECG values between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of QTc, JTc, QT dispersion and JT dispersion prolongation in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of baseline theta/beta and theta/SMR ratios between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of theta/beta and theta/SMR ratios during focussed attention between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of the effect of focussed attention on theta/beta and theta/SMR ratios in controls, stimulant-free ADHD children and ADHD children on stimulant medication

- Comparison of theta/beta and theta/SMR ratio delta values of focussed attention minus baseline between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of baseline alpha values between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of alpha values during focussed attention between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of the effect of focussed attention on alpha values in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of alpha power delta values of focussed attention minus baseline between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls

- ADHD children on stimulant medication and stimulant-free ADHD children

- Assessment of a possible link between baseline theta/beta ratios and autonomic nervous system functioning, either at baseline or during focussed attention, in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Assessment of a possible link between baseline theta/SMR ratios and autonomic nervous system functioning, either at baseline or during focussed attention, in controls, stimulant-free ADHD children and ADHD children on stimulant medication

3.1 Physical characteristics

Table 3-1 represents the physical characteristics of the children with ADHD while Table 3-2 represents the physical characteristics of the control subjects.

Table 3-1: Physical characteristics of children with ADHD

Subject number	Age	Gender	Height	Weight	Waist-to-hip ratio
	[years]		[m]	[kg]	
01	10	Male	1.36	32.3	0.87
03	9	Male	1.47	51.5	0.93
04	8	Female	1.33	30	0.91
05	10	Female	1.43	29.8	0.83
06	8	Male	1.32	51.9	0.87
07	11	Female	1.48	45.9	1.04
08	9	Male	1.39	39	0.88
09	9	Male	1.29	25.7	0.82
10	9	Female	1.35	29.1	0.86
11	8	Female	1.26	22.1	0.92
12	15	Male	1.79	53.5	0.86
13	14	Male	1.60	47	0.78
14	10	Male	1.46	40	0.86
15	7	Male	1.32	28.2	0.85
16	10	Male	1.42	39.4	0.77
17	9	Male	1.46	29.4	0.88
18	9	Male	1.41	36.4	0.98
19	6	Female	1.23	24.5	0.91
20	10	Male	1.46	48.7	0.91
Mean (SD)			1.41 (0.13)	37.07 (10.18)	0.88 (0.06)

Table 3-2: Physical characteristics of control subjects

Subject number	Age	Gender	Height	Weight	Waist-to-hip ratio
	[years]		[m]	[kg]	
21	9	Male	1.39	31.2	0.92
22	9	Male	1.47	33.8	0.77
23	8	Female	1.41	31	0.94
24	10	Female	1.40	30.6	0.77
25	8	Male	1.37	34.7	0.88
26	11	Female	1.47	35.7	0.79
27	9	Male	1.38	31	0.86
28	9	Male	1.42	36.4	0.85
29	9	Female	1.47	42.8	0.85
30	8	Female	1.31	28.4	0.94
31	13	Male	1.59	66.2	1.02
32	10	Male	1.55	57	0.93
33	7	Male	1.30	34	0.95
34	9	Male	1.35	33	0.87
35	9	Male	1.37	31.1	0.99
36	10	Male	1.52	58.5	0.95
37	7	Female	1.25	23.3	0.85
38	10	Male	1.43	33.9	0.86
Mean (SD)			1.41 (0.09)	37.37 (11.48)	0.89 (0.07)

To determine whether the ADHD children and control subjects differed with regards to height, weight and waist-to-hip ratios, these variables were compared by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

The results are presented in Table 3-3.

Table 3-3: Means and standard deviations for height, weight and waist-to-hip ratios in children with ADHD and controls

Variable (unit)	ADHD Children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Height (m)	1.41 (0.13)	1.41 (0.09)	0.9635	0.6925
Weight (kg)	37.07 (10.18)	37.37 (11.48)	0.9349	0.8197
Waist-to-hip ratio	0.88 (0.064)	0.89 (0.072)	0.7279	0.6585

No statistically significant differences between ADHD children and control subjects were found regarding height, weight and waist-to-hip ratios.

3.2 Experimental data on autonomic nervous system functioning

3.2.1 Baseline autonomic nervous system functioning

As previously mentioned, ADHD children were tested while they were stimulant-free and during a period in which they were on stimulant medication. Control subjects were tested once. Parameters used to determine baseline autonomic nervous system functioning included heart rate variability parameters discussed in Chapter 2 (2.3.2.2) and skin conductivity. In order to assess baseline autonomic nervous system functioning in unmedicated children with ADHD as compared to normal children, baseline HRV and skin conductivity values obtained while the ADHD children were stimulant-free were compared to baseline HRV and skin conductivity values obtained for the controls by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess baseline autonomic nervous system functioning in medicated children with ADHD as compared to normal children,

baseline HRV and skin conductivity values obtained while the ADHD children were on stimulant medication were compared to baseline HRV and skin conductivity values obtained for the controls by means of the same two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the autonomic nervous system of children with ADHD, baseline HRV and skin conductivity values obtained while the ADHD children were on stimulant medication were compared to baseline HRV and skin conductivity values obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.2.1.1 Baseline heart rate variability parameters

A baseline POLAR tachogram was obtained for each participant. The raw data was quantified and analysed in terms of time-domain, frequency-domain and Poincaré analyses to obtain a set of possible indicators of autonomic function for each participant. These indicators are described in Table 3-4.

Table 3-4: Indicators calculated by means of POLAR tachograms

	Indicator	Explanation
Time-domain	Mean HR	Average heart rate in beats per minute (bpm)
	STDRR	Standard deviation in the normal RR-interval in seconds (sec)
	RR triangular index	The base of the triangular area under the main peak of the RR interval frequency distribution diagram
	STDHR	Standard deviation of the selected heart rate series in bpm
	RMSSD	Square root of the mean squared differences of successive RR intervals in milliseconds (msec)
Frequency-domain	HF	Spectral power in the high frequency range (ms^2)
	LF	Spectral power in the low frequency range (ms^2)
	HFnu	Spectral power in the high frequency range in normalized units (nu)
	LFnu	Spectral power in the low frequency range in normalized units (nu)
	LF/HF	Ratio of percentage LF to percentage HF
Poincaré Plot	SD1	Standard deviation of instantaneous beat-to-beat variability in msec
	SD2	Standard deviation of continuous long-term variability in msec

The means and standard deviations for the baseline HRV parameters are presented in Table 3-5 for the controls, Table 3-6 for the stimulant-free ADHD children and Table 3-7 for the ADHD children on stimulant medication.

Table 3-5: Means and standard deviations for baseline HRV parameters in controls

	Indicator (unit)	Mean (SD)
Time-domain	HR (bpm)	93.77 (9.90)
	STDRR (sec)	0.036 (0.021)
	RR triangular index	0.070 (0.035)
	STDHR (bpm)	5.26 (2.05)
	RMSSD (msec)	35.99 (26.38)
Frequency-domain	HF (ms^2)	435.67 (595.03)
	LF (ms^2)	372.39 (541.41)
	HF (nu)	53.75 (14.70)
	LF (nu)	46.25 (14.70)
	LF/HF	1.02 (0.67)
Poincaré Plot	SD1 (msec)	25.63 (18.77)
	SD2 (msec)	53.43 (27.95)

Table 3-6: Means and standard deviations for baseline HRV parameters in stimulant-free ADHD children

	Indicator (unit)	Mean (SD)
Time-domain	HR (bpm)	87.67 (7.75)
	STDRR (sec)	0.052 (0.020)
	RR triangular index	0.10 (0.031)
	STDHR (bpm)	6.75 (2.06)
	RMSSD (msec)	52.51 (21.95)
Frequency-domain	HF (ms^2)	659.16 (505.75)
	LF (ms^2)	667 (755.66)
	HF (nu)	51.94 (16.82)
	LF (nu)	48.06 (16.82)
	LF/HF	1.22 (1.01)
Poincaré Plot	SD1 (msec)	37.36 (15.59)
	SD2 (msec)	76.28 (26.86)

Table 3-7: Means and standard deviations for baseline HRV parameters in ADHD children on stimulant medication

	Indicator (unit)	Mean (SD)
Time-domain	HR (bpm)	95.41 (11.03)
	STDRR (sec)	0.044 (0.021)
	RR triangular index	0.074 (0.035)
	STDHR (bpm)	6.29 (2.09)
	RMSSD (msec)	45.71 (26.96)
Frequency-domain	HF (ms^2)	517.32 (496.15)
	LF (ms^2)	541.47 (689.72)
	HF (nu)	51.47 (17.14)
	LF (nu)	48.53 (17.14)
	LF/HF	1.24 (1.02)
Poincaré Plot	SD1 (msec)	32.53 (19.17)
	SD2 (msec)	68.83 (28.22)

3.2.1.1.1 Baseline HRV parameters for stimulant-free ADHD children versus controls

Baseline HRV values obtained while the ADHD children were stimulant-free were compared to baseline HRV values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-8.

Table 3-8: Comparison of baseline HRV parameters between stimulant-free ADHD children and controls

	Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	87.67 (7.75)	93.77 (9.90)	0.0451	0.0245
	STDRR (sec)	0.052 (0.020)	0.036 (0.021)	0.0236	0.0082
	RR triangular index	0.10 (0.031)	0.070 (0.035)	0.0075	0.0020
	STDHR (bpm)	6.75 (2.06)	5.26 (2.05)	0.0340	0.0193
	RMSSD (msec)	52.51 (21.95)	35.99 (26.38)	0.0464	0.0157
Frequency-domain	HF (ms^2)	659.16 (505.75)	435.67 (595.03)	0.2276	0.0596
	LF (ms^2)	667.00 (755.66)	372.39 (541.41)	0.1800	0.0193
	HF (nu)	51.94 (16.82)	53.75 (14.70)	0.7293	0.9033
	LF (nu)	48.06 (16.82)	46.25 (14.70)	0.7293	0.9033
	LF/HF	1.22 (1.01)	1.02 (0.67)	0.4852	0.9033
Poincaré Plot	SD1 (msec)	37.36 (15.59)	25.63 (18.77)	0.0468	0.0157
	SD2 (msec)	76.28 (26.86)	53.43 (27.95)	0.0157	0.0057

Statistically significant differences in baseline HRV parameters between stimulant-free ADHD children and controls were found for HR (p=0.0245), STDRR (p=0.0082), RR triangular index (p=0.002), STDHR (p=0.0193), RMSSD (p=0.0157), LF (p=0.0193), SD1 (p=0.0157) and SD2 (p=0.0057). A marginally statistically significant difference was found regarding HF (p=0.0596). HR was significantly lower, while STDRR, RR triangular index, STDHR, RMSSD, LF, HF, SD1 and SD2 were significantly higher in the stimulant-free ADHD children.

3.2.1.1.2 Baseline HRV parameters for ADHD children on stimulant medication versus controls

Baseline HRV values obtained while the ADHD children were on stimulant medication were compared to baseline HRV values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-9.

Table 3-9: Comparison of baseline HRV parameters between ADHD children on stimulant medication and controls

	Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	95.41 (11.03)	93.77 (9.90)	0.6369	0.6268
	STDRR (sec)	0.044 (0.021)	0.036 (0.021)	0.2630	0.1619
	RR triangular index	0.074 (0.035)	0.070 (0.035)	0.6801	0.3781
	STDHR (bpm)	6.29 (2.09)	5.26 (2.05)	0.1406	0.0833
	RMSSD (msec)	45.71 (26.96)	35.99 (26.38)	0.2748	0.1622
Frequency-domain	HF (ms^2)	517.32 (496.15)	435.67 (595.03)	0.6540	0.3948
	LF (ms^2)	541.47 (689.72)	372.39 (541.41)	0.4111	0.3782
	HF (nu)	51.47 (17.14)	53.75 (14.70)	0.6658	0.6928
	LF (nu)	48.53 (17.14)	46.25 (14.70)	0.6658	0.6928
	LF/HF	1.24 (1.02)	1.02 (0.67)	0.4393	0.6928
Poincaré Plot	SD1 (msec)	32.53 (19.17)	25.63 (18.77)	0.2759	0.1622
	SD2 (msec)	68.83 (28.22)	53.43 (27.95)	0.1039	0.0388

A statistically significant difference in baseline HRV parameters between ADHD children on stimulant medication and controls was found for SD2 (p=0.0388). A marginally statistically significant difference was found regarding STDHR (p=0.0833).

Both SD2 and STDHR values were significantly higher in the ADHD children on stimulant medication.

3.2.1.1.3 Baseline HRV parameters for ADHD children on stimulant medication versus stimulant-free ADHD children

Baseline HRV values obtained while the ADHD children were on stimulant medication were compared to baseline HRV values obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. Results are presented in Table 3-10.

Table 3-10: Comparison of baseline HRV parameters between ADHD children on stimulant medication and stimulant-free ADHD children

	Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	95.41 (11.03)	87.67 (7.75)	0.0017	0.0033
	STDRR (sec)	0.044 (0.021)	0.052 (0.020)	0.0392	0.0421
	RR triangular index	0.074 (0.035)	0.100 (0.031)	0.0062	0.0033
	STDHR (bpm)	6.29 (2.09)	6.75 (2.06)	0.2062	0.4445
	RMSSD (msec)	45.71 (26.96)	52.51 (21.95)	0.2250	0.2514
Frequency-domain	HF (ms^2)	517.32 (496.15)	659.16 (505.75)	0.1265	0.1590
	LF (ms^2)	541.47 (689.72)	667.00 (755.66)	0.2854	0.0766
	HF (nu)	51.47 (17.14)	51.94 (16.82)	0.9363	0.9679
	LF (nu)	48.53 (17.14)	48.06 (16.82)	0.9363	0.9679
	LF/HF	1.24 (1.02)	1.22 (1.01)	0.9488	0.9359
Poincaré Plot	SD1 (msec)	32.53 (19.17)	37.36 (15.59)	0.2247	0.2432
	SD2 (msec)	68.83 (28.22)	76.28 (26.86)	0.1852	0.1589

When comparing the values obtained while the ADHD children were on stimulant medication and those obtained while they were stimulant-free, statistically significant differences in baseline HRV parameters were found for mean HR (p=0.0033), STDRR (p=0.0421) and RR triangular index (p=0.0033), while a marginally statistically significant difference was found for LF (p=0.0766). Mean HR was higher in ADHD children when they were on stimulant medication, while STDRR, RR triangular index and LF were higher in ADHD children while they were stimulant-free.

3.2.1.2 Baseline skin conductivity

Baseline skin conductivity of all patients was determined by means of BioGraph Infiniti Biofeedback apparatus. ADHD children were tested while they were stimulant-free and during a period in which they were on stimulant medication, while controls were tested once. The means and standard deviations for baseline skin conductivity are presented in Table 3-11.

Table 3-11: Means and standard deviations for baseline skin conductivity in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Baseline skin conductivity (µMhos)
	Mean (SD)
Controls	1.96 (1.00)
Stimulant-free ADHD children	1.35 (0.83)
ADHD children on stimulants	2.21 (1.14)

3.2.1.2.1 Baseline skin conductivity for stimulant-free ADHD children versus controls

Baseline skin conductivity values obtained while the ADHD children were stimulant-free were compared to baseline skin conductivity values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-12.

Table 3-12: Comparison of baseline skin conductivity between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline skin conductivity (µMhos)	1.35 (0.83)	1.96 (1.00)	0.0551	0.0754

A marginally statistically significant difference in baseline skin conductivity (p=0.0754) was found between stimulant-free ADHD children and controls, with skin conductivity found to be lower in stimulant-free ADHD children.

3.2.1.2.2 Baseline skin conductivity for ADHD children on stimulant medication versus controls

Baseline skin conductivity values obtained while the ADHD children were on stimulant medication were compared to baseline skin conductivity values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-13.

Table 3-13: Comparison of baseline skin conductivity between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline skin conductivity (µMhos)	2.21 (1.14)	1.96 (1.00)	0.4663	0.5637

No statistically significant difference in baseline skin conductivity values between ADHD children on stimulant medication and controls was found.

3.2.1.2.3 Baseline skin conductivity for ADHD children on stimulant medication versus stimulant-free ADHD children

Baseline skin conductivity values obtained while the ADHD children were on stimulant medication were compared to baseline skin conductivity values obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. Results are presented in Table 3-14.

Table 3-14: Comparison of baseline skin conductivity between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline skin conductivity (µMhos)	2.21 (1.14)	1.35 (0.83)	0.0046	0.0055

A statistically significant difference in baseline skin conductivity (p=0.0055) was found when comparing the values obtained while the ADHD children were on stimulant medication and those obtained while they were stimulant-free. These values indicate that baseline skin conductivity is higher in ADHD children while they are on stimulant medication.

3.2.2 Autonomic nervous system functioning during focussed attention

Parameters used to determine autonomic nervous system functioning during focussed attention included heart rate variability parameters discussed in Chapter 2 (2.3.2.2) and skin conductivity. In order to assess autonomic nervous system functioning during focussed attention in unmedicated children with ADHD as compared to normal children, HRV and skin conductivity values during focussed attention obtained while the ADHD children were stimulant-free were compared to HRV and skin conductivity values during focussed attention obtained for the controls by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess autonomic nervous system functioning during focussed attention in medicated children with ADHD as compared to normal children, HRV and skin conductivity values during focussed attention obtained while the ADHD children were on stimulant medication were compared to HRV and skin conductivity values during focussed attention obtained for the controls by means of the same two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the autonomic nervous system functioning during focussed attention of children with ADHD, HRV and skin

conductivity values during focussed attention obtained while the ADHD children were on stimulant medication were compared to HRV and skin conductivity values during focussed attention obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.2.2.1 Heart rate variability parameters during focussed attention

A POLAR tachogram was obtained for each participant while attention was evoked by means of a program on the BioGraph Infiniti Biofeedback apparatus. This specific program is used to train individuals with ADHD to increase their attentive abilities. Heart rate variability parameters measured were those described in Table 3-4. The means and standard deviations for HRV parameters during focussed attention are presented in Table 3-15 for the controls, Table 3-16 for the stimulant-free ADHD children and Table 3-17 for ADHD children on stimulant medication.

Table 3-15: Means and standard deviations for HRV parameters during focussed attention in controls

	Indicator (unit)	Mean (SD)
Time-domain	**HR (bpm)**	94.73 (8.28)
	STDRR (sec)	0.034 (0.019)
	RR triangular index	0.066 (0.032)
	STDHR (bpm)	5.35 (2.74)
	RMSSD (msec)	34.21 (25.39)
Frequency-domain	**HF (ms^2)**	275.17 (410.86)
	LF (ms^2)	228.78 (238.17)
	HF (nu)	50.31 (18.46)
	LF (nu)	46.69 (18.46)
	LF/HF	1.31 (1.00)
Poincaré Plot	**SD1 (msec)**	24.40 (18.13)
	SD2 (msec)	49.86 (23.29)

Table 3-16: Means and standard deviations for HRV parameters during focussed attention in stimulant-free ADHD children

	Indicator (unit)	Mean (SD)
Time-domain	**HR (bpm)**	90.43 (8.84)
	STDRR (sec)	0.047 (0.016)
	RR triangular index	0.092 (0.026)
	STDHR (bpm)	6.68 (1.84)
	RMSSD (msec)	45.04 (18.24)
Frequency-domain	**HF (ms^2)**	512.37 (411.62)
	LF (ms^2)	607.16 (539.96)
	HF (nu)	44.22 (16.80)
	LF (nu)	55.78 (16.80)
	LF/HF	1.67 (1.26)
Poincaré Plot	**SD1 (msec)**	32.07 (12.95)
	SD2 (msec)	72.17 (20.38)

Table 3-17: Means and standard deviations for HRV parameters during focussed attention in ADHD children on stimulant medication

	Indicator (unit)	Mean (SD)
Time-domain	**HR (bpm)**	96.22 (9.98)
	STDRR (sec)	0.049 (0.044)
	RR triangular index	0.071 (0.034)
	STDHR (bpm)	6.10 (2.20)
	RMSSD (msec)	50.52 (53.48)
Frequency-domain	**HF (ms^2)**	740.53 (1266.40)
	LF (ms^2)	916.79 (1998.11)
	HF (nu)	44.04 (17.11)
	LF (nu)	55.96 (17.11)
	LF/HF	1.64 (1.06)
Poincaré Plot	**SD1 (msec)**	36.01 (38.18)
	SD2 (msec)	69.78 (38.15)

3.2.2.1.1 HRV parameters during focussed attention for stimulant-free ADHD children versus controls

HRV values during focussed attention obtained while the ADHD children were stimulant-free were compared to HRV values during focussed attention obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-18.

Table 3-18: Comparison of HRV parameters during focussed attention between stimulant-free ADHD children and controls

	Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	90.43 (8.84)	94.73 (8.28)	0.1355	0.1913
	STDRR (sec)	0.047 (0.016)	0.034 (0.019)	0.0285	0.0082
	RR triangular index	0.092 (0.026)	0.066 (0.032)	0.0082	0.0019
	STDHR (bpm)	6.68 (1.84)	5.35 (2.74)	0.0952	0.0082
	RMSSD (msec)	45.04 (18.24)	34.21 (25.39)	0.1475	0.0193
Frequency-domain	HF (ms^2)	512.37 (411.62)	275.17 (410.86)	0.0878	0.0133
	LF (ms^2)	607.16 (539.96)	228.78 (238.17)	0.0100	0.0011
	HF (nu)	44.22 (16.80)	50.31 (18.46)	0.3022	0.3462
	LF (nu)	55.78 (16.80)	46.69 (18.46)	0.3022	0.3462
	LF/HF	1.67 (1.26)	1.31 (1.00)	0.3411	0.3462
Poincaré Plot	SD1 (msec)	32.07 (12.95)	24.40 (18.13)	0.1503	0.0185
	SD2 (msec)	72.17 (20.38)	49.86 (23.29)	0.0038	0.0047

Statistically significant differences in HRV parameters during focussed attention between stimulant-free ADHD children and controls were found for STDRR (p=0.0082), RR triangular index (p=0.0019), STDHR (p=0.0082), RMSSD (p=0.0193), HF (p=0.0133), LF (p=0.0011), SD1 (p=0.0185) and SD2 (p=0.0047). All these values were found to be significantly higher in the stimulant-free ADHD children.

3.2.2.1.2 HRV parameters during focussed attention for ADHD children on stimulant medication versus controls

HRV values during focussed attention obtained while the ADHD children were on stimulant medication were compared to HRV values during focussed attention obtained

for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-19.

Table 3-19: Comparison of HRV parameters during focussed attention between ADHD children on stimulant medication and controls

	Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	96.22 (9.98)	94.73 (8.28)	0.6222	0.6595
	STDRR (sec)	0.049 (0.044)	0.034 (0.019)	0.1630	0.1619
	RR triangular index	0.071 (0.034)	0.066 (0.032)	0.6098	0.5132
	STDHR (bpm)	6.10 (2.20)	5.35 (2.74)	0.3681	0.1365
	RMSSD (msec)	50.52 (53.48)	34.21 (25.39)	0.2426	0.2609
Frequency-domain	HF (ms^2)	740.53 (1266.40)	275.17 (410.86)	0.1426	0.3384
	LF (ms^2)	916.79 (1998.11)	228.78 (238.17)	0.1530	0.0417
	HF (nu)	44.04 (17.11)	50.31 (18.46)	0.2918	0.3015
	LF (nu)	55.96 (17.11)	46.69 (18.46)	0.2918	0.3015
	LF/HF	1.64 (1.06)	1.31 (1.00)	0.3289	0.3015
Poincaré Plot	SD1 (msec)	36.01 (38.18)	24.40 (18.13)	0.2439	0.2609
	SD2 (msec)	69.78 (38.15)	49.86 (23.29)	0.0628	0.0417

Statistically significant differences in HRV parameters during focussed attention between ADHD children on stimulant medication and controls were found for LF (p=0.0417) and SD2 (p=0.0417). Both LF and SD2 were significantly higher in the ADHD children on stimulant medication.

3.2.2.1.3 HRV values during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

HRV values during focussed attention obtained while the ADHD children were on stimulant medication were compared to HRV values during focussed attention obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. Results are presented in Table 3-20.

Table 3-20: Comparison of HRV parameters during focussed attention between ADHD children on stimulant medication and stimulant-free ADHD children

	Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	96.22 (9.98)	90.43 (8.84)	0.0207	0.0329
	STDRR (sec)	0.049 (0.044)	0.047 (0.016)	0.7565	0.6580
	RR triangular index	0.071 (0.034)	0.092 (0.026)	0.0117	0.0176
	STDHR (bpm)	6.10 (2.20)	6.68 (1.84)	0.1198	0.1712
	RMSSD (msec)	50.52 (53.48)	45.04 (18.24)	0.6288	0.7172
Frequency-domain	HF (ms^2)	740.53 (1266.40)	512.37 (411.62)	0.3562	0.9039
	LF (ms^2)	916.79 (1998.11)	607.16 (539.96)	0.4298	0.5732
	HF (nu)	44.04 (17.11)	44.22 (16.80)	0.9661	0.9679
	LF (nu)	55.96 (17.11)	55.78 (16.80)	0.9661	0.9679
	LF/HF	1.64 (1.06)	1.67 (1.26)	0.9467	0.8405
Poincaré Plot	SD1 (msec)	36.01 (38.18)	32.07 (12.95)	0.6258	0.6874
	SD2 (msec)	69.78 (38.15)	72.17 (20.38)	0.7485	0.5197

When comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, statistically significant differences in HRV parameters during focussed attention were found for mean HR

(p=0.0329) and RR triangular index (p=0.0176). Mean HR was higher in ADHD children while they were on stimulant medication, while RR triangular index was higher in ADHD children while they were stimulant-free.

3.2.2.2 Skin conductivity during focussed attention

Skin conductivity of all patients was measured while attention was evoked by means of a program on the BioGraph Infiniti Biofeedback apparatus, which is used specifically to train individuals with ADHD to increase their attentive abilities. Children with ADHD were tested while they were stimulant-free and during a period in which they were on stimulant medication, while controls were tested once. The means and standard deviations for skin conductivity during focussed attention are presented in Table 3-21.

Table 3-21: Means and standard deviations for skin conductivity during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Skin conductivity during focussed attention (µMhos)
	Mean (SD)
Controls	2.43 (1.27)
Stimulant-free ADHD children	1.68 (1.08)
ADHD children on stimulants	2.40 (1.08)

3.2.2.2.1 Skin conductivity during focussed attention for stimulant-free ADHD children versus controls

Skin conductivity values during focussed attention obtained while the ADHD children were stimulant-free were compared to skin conductivity values during focussed attention obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-22.

Table 3-22: Comparison of skin conductivity during focussed attention between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity during focussed attention (µMhos)	1.68 (1.08)	2.43 (1.27)	0.0613	0.0556

A marginally statistically significant difference in skin conductivity during focussed attention (p=0.0556) was found between stimulant-free ADHD children and controls, with skin conductivity during focussed attention found to be lower in stimulant-free ADHD children.

3.2.2.2.2 Skin conductivity during focussed attention for ADHD children on stimulant medication versus controls

Skin conductivity values during focussed attention obtained while the ADHD children were on stimulant medication were compared to skin conductivity values during focussed

attention obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-23.

Table 3-23: Comparison of skin conductivity during focussed attention between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney t-test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity during focussed attention (µMhos)	2.40 (1.08)	2.43 (1.27)	0.9456	0.9153

No statistically significant difference in skin conductivity during focussed attention was found between ADHD children on stimulant medication and controls.

3.2.2.2.3 Skin conductivity during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

Skin conductivity values during focussed attention obtained while the ADHD children were on stimulant medication were compared to skin conductivity values during focussed attention obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. Results are presented in Table 3-24.

Table 3-24: Comparison of skin conductivity during focussed attention between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity during focussed attention (µMhos)	2.40 (1.08)	1.68 (1.08)	0.0301	0.0126

A statistically significant difference in skin conductivity during focussed attention (p=0.0126) was found when comparing the values obtained while the ADHD children were on stimulant medication and those obtained while they were stimulant-free. These values indicate that, during focussed attention, skin conductivity is higher in ADHD children while they are on stimulant medication.

3.2.3 The effect of focussed attention on the autonomic nervous system

All children were tested both at baseline and during focussed attention. ADHD children were tested while they were stimulant-free and during a period in which they were on stimulant medication, while controls were tested once. Parameters measured included the HRV parameters discussed in Chapter 2 (2.3.2.2) and skin conductivity. Baseline HRV and skin conductivity values were compared to HRV and skin conductivity values obtained during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.2.3.1 Effect of focussed attention on heart rate variability parameters

3.2.3.1.1 Effect of focussed attention on HRV parameters in controls

As previously mentioned, HRV values at baseline and HRV values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-25.

Table 3-25: Comparison of HRV parameters between baseline and focussed attention in controls

	Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	93.77 (9.90)	94.73 (8.28)	0.3572	0.4460
	STDRR (sec)	0.036 (0.021)	0.034 (0.019)	0.4569	0.6947
	RR triangular index	0.070 (0.035)	0.066 (0.032)	0.4118	0.3058
	STDHR (bpm)	5.26 (2.05)	5.35 (2.74)	0.8169	0.9133
	RMSSD (msec)	35.99 (26.38)	34.21 (25.39)	0.6292	0.8446
Frequency-domain	HF (ms^2)	435.67 (595.03)	275.17 (410.86)	0.1977	0.0347
	LF (ms^2)	372.39 (541.41)	228.78 (238.17)	0.1503	0.0611
	HF (nu)	53.75 (14.70)	50.31 (18.46)	0.2904	0.1570
	LF (nu)	46.25 (14.70)	46.69 (18.46)	0.2904	0.1570
	LF/HF	1.02 (0.67)	1.31 (1.00)	0.0597	0.0777
Poincaré Plot	SD1 (msec)	25.63 (18.77)	24.40 (18.13)	0.6387	0.8276
	SD2 (msec)	53.43 (27.95)	49.86 (23.29)	0.2986	0.4724

Regarding the controls, a statistically significant difference in HRV parameters between baseline and focussed attention was found for HF (p=0.0347), while marginally statistically significant differences were found for LF (p=0.0611) and the LF/HF ratio (p=0.0777). Both HF and LF decreased, while the LF/HF ratio increased from baseline to focussed attention.

3.2.3.1.2 Effect of focussed attention on HRV parameters in stimulant-free ADHD children

As previously mentioned, HRV values at baseline and HRV values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-26.

Table 3-26: Comparison of HRV parameters between baseline and focussed attention in stimulant-free ADHD children

	Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	87.67 (7.75)	90.43 (8.84)	0.0003	0.0006
	STDRR (sec)	0.052 (0.020)	0.047 (0.016)	0.0483	0.0640
	RR triangular index	0.100 (0.031)	0.092 (0.026)	0.0528	0.0909
	STDHR (bpm)	6.75 (2.06)	6.68 (1.84)	0.8348	0.5732
	RMSSD (msec)	52.51 (21.95)	45.04 (18.24)	0.0059	0.0035
Frequency-domain	HF (ms^2)	659.16 (505.75)	512.37 (411.62)	0.0095	0.0112
	LF (ms^2)	667.00 (755.66)	607.16 (539.96)	0.5475	0.8092
	HF (nu)	51.94 (16.82)	44.22 (16.80)	0.0273	0.0329
	LF (nu)	48.06 (16.82)	55.78 (16.80)	0.0273	0.0329
	LF/HF	1.22 (1.01)	1.67 (1.26)	0.0888	0.0534
Poincaré Plot	SD1 (msec)	37.36 (15.59)	32.07 (12.95)	0.0059	0.0035
	SD2 (msec)	76.28 (26.86)	72.17 (20.38)	0.3397	0.3144

When tested while they were stimulant-free, the ADHD children displayed statistically significant differences in HRV parameters between baseline and focussed attention for mean HR (p=0.0006), STDRR (p=0.0483), RMSSD (p=0.0035), HF (p=0.0112), HFnu (p=0.0329), LFnu (p=0.0329) and SD1 (p=0.0035). Marginally statistically significant differences between baseline and focussed attention were also found for RR triangular index (p=0.0909) and LF/HF (p=0.0534). Mean HR, LFnu and LF/HF increased from baseline to focussed attention while STDRR, RR triangular index, RMSSD, HF, HFnu and SD1 decreased from baseline to focussed attention.

3.2.3.1.3 Effect of focussed attention on HRV parameters in ADHD children on stimulant medication

As previously mentioned, HRV values at baseline and HRV values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-27.

Table 3-27: Comparison of HRV parameters between baseline and focussed attention in ADHD children on stimulant medication

	Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
		Mean (SD)	Mean (SD)	p-value	p-value
Time-domain	HR (bpm)	95.41 (11.03)	96.22 (9.98)	0.4665	0.2432
	STDRR (sec)	0.044 (0.021)	0.049 (0.044)	0.4893	0.8404
	RR triangular index	0.074 (0.035)	0.071 (0.034)	0.5035	0.2120
	STDHR (bpm)	6.29 (2.09)	6.10 (2.20)	0.4808	0.2513
	RMSSD (msec)	45.71 (26.96)	50.52 (53.48)	0.6230	0.6873
Frequency-domain	HF (ms^2)	517.32 (496.15)	740.53 (1266.40)	0.3132	0.3759
	LF (ms^2)	541.47 (689.72)	916.79 (1998.11)	0.3711	0.4326
	HF (nu)	51.47 (17.14)	44.04 (17.11)	0.0942	0.1588
	LF (nu)	48.53 (17.14)	55.96 (17.11)	0.0942	0.1589
	LF/HF	1.24 (1.02)	1.64 (1.06)	0.1521	0.1365
Poincaré Plot	SD1 (msec)	32.53 (19.17)	36.01 (38.18)	0.6186	0.6874
	SD2 (msec)	68.83 (28.22)	69.78 (38.15)	0.8913	0.6726

When the ADHD children were tested while they were on stimulant medication, only marginally statistically significant differences in HRV parameters between baseline and focussed attention were found regarding the normalized units of HFnu (p=0.0942) and LFnu (p=0.0942). LFnu increased and HFnu decreased from baseline to focussed

attention. With the Wilcoxon signed-rank test no statistically significant differences between baseline and focussed attention were found.

3.2.3.2 Effect of focussed attention on skin conductivity

3.2.3.2.1 Effect of focussed attention on skin conductivity in controls

As previously mentioned, skin conductivity values at baseline and skin conductivity values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-28.

Table 3-28: Comparison of skin conductivity between baseline and focussed attention in controls

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity (µMhos)	1.96 (1.00)	2.43 (1.27)	0.0049	0.0033

Regarding the controls, a statistically significant difference in skin conductivity at baseline and during focussed attention was found using both the paired t-test (p=0.0049) and Wilcoxon signed-rank test (p=0.0033), with skin conductivity increasing from baseline to focussed attention.

3.2.3.2.2 Effect of focussed attention on skin conductivity in stimulant-free ADHD children

As previously mentioned, skin conductivity values at baseline and skin conductivity values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-29.

Table 3-29: Comparison of skin conductivity between baseline and focussed attention in stimulant-free ADHD children

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity (µMhos)	1.35 (0.83)	1.68 (1.08)	0.0065	0.0025

When the ADHD children were tested while stimulant-free, a statistically significant difference in skin conductivity at baseline and during focussed attention was found using both the paired t-test (p=0.0065) and Wilcoxon signed-rank test (p=0.0025), with skin conductivity increasing from baseline to focussed attention.

3.2.3.2.3 Effect of focussed attention on skin conductivity in ADHD children on stimulant medication

As previously mentioned, skin conductivity values at baseline and skin conductivity values during focussed attention were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-30.

Table 3-30: Comparison of skin conductivity between baseline and focussed attention in ADHD children on stimulant medication

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity (µMhos)	2.21 (1.14)	2.40 (1.08)	0.1910	0.0989

Only a marginally statistically significant difference in skin conductivity at baseline and during focussed attention was found for the ADHD children on stimulant medication using the Wilcoxon signed-rank test (p=0.0989), with skin conductivity increasing from baseline to focussed attention. However, no statistically significant difference in skin conductivity at baseline and during focussed attention was found using the paired t-test.

3.2.4 Comparison of delta values of autonomic nervous system functioning

Delta values (Δ = focussed attention - baseline) were established for the differences in baseline values and values during focussed attention. Parameters measured included heart rate variability parameters discussed in Chapter 2 (2.3.2.2) and skin conductivity. In order to determine the magnitude of the change in autonomic nervous system activity from baseline to focussed attention in unmedicated children with ADHD as compared to normal children, delta values obtained while the ADHD children were stimulant-free were compared to delta values obtained for the controls by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the magnitude of the change in autonomic nervous

system activity from baseline to focussed attention in medicated children with ADHD as compared to normal children, delta values obtained while the ADHD children were on stimulant medication were compared to delta values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the effect of stimulant medication on the magnitude of the change in autonomic nervous system activity from baseline to focussed attention in children with ADHD, delta values obtained while the ADHD children were on stimulant medication were compared to delta values obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.2.4.1 Delta values of heart rate variability parameters

Heart rate variability parameters measured were those described in Table 3-4. Delta value means and standard deviations for HRV parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-31.

Table 3-31: Means and standard deviations for delta values of HRV parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Indicator (unit)	Controls	Stimulant-free ADHD children	ADHD children on stimulants
		Mean (SD)	Mean (SD)	Mean (SD)
Time-domain	HR Δ (bpm)	0.95 (4.28)	2.76 (2.69)	0.81 (4.75)
	STDRR Δ (sec)	-0.0021 (0.011)	-0.0051 (0.011)	0.0057 (0.035)
	RR triangular index Δ	-0.0041 (0.021)	-0.0087 (0.018)	-0.0034 (0.022)
	STDHR Δ (bpm)	0.092 (1.65)	-0.072 (1.47)	-0.19 (1.13)
	RMSSD Δ (msec)	-1.78 (15.38)	-7.47 (10.42)	4.81 (41.87)
Frequency-domain	HF Δ (ms^2)	-160.50 (507.90)	-146.79 (220.53)	223.21 (937.76)
	LF Δ (ms^2)	-143.61 (404.42)	-59.84 (425.46)	375.32 (1783.37)
	HF Δ (nu)	-3.44 (13.39)	-7.72 (14.01)	-7.43 (18.33)
	LF Δ (nu)	3.44 (13.39)	7.72 (14.01)	7.43 (18.33)
	LF/HF Δ	0.28 (0.60)	0.45 (1.08)	0.40 (1.16)
Poincaré Plot	SD1 Δ (msec)	-1.23 (10.95)	-5.29 (7.40)	3.48 (29.93)
	SD2 Δ (msec)	-3.58 (14.16)	-4.12 (18.29)	0.95 (29.95)

3.2.4.1.1 Delta values of HRV parameters for stimulant-free ADHD children versus controls

Delta values of HRV parameters obtained while the ADHD children were stimulant-free were compared to delta values of HRV parameters obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-32.

Table 3-32: Comparison of delta values of HRV parameters between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
HR Δ (bpm)	2.76 (2.69)	0.95 (4.28)	0.1370	0.0500
STDRR Δ (sec)	-0.0051 (0.011)	-0.0021 (0.011)	0.4049	0.2125
RR triangular index Δ	-0.0087 (0.018)	-0.0041 (0.021)	0.4819	0.4750
STDHR Δ (bpm)	-0.072 (1.47)	0.092 (1.65)	0.7536	0.6376
RMSSD Δ (msec)	-7.47 (10.42)	-1.78 (15.38)	0.2001	0.0298
HF Δ (ms^2)	-146.79 (220.53)	-160.50 (507.90)	0.9169	0.8553
LF Δ (ms^2)	-59.84 (425.46)	-143.61 (404.42)	0.5430	0.6485
HF Δ (nu)	-7.72 (14.01)	-3.44 (13.39)	0.3485	0.4295
LF Δ (nu)	7.72 (14.01)	3.44 (13.39)	0.3485	0.4295
LF/HF Δ	0.45 (1.08)	0.28 (0.60)	0.5737	0.5433
SD1 Δ (msec)	-5.29 (7.40)	-1.23 (10.95)	0.1981	0.0245
SD2 Δ (msec)	-4.12 (18.29)	-3.58 (14.16)	0.9206	0.6705

Statistically significant differences in delta values of HRV parameters between stimulant-free ADHD children and controls were found for RMSSD Δ (p=0.0298) and SD1 Δ (p=0.0245). The changes in RMSSD and SD1 between baseline and focussed attention were greater in the stimulant-free ADHD children than the controls. A marginally statistically significant difference in delta values of HRV parameters between stimulant-free ADHD children and controls was found regarding HR Δ (p=0.0500), with the change in HR between focussed attention and baseline found to be greater in the stimulant-free ADHD children.

3.2.4.1.2 Delta values of HRV parameters for ADHD children on stimulant medication versus controls

Delta values of HRV parameters obtained while the ADHD children were on stimulant medication were compared to delta values of HRV parameters obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-33.

Table 3-33: Comparison of delta values of HRV parameters between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
HR Δ (bpm)	0.81 (4.75)	0.95 (4.28)	0.9236	0.6705
STDRR Δ (sec)	0.0057 (0.035)	-0.0021 (0.011)	0.3718	0.9636
RR triangular index Δ	-0.0034 (0.022)	-0.0041 (0.021)	0.9154	0.9879
STDHR Δ (bpm)	-0.19 (1.13)	0.092 (1.65)	0.5559	0.5534
RMSSD Δ (msec)	4.81 (41.87)	-1.78 (15.38)	0.5273	0.9032
HF Δ (ms^2)	223.21 (937.76)	-160.50 (507.90)	0.1299	0.5844
LF Δ (ms^2)	375.32 (1783.37)	-143.61 (404.42)	0.2309	0.1212
HF Δ (nu)	-7.43 (18.33)	-3.44 (13.39)	0.4534	0.6928
LF Δ (nu)	7.43 (18.33)	3.44 (13.39)	0.4534	0.6928
LF/HF Δ	0.40 (1.16)	0.28 (0.60)	0.7065	0.8553
SD1 Δ (msec)	3.48 (29.93)	-1.23 (10.95)	0.5268	0.8673
SD2 Δ (msec)	0.95 (29.95)	-3.58 (14.16)	0.5580	0.9758

No statistically significant differences were found when comparing the delta values of HRV parameters obtained while the ADHD children were on stimulant medication and the delta values of HRV parameters obtained for the controls.

3.2.4.1.3 Delta values of HRV parameters for ADHD children on stimulant medication versus stimulant-free ADHD children

Delta values of HRV parameters obtained while the ADHD children were on stimulant medication were compared to delta values of HRV parameters obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-34.

Table 3-34: Comparison of delta values of HRV parameters between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
HR Δ (bpm)	0.81 (4.75)	2.76 (2.69)	0.1428	0.2122
STDRR Δ (sec)	0.0057 (0.035)	-0.0051 (0.011)	0.2262	0.2272
RR triangular index Δ	-0.0034 (0.022)	-0.0087 (0.018)	0.3741	0.5066
STDHR Δ (bpm)	-0.19 (1.13)	-0.072 (1.47)	0.7846	0.5197
RMSSD Δ (msec)	4.81 (41.87)	-7.47 (10.42)	0.2220	0.1712
HF Δ (ms^2)	223.21 (937.76)	-146.79 (220.53)	0.1215	0.3144
LF Δ (ms^2)	375.32 (1783.37)	-59.84 (425.46)	0.2885	0.4445
HF Δ (nu)	-7.43 (18.33)	-7.72 (14.01)	0.9524	0.8405
LF Δ (nu)	7.43 (18.33)	7.72 (14.01)	0.9524	0.8405
LF/HF Δ	0.40 (1.16)	0.45 (1.08)	0.8962	0.9039
SD1 Δ (msec)	3.48 (29.93)	-5.29 (7.40)	0.2218	0.1712
SD2 Δ (msec)	0.95 (29.95)	-4.12 (18.29)	0.5710	0.3760

No statistically significant differences were found when comparing the delta values of HRV parameters obtained while the ADHD children were on stimulant medication and the delta values of HRV parameters obtained while they were stimulant-free.

3.2.4.2 Delta values of skin conductivity

Skin conductivity of all children was measured both at baseline and during focussed attention. Delta values (Δ = focussed attention - baseline) were calculated by determining the difference between baseline values and values during focussed attention. Skin conductivity delta value means and standard deviations for controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-35.

Table 3-35: Means and standard deviations for delta values of skin conductivity in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Skin conductivity Δ (µMhos)
	Mean (SD)
Controls	0.47 (0.62)
Stimulant-free ADHD children	0.32 (0.46)
ADHD children on stimulants	0.19 (0.60)

3.2.4.2.1 Delta values of skin conductivity for stimulant-free ADHD children versus controls

Delta values of skin conductivity obtained while the ADHD children were stimulant-free were compared to delta values of skin conductivity obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-36.

Table 3-36: Comparison of delta values of skin conductivity between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity Δ (µMhos)	0.32 (0.46)	0.47 (0.62)	0.4116	0.4658

No statistically significant differences were found when comparing the delta values of skin conductivity obtained while the ADHD children were stimulant-free and the delta values of skin conductivity obtained for the controls.

3.2.4.2.2 Delta values of skin conductivity for ADHD children on stimulant medication versus controls

Delta values of skin conductivity obtained while the ADHD children were on stimulant medication were compared to delta values of skin conductivity obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-37.

Table 3-37: Comparison of delta values of skin conductivity between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity Δ (µMhos)	0.19 (0.60)	0.47 (0.62)	0.1622	0.4473

No statistically significant differences were found when comparing the delta values of skin conductivity obtained while the ADHD children were on stimulant medication and the delta values of skin conductivity obtained for the control subjects.

3.2.4.2.3 Delta values of skin conductivity for ADHD children on stimulant medication versus stimulant-free ADHD children

Delta values of skin conductivity obtained while the ADHD children were on stimulant medication were compared to delta values of skin conductivity obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-38.

Table 3-38: Comparison of delta values of skin conductivity between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Skin conductivity Δ (µMhos)	0.19 (0.60)	0.32 (0.46)	0.2993	0.3651

No statistically significant differences were found when comparing the delta values of skin conductivity obtained while the ADHD children were on stimulant medication and the delta values of skin conductivity obtained while they were stimulant-free.

3.3 Experimental data on cardiac functioning

3.3.1 Comparison of cardiac functioning between experimental and control groups

As previously mentioned, ADHD children were tested while they were stimulant-free and during a period in which they were on stimulant medication. Control subjects were tested once. Parameters used to determine cardiac functioning included blood pressure and ECG parameters discussed in Chapter 2 (2.3.2.5). In order to assess baseline cardiac functioning in unmedicated children with ADHD as compared to normal children, blood pressure and ECG values obtained while the ADHD children were stimulant-free were compared to blood pressure and ECG values obtained for the controls by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess baseline cardiac functioning in medicated children with ADHD as compared to normal children, blood pressure and ECG values obtained while the ADHD children were on stimulant medication were compared to blood pressure and ECG values obtained for the controls by means of the same two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the cardiac function of children with ADHD, blood pressure and ECG values obtained while the ADHD children were on stimulant medication were compared to blood pressure and ECG values obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.3.1.1 Blood pressure

Blood pressure of all children was measured by means of a stethoscope and a mercurial sphygmomanometer. Means and standard deviations for systolic and diastolic blood pressure in controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-39.

Table 3-39: Means and standard deviations for blood pressure in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Systolic blood pressure (mmHg)	**Diastolic blood pressure (mmHg)**
	Mean (SD)	**Mean (SD)**
Controls	97.17 (9.97)	70.39 (8.51)
Stimulant-free ADHD children	95.00 (7.64)	65.95 (5.97)
ADHD children on stimulants	111.53 (7.93)	69.74 (8.77)

3.3.1.1.1 Blood pressure values for stimulant-free ADHD children versus controls

Blood pressure values obtained while the ADHD children were stimulant-free were compared to blood pressure values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-40.

Table 3-40: Comparison of systolic and diastolic blood pressure between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Systolic blood pressure (mmHg)	95.00 (7.64)	97.17 (9.97)	0.4648	0.4557
Diastolic blood pressure (mmHg)	65.95 (5.97)	70.39 (8.51)	0.0767	0.1612

No statistically significant difference in systolic blood pressure was found between stimulant-free ADHD children and controls. However, a marginally statistically significant difference was found regarding diastolic blood pressure (p=0.0767), with diastolic blood pressure found to be lower in stimulant-free ADHD children.

3.3.1.1.2 Blood pressure values for ADHD children on stimulant medication versus controls

Blood pressure values obtained while the ADHD children were on stimulant medication were compared to blood pressure values obtained for the controls using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-41.

Table 3-41: Comparison of systolic and diastolic blood pressure between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Systolic blood pressure (mmHg)	111.53 (7.93)	97.17 (9.97)	<0.0001	0.0003
Diastolic blood pressure (mmHg)	69.74 (8.77)	70.39 (8.51)	0.8197	0.9515

A statistically significant difference between ADHD children on stimulant medication and control subjects was found regarding systolic blood pressure (p=0.0003), with systolic blood pressure found to be higher in ADHD children on stimulant medication. No statistically significant difference in diastolic blood pressure values was found.

3.3.1.1.3 Blood pressure values for ADHD children on stimulant medication versus stimulant-free ADHD children

Blood pressure values obtained while the ADHD children were on stimulant medication were compared to blood pressure values obtained while they were stimulant-free using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-42.

Table 3-42: Comparison of systolic and diastolic blood pressure between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Systolic blood pressure (mmHg)	111.53 (7.93)	95.00 (7.64)	< 0.0001	0.0003
Diastolic blood pressure (mmHg)	69.74 (8.77)	65.95 (5.97)	0.0235	0.0553

When comparing the values obtained while the ADHD children were on stimulant medication and those obtained while they were stimulant-free, statistically significant differences were found regarding systolic (p=0.0003) and diastolic (p=0.0235) blood pressure. While they were on stimulant medication, the ADHD children had significantly higher values for both systolic and diastolic blood pressure.

3.3.1.2 ECG parameters

ECGs were conducted on all children while they were resting quietly in a supine position. The raw data was quantified and analysed to obtain a set of indicators of cardiac function. These indicators are presented in Table 3-43.

Table 3-43: ECG indicators used

Indicator	Explanation
RR	Distance between the R wave of a QRS complex and the R wave of a successive QRS complex in seconds
HR	Heart rate in beats per minute
QT	Distance from the Q wave initiation to the terminal inscription of the T wave in milliseconds
JT	Distance from the J point to the terminal inscription of the T wave in milliseconds
QTc (data-derived)	QT interval in milliseconds corrected for heart rate by using a data-derived formula established by Wernicke *et al* (1)
JTc (data-derived)	JT interval in milliseconds corrected for heart rate by using a data-derived formula established by Wernicke *et al* (1)
QTc (Bazett)	QT interval in milliseconds corrected for heart rate by using Bazett's formula (2)
JTc (Bazett)	JT interval in milliseconds corrected for heart rate by using Bazett's formula (2)
QTd	The difference between QT intervals of leads II and V6 in milliseconds
JTd	The difference between JT intervals of leads II and V6 in milliseconds
QTcd	The difference between QTc intervals of leads II and V6 in milliseconds with QT corrected for heart rate using a data-derived formula established by Wernicke *et al* (1)
JTcd	The difference between JTc intervals of leads II and V6 in milliseconds with JT corrected for heart rate using a data-derived formula established by Wernicke *et al* (1)

Means and standard deviations for ECG parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-44.

Table 3-44: Mean and standard deviations for ECG parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication

Indicator (unit)	Controls	Stimulant-free ADHD children	ADHD children on stimulants
	Mean (SD)	Mean (SD)	Mean (SD)
RR (sec)	0.74 (0.08)	0.81 (0.11)	0.70 (0.10)
HR (bpm)	80.67 (10.17)	74.32 (8.53)	83.95 (15.22)
QT (msec)	372.83 (21.63)	383.95 (18.46)	358.25 (23.96)
JT (msec)	293.96 (22.97)	305.44 (13.11)	282.89 (18.25)
QTc (data-derived) (msec)	418.84 (13.60)	416.81 (17.51)	410.48 (20.26)
JTc (data-derived) (msec)	330.10 (17.71)	331.83 (17.68)	324.24 (16.58)
QTc (Bazett) (msec)	434.66 (13.96)	427.96 (21.81)	428.76 (23.55)
JTc (Bazett) (msec)	342.52 (17.39)	340.78 (21.88)	338.72 (19.70)
QTd (msec)	9.74 (6.27)	9.65 (5.65)	9.12 (5.43)
JTd (msec)	9.41 (7.68)	10.35 (7.44)	9.65 (8.16)
QTcd (msec)	10.99 (7.04)	10.77 (6.42)	10.48 (6.55)
JTcd (msec)	10.79 (9.40)	11.74 (9.16)	11.11 (9.88)

3.3.1.2.1 ECG parameters for stimulant-free ADHD children versus controls

ECG values obtained while the ADHD children were stimulant-free were compared to ECG values obtained for the controls, using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-45.

Table 3-45: Comparison of ECG parameters between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
RR (sec)	0.81 (0.11)	0.74 (0.08)	0.0248	0.0227
HR (bpm)	74.32 (8.53)	80.67 (10.17)	0.0477	0.0386
QT (msec)	383.95 (18.46)	372.83 (21.63)	0.1023	0.1069
JT (msec)	305.44 (13.11)	293.96 (22.97)	0.0746	0.0703
QTc (data-derived) (msec)	416.81 (17.51)	418.84 (13.60)	0.6954	0.6928
JTc (data-derived) (msec)	331.83 (17.68)	330.10 (17.71)	0.7679	0.9758
QTc (Bazett) (msec)	427.96 (21.81)	434.66 (13.96)	0.2718	0.2128
JTc (Bazett) (msec)	340.78 (21.88)	342.52 (17.39)	0.7903	0.6928
QTd (msec)	9.65 (5.65)	9.74 (6.27)	0.9631	0.9756
JTd (msec)	10.35 (7.44)	9.41 (7.68)	0.7067	0.4002
QTcd (msec)	10.77 (6.42)	10.99 (7.04)	0.9211	0.8076
JTcd (msec)	11.74 (9.16)	10.79 (9.40)	0.7582	0.5430

Statistically significant differences between ECG parameters of stimulant-free ADHD children and control subjects were obtained for RR (p=0.0227) and HR (p=0.0386). RR intervals were larger, while HR values were lower in stimulant-free ADHD children. A marginally significant difference was found for JT (p=0.0703), with JT intervals found to be larger in ADHD children while they were stimulant-free.

3.3.1.2.2 ECG parameters for ADHD children on stimulant medication versus controls

ECG values obtained while the ADHD children were on stimulant medication were compared to ECG values obtained for the controls using the two-sample t-test with

Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-46.

Table 3-46: Comparison of ECG parameters between ADHD children on stimulant medication and controls

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
RR (sec)	0.70 (0.10)	0.74 (0.08)	0.2676	0.3947
HR (bpm)	83.95 (15.22)	80.67 (10.17)	0.4442	0.4291
QT (msec)	358.25 (23.96)	372.83 (21.63)	0.0593	0.1432
JT (msec)	282.89 (18.25)	293.96 (22.97)	0.1150	0.0943
QTc (data-derived) (msec)	410.48 (20.26)	418.84 (13.60)	0.1481	0.3015
JTc (data-derived) (msec)	324.24 (16.58)	330.10 (17.71)	0.3065	0.2019
QTc (Bazett) (msec)	428.76 (23.55)	434.66 (13.96)	0.3586	0.4475
JTc (Bazett) (msec)	338.72 (19.70)	342.52 (17.39)	0.5368	0.4658
QTd (msec)	9.12 (5.43)	9.74 (6.27)	0.7510	0.9147
JTd (msec)	9.65 (8.16)	9.41 (7.68)	0.9265	0.7712
QTcd (msec)	10.48 (6.55)	10.99 (7.04)	0.8208	0.7263
JTcd (msec)	11.11 (9.88)	10.79 (9.40)	0.9217	0.7149

No statistically significant differences between ECG parameters of ADHD children on stimulant medication and control subjects were obtained. However, marginally statistically significant differences were obtained for QT (p=0.0593) and JT (p=0.0943), with both QT and JT intervals found to be smaller in the ADHD children on stimulant medication.

3.3.1.2.3 ECG parameters for ADHD children on stimulant medication versus stimulant-free ADHD children

ECG values obtained while the ADHD children were on stimulant medication were compared to ECG values obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-47.

Table 3-47: Comparison of ECG parameters between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
RR (sec)	0.70 (0.10)	0.81 (0.11)	0.0012	0.0025
HR (bpm)	83.95 (15.22)	74.32 (8.53)	0.0063	0.0070
QT (msec)	358.25 (23.96)	383.95 (18.46)	< 0.0001	0.0002
JT (msec)	282.89 (18.25)	305.44 (13.11)	< 0.0001	0.0002
QTc (data-derived) (msec)	410.48 (20.26)	416.81 (17.51)	0.2401	0.6292
JTc (data-derived) (msec)	324.24 (16.58)	331.83 (17.68)	0.0536	0.0990
QTc (Bazett) (msec)	428.76 (23.55)	427.96 (21.81)	0.9048	0.4688
JTc (Bazett) (msec)	338.72 (19.70)	340.78 (21.88)	0.6713	0.8092
QTd (msec)	9.12 (5.43)	9.65 (5.65)	0.6972	0.4602
JTd (msec)	9.65 (8.16)	10.35 (7.44)	0.7210	0.4432
QTcd (msec)	10.48 (6.55)	10.77 (6.42)	0.8527	0.5275
JTcd (msec)	11.11 (9.88)	11.74 (9.16)	0.7740	0.6227

Statistically significant differences between ECG parameters of ADHD children on stimulant medication and stimulant-free ADHD children were obtained for RR (p=0.0025), HR (p=0.0070), QT (p=0.0002) and JT (p=0.0002). HR values were larger in ADHD children while they were on stimulant medication, while RR, QT and JT intervals were larger in ADHD children while they were stimulant-free. A marginally

statistically significant difference was found for the data-derived JTc (p=0.0536), with JTc values found to be larger in ADHD children while they were stimulant-free.

3.3.2 Prolongation of ECG parameters

3.3.2.1 Prolongation of the QTc interval based on the Moss and Robinson criteria

The Bazett-corrected QTc interval was characterised as being prolonged based on the Moss and Robinson (3) criteria for children and females of QTc > 460 ms. Bazett-corrected QTc values for controls, stimulant-free ADHD children and ADHD children on stimulant medication are represented in Table 3-48.

Table 3-48: Bazett-corrected QTc values for controls, stimulant-free ADHD children and ADHD children on stimulant medication

Controls	Stimulant-free ADHD children	ADHD children on stimulants
QTc (msec)	QTc (msec)	QTc (msec)
449.70	419.64	392.95
424.53	**461.95**	384.41
466.35	439.12	402.47
432.87	**463.49**	420.60
420.95	443.18	440.16
422.69	450.69	**462.37**
436.56	434.44	439.81
448.36	418.51	416.77
427.20	402.25	424.55
423.27	399.29	425.29
423.32	404.04	432.96
439.96	418.82	418.22
432.52	**463.05**	**483.96**
430.19	397.18	407.58
462.26	404.91	446.01
437.80	430.41	445.43
418.92	438.62	437.57
426.40	422.45	440.07
	419.26	425.32

Based on the Moss and Robinson criteria of QTc prolongation, two of the controls, three of the stimulant-free ADHD children and two of the ADHD children on stimulant medication experienced a prolongation of the Bazett-corrected QTc interval. It is important to note that one of the two ADHD children who experienced a QTc prolongation while on stimulant medication, also experienced a QTc prolongation while stimulant-free.

3.3.2.2 Within-patient QTc prolongation

Bazett-corrected QTc intervals obtained while the ADHD children were stimulant-free were compared to those obtained while they were on stimulant medication, in order to determine if a within-patient difference of 30 msec or more was found. As previously mentioned, a within-patient increase of 30 msec or more is defined as a prolongation of the QTc interval by the drug under question (4). Table 3-49 represents the Bazett-corrected QTc values obtained while the ADHD children were on stimulant medication, the Bazett-corrected QTc values obtained while they were stimulant-free and the difference between the respective values.

Table 3-49: Bazett-corrected QTc values in ADHD children while on stimulant medication, while stimulant-free and the difference between them

	On stimulants	Stimulant-free	Difference
Subject	**QTc (msec)**	**QTc (msec)**	**(msec)**
01	392.95	419.64	-26.69
03	384.41	461.95	-77.54
04	402.47	439.12	-36.65
05	420.60	463.49	-42.89
06	440.16	443.18	-3.02
07	462.37	450.69	11.68
08	439.81	434.44	5.37
09	416.77	418.51	-1.74
10	424.55	402.25	22.30
11	425.29	399.29	26.00
12	432.96	404.04	28.92
13	418.22	418.82	-0.60
14	483.96	463.05	20.91
15	407.58	397.18	10.40
16	**446.01**	**404.91**	**41.10**
17	445.43	430.41	15.02
18	437.57	438.62	-1.05
19	440.07	422.45	17.62
20	425.32	419.26	6.06

Only one child experienced a within-patient increase of 30 msec or more with the usage of stimulant medication. Furthermore, eight of the children actually experienced a decrease in the Bazett-corrected QTc interval with the usage of stimulant medication.

3.3.2.3 JTc prolongation

Bazett-corrected JTc values were characterised as being prolonged based on the criteria established in the study by Berul *et al* (5), i.e. JTc > 340 msec. Bazett-corrected JTc values for the controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-50.

Table 3-50: Bazett-corrected JTc values for controls, stimulant-free ADHD children and ADHD children on stimulant medication

Controls	Stimulant-free ADHD children	ADHD children on stimulants
JTc (msec)	JTc (msec)	JTc (msec)
341.09	338.66	314.36
353.20	**350.37**	306.83
352.20	**356.16**	330.12
351.08	**383.23**	**340.30**
344.48	**344.48**	**345.23**
316.03	**360.93**	**368.29**
357.34	**356.00**	**350.22**
340.03	328.96	325.01
323.31	330.05	**350.80**
349.64	332.75	**349.49**
322.35	293.70	316.89
326.94	322.73	320.58
359.76	**379.58**	**383.13**
347.31	309.12	328.63
372.06	324.61	**353.36**
363.24	337.58	**347.11**
307.73	**352.72**	**354.79**
337.57	334.12	322.99
	339.14	327.48

Twelve of the controls experienced a prolongation of the Bazett-corrected JTc interval based on the criteria established by Berul *et al* (5). Eight of the stimulant-free ADHD children and ten of the ADHD children on stimulant medication experienced a prolongation of the Bazett-corrected JTc interval based on the same criteria. It is important to note that six of the ten ADHD children who experienced a JTc prolongation while on stimulant medication, also experienced a Bazett-corrected JTc prolongation while stimulant-free.

3.3.2.4 QTd and JTd prolongation

QTd and JTd values equal to or more than 55 msec were highlighted as an increased risk for critical ventricular arrhythmias (6). Table 3-51 represents the QTd and JTd values for the controls, stimulant-free ADHD children and ADHD children on stimulant medication.

Table 3-51: QTd and JTd values for controls, stimulant-free ADHD children and ADHD children on stimulant medication

Controls		Stimulant-free ADHD children		ADHD children on stimulants	
QTd (msec)	**JTd (msec)**	**QTd (msec)**	**JTd (msec)**	**QTd (msec)**	**JTd (msec)**
6.67	6.67	6.67	13.33	6.67	13.33
24.0	13.33	6.67	3.33	6.67	20.00
20.0	33.33	20.00	33.33	20.00	33.33
13.33	6.67	13.33	6.67	13.33	6.67
14.67	2.67	3.33	0.00	13.33	13.33
13.33	13.33	13.33	13.33	10.00	13.33
0	10.67	0	16.67	0	0
13.33	2.67	13.33	13.33	13.33	6.67
2.67	6.67	20.00	13.33	13.33	10.00
6.67	6.67	6.67	6.67	6.67	6.67
10.0	13.33	10.00	13.33	10.00	13.33
10.0	6.67	10.00	6.67	10.00	6.67
6.67	3.33	10.00	3.33	0	3.33
6.67	0	16.67	0.00	3.33	13.33
6.67	20.0	3.33	6.67	16.67	0
13.33	10.0	13.33	10.00	13.33	10.00
0.67	6.67	6.67	10.00	6.67	0
6.67	6.67	6.67	13.33	6.67	0
		3.33	13.33	3.33	13.33

None of the controls displayed a QTd or JTd equal to or greater than 55 msec. Moreover, none of the ADHD children displayed a QTd or JTd equal to or greater than 55 msec, whether they were stimulant-free or on stimulant medication.

3.4 Experimental data on theta/beta and theta/SMR ratios

Theta/beta and theta/SMR ratios of all children were measured at baseline and during focussed attention. Means and standard deviations for theta/beta and theta/SMR ratios at baseline and during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication are presented in Table 3-52.

Table 3-52: Means and standard deviations for theta/beta and theta/SMR ratios at baseline and during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Baseline theta/beta	Baseline theta/SMR	Theta/beta during focussed attention	Theta/SMR during focussed attention
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Controls	3.70 (3.51)	5.13 (4.68)	6.29 (14.14)	3.94 (3.54)
Stimulant-free ADHD children	4.26 (3.83)	6.67 (7.64)	3.93 (2.45)	4.15 (2.66)
ADHD children on stimulants	3.49 (2.01)	3.51 (2.55)	3.66 (4.04)	5.42 (5.82)

3.4.1 Baseline theta/beta and theta/SMR ratios

EEG theta/beta and theta/SMR ratios were determined by BioGraph Infiniti Biofeedback apparatus, both at baseline and during focussed attention. To assess baseline EEG functioning in unmedicated children with ADHD as compared to normal children, baseline theta/beta and theta/SMR ratios obtained while the ADHD children were stimulant-free were compared to baseline theta/beta and theta/SMR ratios obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess baseline

EEG functioning in medicated children with ADHD as compared to normal children, baseline theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to baseline theta/beta and theta/SMR ratios obtained for the control subjects by means of the same two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the EEG functioning of children with ADHD, baseline theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to baseline theta/beta and theta/SMR ratios obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.4.1.1 Baseline theta/beta and theta/SMR ratios for stimulant-free ADHD children versus controls

Baseline EEG theta/beta and theta/SMR ratios obtained while the ADHD children were stimulant-free were compared to baseline EEG theta/beta and theta/SMR ratios obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-53.

Table 3-53: Comparison of baseline theta/beta and theta/SMR ratios between stimulant-free ADHD children and controls

Indicator	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline theta/beta	4.26 (3.83)	3.70 (3.51)	0.6463	0.7041
Baseline theta/SMR	6.67 (7.64)	5.13 (4.68)	0.4624	0.7845

No statistically significant differences in baseline theta/beta or theta/SMR ratios were found between stimulant-free ADHD children and controls.

3.4.1.2 Baseline theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus controls

Baseline EEG theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to baseline EEG theta/beta and theta/SMR ratios obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-54.

Table 3-54: Comparison of baseline theta/beta and theta/SMR ratios between ADHD children on stimulant medication and controls

Indicator	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline theta/beta	3.49 (2.01)	3.70 (3.51)	0.8235	0.6485
Baseline theta/SMR	3.51 (2.55)	5.13 (4.68)	0.2062	0.5948

No statistically significant differences in baseline theta/beta or theta/SMR ratios were found between ADHD children on stimulant medication and control subjects.

3.4.1.3 Baseline theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus stimulant-free ADHD children

Baseline EEG theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to baseline EEG theta/beta and theta/SMR ratios obtained while they were stimulant-free using the paired t-test and Wilcoxon signed-rank test. Results are presented in Table 3-55.

Table 3-55: **Comparison of baseline theta/beta and theta/SMR ratios between ADHD children on stimulant medication and stimulant-free ADHD children**

Indicator	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline theta/beta	3.49 (2.01)	4.26 (3.83)	0.3297	0.5461
Baseline theta/SMR	3.51 (2.55)	6.67 (7.64)	0.1187	0.2598

No statistically significant differences in baseline theta/beta or theta/SMR ratios were found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free.

3.4.2 Theta/beta and theta/SMR ratios during focussed attention

EEG theta/beta and theta/SMR ratios were determined by BioGraph Infiniti Biofeedback apparatus at baseline and during focussed attention. To assess EEG functioning during focussed attention in unmedicated children with ADHD as compared to normal children, theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were stimulant-free were compared to theta/beta and theta/SMR ratios during focussed attention obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess EEG functioning during focussed attention in medicated children with ADHD as compared to normal children, theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were on stimulant medication were compared to theta/beta and theta/SMR ratios during focussed attention obtained for the control subjects by means of the same two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the EEG functioning of the children with ADHD during focussed attention, theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were on stimulant medication were compared to theta/beta and theta/SMR ratios during focussed attention obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference

- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.4.2.1 Theta/beta and theta/SMR ratios during focussed attention for stimulant-free ADHD children versus controls

EEG theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were stimulant-free were compared to EEG theta/beta and theta/SMR ratios during focussed attention obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-56.

Table 3-56: Comparison of theta/beta and theta/SMR ratios during focussed attention between stimulant-free ADHD children and controls

Indicator	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta during focussed attention	3.93 (2.45)	6.29 (14.14)	0.4946	0.2544
Theta/SMR during focussed attention	4.15 (2.66)	3.94 (3.54)	0.8381	0.4846

No statistically significant differences in theta/beta or theta/SMR ratios during focussed attention were found between stimulant-free ADHD children and control subjects.

3.4.2.2 Theta/beta and theta/SMR ratios during focussed attention for ADHD children on stimulant medication versus controls

EEG theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were on stimulant medication were compared to EEG theta/beta and theta/SMR ratios during focussed attention obtained for the control subjects, using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-57.

Table 3-57: Comparison of theta/beta and theta/SMR ratios during focussed attention between ADHD children on stimulant medication and controls

Indicator	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta during focussed attention	3.66 (4.04)	6.29 (14.14)	0.4560	0.9032
Theta/SMR during focussed attention	5.42 (5.82)	3.94 (3.54)	0.3543	0.2609

No statistically significant differences were found for the theta/beta or theta/SMR ratios during focussed attention between ADHD children on stimulant medication and control subjects.

3.4.2.3 Theta/beta and theta/SMR ratios during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

EEG theta/beta and theta/SMR ratios during focussed attention obtained while the ADHD children were on stimulant medication were compared to the EEG theta/beta and

theta/SMR ratios during focussed attention obtained while they were stimulant-free using the paired t-test and Wilcoxon signed-rank test. Results are presented in Table 3-58.

Table 3-58: **Comparison of theta/beta and theta/SMR ratios during focussed attention between ADHD children on stimulant medication and stimulant-free ADHD children**

Indicator	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta during focussed attention	3.66 (4.04)	3.93 (2.45)	0.8014	0.3443
Theta/SMR during focussed attention	5.42 (5.82)	4.15 (2.66)	0.4282	0.4209

No statistically significant differences in theta/beta or theta/SMR ratios during focussed attention were found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free.

3.4.3 Effect of focussed attention on theta/beta and theta/SMR ratios

EEG theta/beta and theta/SMR ratios were determined by BioGraph Infiniti Biofeedback apparatus at baseline and during focussed attention. To determine the effect of focussed attention on both theta/beta and theta/SMR ratios, baseline theta/beta and theta/SMR ratios were compared to theta/beta and theta/SMR ratios obtained during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, using the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance

of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.4.3.1 Effect of focussed attention on theta/beta and theta/SMR ratios in controls

As previously mentioned, theta/beta and theta/SMR ratios at baseline and during focussed attention in controls were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-59.

Table 3-59: Comparison of theta/beta and theta/SMR ratios between baseline and focussed attention in controls

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta	3.70 (3.51)	6.29 (14.14)	0.4577	0.6165
Theta/SMR	5.13 (4.68)	3.94 (3.54)	0.4481	0.5277

No statistically significant differences between baseline and focussed attention were found for the theta/beta or theta/SMR ratios in the controls.

3.4.3.2 Effect of focussed attention on theta/beta and theta/SMR ratios in stimulant-free ADHD children

As previously mentioned, theta/beta and theta/SMR ratios at baseline and during focussed attention in stimulant-free ADHD children were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-60.

Table 3-60: Comparison of theta/beta and theta/SMR ratios between baseline and focussed attention in stimulant-free ADHD children

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta	4.26 (3.83)	3.93 (2.45)	0.7706	0.9359
Theta/SMR	6.67 (7.64)	4.15 (2.66)	0.1002	0.4688

No statistically significant differences between baseline and focussed attention were found for the theta/beta or theta/SMR ratios in stimulant-free ADHD children.

3.4.3.3 Effect of focussed attention on theta/beta and theta/SMR ratios in ADHD children on stimulant medication

As previously mentioned, theta/beta and theta/SMR ratios at baseline and during focussed attention in ADHD children on stimulant medication were compared using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-61.

Table 3-61: Comparison of theta/beta and theta/SMR ratios between baseline and focussed attention in ADHD children on stimulant medication

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta	3.49 (2.01)	3.66 (4.04)	0.8016	0.5197
Theta/SMR	3.51 (2.55)	5.42 (5.82)	0.2276	0.4445

No statistically significant differences between baseline and focussed attention were found for the theta/beta and theta/SMR ratios in ADHD children on stimulant medication.

3.4.4 Comparison of delta values of theta/beta and theta/SMR ratios

Theta/beta and theta/SMR ratios were measured for all children, both at baseline and during focussed attention. Delta values (Δ = focussed attention - baseline) were calculated by determining the difference between baseline values and values during focussed attention. Delta value means and standard deviations for both theta/beta and theta/SMR ratios in controls, stimulant-free ADHD children and ADHD children on stimulant medication are represented in Table 3-62.

Table 3-62: Means and standard deviations for the delta values of theta/beta and theta/SMR ratios in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Theta/beta Δ	Theta/SMR Δ
	Mean (SD)	Mean (SD)
Controls	2.59 (14.45)	-1.19 (6.51)
Stimulant-free ADHD children	-0.33 (4.82)	-2.52 (6.34)
ADHD children on stimulants	0.17 (2.92)	1.91 (6.65)

To determine the difference in the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention between unmedicated children with ADHD and normal children, the delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were stimulant-free were compared to the delta values of theta/beta and theta/SMR ratios obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the difference in the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention between medicated children with ADHD and normal children, the delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to the delta values of theta/beta and theta/SMR ratios obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the effect of stimulant medication on the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention in children with ADHD, the delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to the delta values of theta/beta and theta/SMR ratios obtained while they were stimulant-free using both the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.4.4.1 Delta values of theta/beta and theta/SMR ratios for stimulant-free ADHD children versus controls

Delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were stimulant-free were compared to delta values of theta/beta and theta/SMR ratios obtained for the control subjects using both the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-63.

Table 3-63: Comparison of delta values of theta/beta and theta/SMR ratios between stimulant-free ADHD children and controls

Indicator	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta ratio Δ	-0.33 (4.82)	2.59 (14.45)	0.4246	0.8079
Theta/SMR ratio Δ	-2.52 (6.34)	-1.19 (6.51)	0.5338	0.6928

No statistically significant differences between the delta values of theta/beta and theta/SMR ratios were found between the stimulant-free ADHD children and the control subjects.

3.4.4.2 Delta values of theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus controls

Delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to delta values of theta/beta and theta/SMR ratios obtained for the controls using the two-sample t-test with Welch's correction for

unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-64.

Table 3-64: **Comparison of delta values of theta/beta and theta/SMR ratios between ADHD children on stimulant medication and controls**

Indicator	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta ratio Δ	0.17 (2.92)	2.59 (14.45)	0.4949	0.5234
Theta/SMR ratio Δ	1.91 (6.65)	-1.19 (6.51)	0.1607	0.2609

No statistically significant differences between the delta values of theta/beta and theta/SMR ratios were found between the ADHD children on stimulant medication and the control subjects.

3.4.4.3 Delta values of theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus stimulant-free ADHD children

Delta values of theta/beta and theta/SMR ratios obtained while the ADHD children were on stimulant medication were compared to delta values of theta/beta and theta/SMR ratios obtained while they were stimulant-free using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-65.

Table 3-65: **Comparison of delta values of theta/beta and theta/SMR ratios between ADHD children on stimulant medication and stimulant-free ADHD children**

Indicator	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Theta/beta ratio Δ	0.17 (2.92)	-0.33 (4.82)	0.7254	0.9679
Theta/SMR ratio Δ	1.91 (6.65)	-2.52 (6.34)	0.0485	0.0836

No statistically significant differences between the delta values of theta/beta ratios were found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free. A statistically significant difference was, however, found between the delta values of the theta/SMR ratio ($p=0.0485$). The mean delta values of attention minus baseline for the theta/SMR ratio in ADHD children on stimulant medication was positive (1.91 ± 6.65), indicating an increase in the theta/SMR ratio from baseline to focussed attention, while the mean delta value for the theta/SMR ratio in stimulant-free ADHD children was negative (-2.52 ± 6.34), indicating a decrease in the theta/SMR ratio from baseline to focussed attention.

3.5 Experimental data on alpha power

Alpha frequency power of all children was measured both at baseline and during focussed attention. Three different alpha frequencies were measured; namely thalpha (6-10 Hz), low alpha (8-10 Hz) and high alpha (11-12 Hz). Means and standard deviations for alpha power at baseline and during focussed attention in controls, stimulant-free

ADHD children and ADHD children on stimulant medication are presented in Table 3-66.

Table 3-66: Means and standard deviations for alpha power at baseline and during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Thalpha (µV)		Low alpha (µV)		High alpha (µV)	
	Baseline	**Focussed attention**	**Baseline**	**Focussed attention**	**Baseline**	**Focussed attention**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Controls	2.91 (11.72)	-4.94 (14.15)	2.79 (11.63)	0.67 (5.05)	1.24 (2.76)	-4.82 (11.88)
Stimulant-free ADHD children	0.83 (4.85)	-4.75 (16.95)	0.70 (3.06)	-3.57 (17.85)	1.03 (1.63)	-1.04 (1.74)
ADHD children on stimulants	-0.41 (4.40)	0.37 (3.95)	-0.51 (3.71)	-0.96 (2.18)	0.10 (1.71)	-0.09 (1.38)

3.5.1 Baseline alpha power

EEG alpha power was determined by BioGraph Infiniti Biofeedback apparatus, at baseline and during focussed attention. To assess baseline EEG functioning in unmedicated children with ADHD as compared to normal children, baseline alpha power obtained while the ADHD children were stimulant-free was compared to baseline alpha power obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess baseline EEG functioning in medicated children with ADHD as compared to

normal children, baseline alpha power obtained while the ADHD children were on stimulant medication was compared to baseline alpha power obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the EEG functioning of children with ADHD, baseline alpha power obtained while the ADHD children were on stimulant medication was compared to baseline alpha power obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.5.1.1 Baseline alpha power for stimulant-free ADHD children versus controls

Baseline EEG alpha power obtained while the ADHD children were stimulant-free was compared to baseline EEG alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-67.

Table 3-67: Comparison of baseline alpha power between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline thalpha (µV)	0.83 (4.85)	2.91 (11.72)	0.4934	0.6485
Baseline low alpha (µV)	0.70 (3.06)	2.79 (11.63)	0.4700	0.5637
Baseline high alpha (µV)	1.03 (1.63)	1.24 (2.76)	0.7868	0.6928

No statistically significant differences in baseline alpha power between stimulant-free ADHD children and control subjects were found.

3.5.1.2 Baseline alpha power for ADHD children on stimulant medication versus controls

Baseline alpha power obtained while the ADHD children were on stimulant medication was compared to baseline alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-68.

Table 3-68: **Comparison of baseline alpha power between ADHD children on stimulant medication and controls**

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline thalpha (µV)	-0.41 (4.40)	2.91 (11.72)	0.2713	0.7154
Baseline low alpha (µV)	-0.51 (3.71)	2.79 (11.63)	0.2639	0.3540
Baseline high alpha (µV)	0.10 (1.71)	1.24 (2.76)	0.1440	0.3949

No statistically significant differences in baseline alpha power between ADHD children on stimulant medication and control subjects were found.

3.5.1.3 Baseline alpha power for ADHD children on stimulant medication versus stimulant-free ADHD children

Baseline EEG alpha power obtained while the ADHD children were on stimulant medication was compared to baseline EEG alpha power obtained while they were stimulant-free using the paired t-test and Wilcoxon signed-rank test. Results are presented in Table 3-69.

Table 3-69: **Comparison of baseline alpha power between ADHD children on stimulant medication and stimulant-free ADHD children**

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Baseline thalpha (µV)	-0.41 (4.40)	0.83 (4.85)	0.4456	0.2122
Baseline low alpha (µV)	-0.51 (3.71)	0.70 (3.06)	0.1226	0.1712
Baseline high alpha (µV)	0.10 (1.71)	1.03 (1.63)	0.0372	0.0298

A statistically significant difference in baseline high alpha power (p=0.0298) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free. High alpha power was found to be higher in ADHD children while they were stimulant-free (0.10 ± 1.71 µV *vs.* 1.03 ± 1.63 µV). No statistically significant differences in baseline thalpha and low alpha power were found.

3.5.2 Alpha power during focussed attention

EEG alpha power was determined by BioGraph Infiniti Biofeedback apparatus, both at baseline and during focussed attention. To assess EEG functioning during focussed attention in unmedicated children with ADHD as compared to normal children, alpha power during focussed attention obtained while the ADHD children were stimulant-free was compared to alpha power during focussed attention obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to assess EEG functioning during

focussed attention in medicated children with ADHD as compared to normal children, alpha power during focussed attention obtained while the ADHD children were on stimulant medication was compared to alpha power during focussed attention obtained for the control subjects by means of two statistical tests, the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. To determine the effect of stimulant medication on the EEG functioning of children with ADHD, alpha power during focussed attention obtained while the ADHD children were on stimulant medication was compared to alpha power during focussed attention obtained while they were stimulant-free by means of two statistical tests, the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.5.2.1 Alpha power during focussed attention for stimulant-free ADHD children versus controls

EEG alpha power during focussed attention obtained while the ADHD children were stimulant-free was compared to EEG alpha power during focussed attention obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-70.

Table 3-70: Comparison of alpha power during focussed attention between stimulant-free ADHD children and controls

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha during focussed attention (µV)	-4.75 (16.95)	-4.94 (14.15)	0.9707	0.8673
Low alpha during focussed attention (µV)	-3.57 (17.85)	0.67 (5.05)	0.3311	0.3159
High alpha during focussed attention (µV)	-1.04 (1.74)	-4.82 (11.88)	0.1988	0.1913

No statistically significant differences in alpha power during focussed attention were found between stimulant-free ADHD children and control subjects.

3.5.2.2 Alpha power during focussed attention for ADHD children on stimulant medication versus controls

EEG alpha power during focussed attention obtained while the ADHD children were on stimulant medication was compared to EEG alpha power during focussed attention obtained for the control subjects, using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. Results are presented in Table 3-71.

Table 3-71: **Comparison of alpha power during focussed attention between ADHD children on stimulant medication and controls**

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha during focussed attention (µV)	0.37 (3.95)	-4.94 (14.15)	0.1400	0.3462
Low alpha during focussed attention (µV)	-0.96 (2.18)	0.67 (5.05)	0.2196	0.0418
High alpha during focussed attention (µV)	-0.09 (1.38)	-4.82 (11.88)	0.1115	0.0164

Statistically significant differences in low alpha power (p=0.0418) and high alpha power (p=0.0164) during focussed attention were found between ADHD children on stimulant medication and control subjects, with low alpha power during focussed attention found to be lower (-0.96 ± 2.18 µV *vs.* 0.67 ± 5.05 µV) and high alpha power during focussed attention found to be higher (-0.09 ± 1.38 µV *vs.* -4.82 ± 11.88 µV) in ADHD children on stimulant medication. No statistically significant differences in thalpha power were found between ADHD children on stimulant medication and controls.

3.5.2.3 Alpha power during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

EEG alpha power during focussed attention obtained while the ADHD children were on stimulant medication was compared to the EEG alpha power during focussed attention obtained while they were stimulant-free using the paired t-test and Wilcoxon signed-rank test. Results are presented in Table 3-72.

Table 3-72: Comparison of alpha power during focussed attention between ADHD children on stimulant medication and stimulant-free ADHD children

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha during focussed attention (µV)	0.37 (3.95)	-4.75 (16.95)	0.1977	0.2432
Low alpha during focussed attention (µV)	-0.96 (2.18)	-3.57 (17.85)	0.5126	0.2772
High alpha during focussed attention (µV)	-0.09 (1.38)	-1.04 (1.74)	0.0467	0.0486

A statistically significant difference in high alpha power during focussed attention (p=0.0486) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, with high alpha power during focussed attention found to be higher in ADHD children on stimulant medication (-0.09 ± 1.38 µV *vs.* -1.04 ± 1.74 µV). No statistically significant differences in thalpha power and low alpha power were found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free.

3.5.3 Effect of focussed attention on alpha power

EEG alpha power was determined by BioGraph Infiniti Biofeedback apparatus, both at baseline and during focussed attention. To determine the effect of focussed attention on alpha power, alpha power values obtained at baseline were compared to alpha power

values obtained during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication using the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis (H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.5.3.1 Effect of focussed attention on alpha power in controls

As previously mentioned, alpha power values at baseline and during focussed attention in controls were compared using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-73.

Table 3-73: Comparison of alpha power between baseline and focussed attention in controls

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha (µV)	2.91 (11.72)	-4.94 (14.15)	0.0803	0.1221
Low alpha (µV)	2.79 (11.63)	0.67 (5.05)	0.4509	0.9133
High alpha (µV)	1.24 (2.76)	-4.82 (11.88)	0.0547	0.0016

A statistically significant difference between baseline and focussed attention was found for high alpha values (p=0.0016), while a marginally statistically significant difference between baseline and focussed attention was found for thalpha values (p=0.0803). Both

high alpha (1.24 ± 2.76 µV *vs.* -4.82 ± 11.88 µV) and thalpha (2.91 ± 11.72 µV *vs.* -4.94 ± 14.15 µV) decreased from baseline to focussed attention. No statistically significant difference in low alpha values between baseline and focussed attention was found.

3.5.3.2 Effect of focussed attention on alpha power in stimulant-free ADHD children

As previously mentioned, alpha power values at baseline and during focussed attention in stimulant-free ADHD children were compared using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-74.

Table 3-74: Comparison of alpha power between baseline and focussed attention in stimulant-free ADHD children

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha (µV)	0.83 (4.85)	-4.75 (16.95)	0.1565	0.1365
Low alpha (µV)	0.70 (3.06)	-3.57 (17.85)	0.3408	0.4209
High alpha (µV)	1.03 (1.63)	-1.04 (1.74)	0.0008	0.0022

A statistically significant difference in high alpha (p=0.0022) between baseline and focussed attention was found, with high alpha decreasing from baseline (1.03 ± 1.63 µV) to focussed attention (-1.04 ± 1.74 µV). No statistically significant differences between baseline and focussed attention were found for thalpha and low alpha.

3.5.3.3 Effect of focussed attention on alpha power in ADHD children on stimulant medication

As previously mentioned, alpha power values at baseline and during focussed attention in ADHD children on stimulant medication were compared using the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-75.

Table 3-75: Comparison of alpha power between baseline and focussed attention in ADHD children on stimulant medication

Indicator (unit)	Baseline	Focussed attention	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha (µV)	-0.41 (4.40)	0.37 (3.95)	0.5826	0.6874
Low alpha (µV)	-0.51 (3.71)	-0.96 (2.18)	0.6976	0.7782
High alpha (µV)	0.10 (1.71)	-0.09 (1.38)	0.7100	0.7323

No statistically significant differences between baseline and focussed attention were found for thalpha, low alpha and high alpha while the ADHD children were on stimulant medication.

3.5.4 Comparison of delta values of alpha power

Alpha power was measured for all children both at baseline and during focussed attention. Delta values (Δ = focussed attention - baseline) were calculated by determining the difference between baseline values and values during focussed attention. Delta value means and standard deviations for alpha power in controls, stimulant-free ADHD children and ADHD children on stimulant medication are represented in Table 3-76.

Table 3-76: Means and standard deviations for alpha power in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Thalpha Δ (μV)	Low alpha Δ (μV)	High alpha Δ (μV)
	Mean (SD)	Mean (SD)	Mean (SD)
Controls	-7.85 (17.90)	-2.12 (11.64)	-6.06 (12.45)
Stimulant-free ADHD children	-5.58 (16.46)	-4.27 (19.03)	-2.08 (2.25)
ADHD children on stimulants	0.79 (6.12)	-0.45 (4.96)	-0.19 (2.23)

To determine the difference in the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention between unmedicated children with ADHD and normal children, delta values of alpha power obtained while the ADHD children were stimulant-free were compared to delta values of alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the difference in the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention between medicated children with ADHD and normal children, delta values of alpha power obtained while the ADHD children were on stimulant medication were compared to delta values of alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. In order to determine the effect of stimulant medication on the magnitude of the shift in the specific EEG frequency components from baseline to focussed attention, delta values of alpha power obtained while the ADHD children were on stimulant medication were compared to delta values of alpha power obtained while they were stimulant-free using the paired t-test and the Wilcoxon signed-rank test. In all cases the null hypothesis

(H0) was that the means of the two groups were equal. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

3.5.4.1 Delta values of alpha power for stimulant-free ADHD children versus controls

Delta values of alpha power obtained while the ADHD children were stimulant-free were compared to delta values of alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-77.

Table 3-77: **Comparison of delta values of alpha power between stimulant-free ADHD children and controls**

Indicator (unit)	Stimulant-free ADHD children	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha Δ (µV)	-5.58 (16.46)	-7.85 (17.90)	0.6918	0.9033
Low alpha Δ (µV)	-4.27 (19.03)	-2.12 (11.64)	0.6787	0.5637
High alpha Δ (µV)	-2.08 (2.25)	-6.06 (12.45)	0.1983	0.3620

No statistically significant differences between the delta values of alpha power were found between the stimulant-free ADHD children and the control subjects.

3.5.4.2 Delta values of alpha power for ADHD children on stimulant medication versus controls

Delta values of alpha power obtained while the ADHD children were on stimulant medication were compared to delta values of alpha power obtained for the control subjects using the two-sample t-test with Welch's correction for unequal variances and the Mann-Whitney test. The results obtained are presented in Table 3-78.

Table 3-78: **Comparison of delta values of alpha power between ADHD children on stimulant medication and controls**

Indicator (unit)	ADHD children on stimulants	Controls	Two-sample t-test	Mann-Whitney test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha Δ (μV)	0.79 (6.12)	-7.85 (17.90)	0.0656	0.1325
Low alpha Δ (μV)	-0.45 (4.96)	-2.12 (11.64)	0.5797	0.9636
High alpha Δ (μV)	-0.19 (2.23)	-6.06 (12.45)	0.0646	0.0127

A statistically significant difference in the delta values of high alpha (p=0.0127) and a marginally statistically significant differences in the delta values of thalpha (p=0.0656) was found between ADHD children on stimulant medication and control subjects, with mean delta values of high alpha (-0.19 ± 2.23 μV *vs.* -6.06 ± 12.45 μV) and thalpha (0.79 ± 6.12 μV *vs.* -7.85 ± 17.90 μV) found to be smaller in ADHD children on stimulant medication. No statistically significant differences in delta values of low alpha were found between ADHD children on stimulant medication and controls.

3.5.4.3 Delta values of alpha power for ADHD children on stimulant medication versus stimulant-free ADHD children

Delta values of alpha power obtained while the ADHD children were on stimulant medication were compared to delta values of alpha power obtained while they were stimulant-free using both the paired t-test and the Wilcoxon signed-rank test. The results obtained are presented in Table 3-79.

Table 3-79: **Comparison of delta values of alpha power between ADHD children on stimulant medication and stimulant-free ADHD children**

Indicator (unit)	ADHD children on stimulants	Stimulant-free ADHD children	Paired t-test	Wilcoxon test
	Mean (SD)	Mean (SD)	p-value	p-value
Thalpha Δ (μV)	0.79 (6.12)	-5.58 (16.46)	0.1218	0.0990
Low alpha Δ (μV)	-0.45 (4.96)	-4.27 (19.03)	0.3581	0.5197
High alpha Δ (μV)	-0.19 (2.23)	-2.08 (2.25)	0.0029	0.0048

A statistically significant difference in delta values of high alpha (p=0.0048) and a marginally statistically significant difference in delta values of thalpha (p=0.0990) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free. Delta values of high alpha (-0.19 ± 2.23 μV *vs.* -2.08 ± 2.25 μV) and thalpha (0.79 ± 6.12 μV *vs.* -5.58 ± 16.46 μV) were found to be larger in stimulant-free ADHD children. No statistically significant differences in delta values of low alpha were found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free.

3.6 Link between baseline theta/beta ratios and autonomic functioning

To determine whether a link existed between baseline theta/beta ratios and autonomic nervous system functioning, either at baseline or during focussed attention; baseline theta/beta ratios were compared to baseline HRV parameters, HRV parameters during focussed attention, baseline skin conductivity values, skin conductivity values during focussed attention, blood pressure values and ECG parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication. All indicators were compared using a correlation analysis. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

Furthermore, a significant correlation was interpreted as an r-value larger than 0.7.

3.6.1 Link between baseline theta/beta ratios and baseline HRV parameters

Baseline theta/beta ratios were compared to baseline HRV parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-80 for the controls, Table 3-81 for the stimulant-free ADHD children and Table 3-82 for the ADHD children on stimulant medication.

Table 3-80: Correlations between baseline theta/beta ratios and baseline HRV parameters in controls

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Controls	Mean HR (bpm)	-0.0302	0.9053
	STDRR (sec)	0.2790	0.2623
	RR triangular index	0.2166	0.3879
	STDHR (bpm)	0.5559	0.0166
	RMSSD (msec)	0.1826	0.4683
	HF (ms^2)	0.2226	0.3747
	LF (ms^2)	0.1126	0.6564
	HF (nu)	0.3339	0.1757
	LF (nu)	-0.3339	0.1757
	LF/HF	-0.3527	0.1511
	SD1 (msec)	0.1838	0.4654
	SD2 (msec)	0.3434	0.1630

No statistically significant relationships were found.

Table 3-81: Correlations between baseline theta/beta ratios and baseline HRV parameters in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Stimulant-free ADHD children	Mean HR (bpm)	-0.2078	0.3933
	STDRR (sec)	0.0513	0.8347
	RR triangular index	0.1431	0.5590
	STDHR (bpm)	-0.0356	0.8851
	RMSSD (msec)	0.2391	0.3243
	HF (ms^2)	0.1101	0.6535
	LF (ms^2)	-0.1855	0.4472
	HF (nu)	0.2374	0.3278
	LF (nu)	-0.2374	0.3278
	LF/HF	-0.1802	0.4604
	SD1 (msec)	0.2388	0.3248
	SD2 (msec)	-0.0679	0.7824

No statistically significant relationships were found.

Table 3-82: Correlations between baseline theta/beta ratios and baseline HRV parameters in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
ADHD children on stimulants	Mean HR (bpm)	-0.0964	0.6946
	STDRR (sec)	0.1440	0.5565
	RR triangular index	0.1580	0.5183
	STDHR (bpm)	0.1651	0.4993
	RMSSD (msec)	0.2178	0.3703
	HF (ms^2)	0.1472	0.5477
	LF (ms^2)	0.0973	0.6918
	HF (nu)	0.2552	0.2916
	LF (nu)	-0.2552	0.2916
	LF/HF	-0.2548	0.2924
	SD1 (msec)	0.2197	0.3662
	SD2 (msec)	-0.0656	0.7897

No statistically significant relationships were found.

3.6.2 Link between baseline theta/beta ratios and HRV parameters during focussed attention

Baseline theta/beta ratios were compared to HRV parameters during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-83 for the controls, Table 3-84 for the stimulant-free ADHD children and Table 3-85 for the ADHD children on stimulant medication.

Table 3-83: Correlations between baseline theta/beta ratios and HRV parameters during focussed attention in controls

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Controls	Mean HR (bpm)	-0.1034	0.6831
	STDRR (sec)	0.2822	0.2565
	RR triangular index	0.1204	0.6341
	STDHR (bpm)	0.4961	0.0362
	RMSSD (msec)	0.2519	0.3133
	HF (ms^2)	0.1462	0.5626
	LF (ms^2)	-0.0161	0.9496
	HF (nu)	0.3338	0.1758
	LF (nu)	-0.3338	0.1758
	LF/HF	-0.3389	0.1689
	SD1 (msec)	0.2559	0.3054
	SD2 (msec)	0.1949	0.4384

No statistically significant relationships were found.

Table 3-84: Correlations between baseline theta/beta ratios and HRV parameters during focussed attention in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Stimulant-free ADHD children	Mean HR (bpm)	-0.2398	0.3227
	STDRR (sec)	0.1551	0.5260
	RR triangular index	0.2774	0.2503
	STDHR (bpm)	0.0394	0.8729
	RMSSD (msec)	0.3672	0.1220
	HF (ms^2)	0.1153	0.6384
	LF (ms^2)	-0.1550	0.5263
	HF (nu)	0.3065	0.2019
	LF (nu)	-0.3065	0.2019
	LF/HF	-0.1570	0.5209
	SD1 (msec)	0.3666	0.1226
	SD2 (msec)	0.1557	0.5244

No statistically significant relationships were found.

Table 3-85: Correlations between baseline theta/beta ratios and HRV parameters during focussed attention in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
ADHD children on stimulants	Mean HR (bpm)	0.0600	0.8073
	STDRR (sec)	0.1004	0.6824
	RR triangular index	0.1381	0.5728
	STDHR (bpm)	0.1275	0.6031
	RMSSD (msec)	0.0735	0.7650
	HF (ms^2)	0.0946	0.7001
	LF (ms^2)	0.1210	0.6217
	HF (nu)	-0.2702	0.2632
	LF (nu)	0.2702	0.2632
	LF/HF	0.3141	0.1903
	SD1 (msec)	0.0740	0.7634
	SD2 (msec)	0.0892	0.7165

No statistically significant relationships were found.

3.6.3 Link between baseline theta/beta ratios and skin conductivity

Baseline theta/beta ratios were compared to baseline skin conductivity values and skin conductivity values during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-86.

Table 3-86: Correlations between baseline theta/beta ratios and skin conductivity in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Controls	**Baseline SC (µMhos)**	-0.0253	0.9207
	SC during focussed attention (µMhos)	-0.0870	0.7313
Stimulant-free ADHD children	**Baseline SC (µMhos)**	-0.3580	0.1324
	SC during focussed attention (µMhos)	-0.3539	0.1371
ADHD children on stimulants	**Baseline SC (µMhos)**	-0.0759	0.7574
	SC during focussed attention (µMhos)	-0.1004	0.6827

No statistically significant relationships were found.

3.6.4 Link between baseline theta/beta ratios and blood pressure

Baseline theta/beta ratios were compared to systolic and diastolic blood pressure values in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-87.

Table 3-87: Correlations between baseline theta/beta ratios and systolic and diastolic blood pressure in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/beta ratio	
		r-value	p-value
Controls	**Systolic blood pressure (mmHg)**	0.4984	0.0353
	Diastolic blood pressure (mmHg)	0.2804	0.2597
Stimulant-free ADHD children	**Systolic blood pressure (mmHg)**	-0.2967	0.2173
	Diastolic blood pressure (mmHg)	-0.1738	0.4768
ADHD children on stimulants	**Systolic blood pressure (mmHg)**	-0.1202	0.6240
	Diastolic blood pressure (mmHg)	-0.2851	0.2368

No statistically significant relationships were found.

3.6.5 Link between baseline theta/beta ratios and ECG parameters

Baseline theta/beta ratios were compared to ECG parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-88 for controls, Table 3-89 for stimulant-free ADHD children and Table 3-90 for ADHD children on stimulant medication.

Table 3-88: Correlations between baseline theta/beta ratios and ECG parameters in controls

	Indicator (unit)	Baseline theta/beta ratios	
		r-value	p-value
Controls	RR (sec)	0.0873	0.7304
	HR (bpm)	-0.1579	0.5315
	QT (msec)	-0.0790	0.7554
	JT (msec)	0.0705	0.7810
	QTc (data-derived) (msec)	-0.2650	0.2879
	JTc (data-derived) (msec)	0.0339	0.8937
	QTc (Bazett) (msec)	-0.3110	0.2091
	JTc (Bazett) (msec)	0.0106	0.9669
	QTd (msec)	0.1749	0.4877
	JTd (msec)	-0.1413	0.5760
	QTcd (msec)	0.1543	0.5410
	JTcd (msec)	-0.1551	0.5387

No statistically significant relationships were found.

Table 3-89: Correlations between baseline theta/beta ratios and ECG parameters in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/beta ratios	
		r-value	p-value
Stimulant-free ADHD children	RR (sec)	0.0967	0.6937
	HR (bpm)	-0.0655	0.7899
	QT (msec)	-0.1981	0.4163
	JT (msec)	-0.0312	0.8992
	QTc (data-derived) (msec)	-0.3541	0.1369
	JTc (data-derived) (msec)	-0.1266	0.6055
	QTc (Bazett) (msec)	-0.3260	0.1732
	JTc (Bazett) (msec)	-0.1324	0.5891
	QTd (msec)	-0.0448	0.8556
	JTd (msec)	-0.2940	0.2217
	QTcd (msec)	-0.0361	0.8835
	JTcd (msec)	-0.2573	0.2876

No statistically significant relationships were found.

Table 3-90: Correlations between baseline theta/beta ratios and ECG parameters in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/beta ratios	
		r-value	p-value
ADHD children on stimulants	RR (sec)	0.0403	0.8700
	HR (bpm)	-0.0140	0.9546
	QT (msec)	-0.1490	0.5426
	JT (msec)	-0.0589	0.8107
	QTc (data-derived) (msec)	-0.2588	0.2847
	JTc (data-derived) (msec)	-0.1291	0.5983
	QTc (Bazett) (msec)	-0.2503	0.3013
	JTc (Bazett) (msec)	-0.1304	0.5948
	QTd (msec)	-0.2621	0.2784
	JTd (msec)	-0.1990	0.4140
	QTcd (msec)	-0.2739	0.2565
	JTcd (msec)	-0.2060	0.3975

No statistically significant relationships were found.

3.7 Link between baseline theta/SMR ratios and autonomic functioning

To determine whether a link existed between baseline theta/SMR ratios and autonomic nervous system functioning, either at baseline or during focussed attention; baseline theta/SMR ratios were compared to baseline HRV parameters, HRV parameters during focussed attention, baseline skin conductivity values, skin conductivity values during focussed attention, blood pressure values and ECG parameters in controls, stimulant-free

ADHD children and ADHD children on stimulant medication. All indicators were compared using a correlation analysis. The significance of the difference between the means (p-values) was calculated, and interpreted as follows:

- $0 \leq p < 0.05$ Statistically significant difference
- $0.05 \leq p < 0.1$ Marginally statistically significant difference
- $0.1 \leq p < 1.0$ No statistically significant difference

Furthermore, a significant correlation was interpreted as an r-value larger than 0.7.

3.7.1 Link between baseline theta/SMR ratios and baseline HRV parameters

Baseline theta/SMR ratios were compared to baseline HRV parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-91 for the controls, Table 3-92 for the stimulant-free ADHD children and Table 3-93 for the ADHD children on stimulant medication.

Table 3-91: Correlations between baseline theta/SMR ratios and baseline HRV parameters in controls

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Controls	Mean HR (bpm)	0.1473	0.5597
	STDRR (sec)	-0.1537	0.5425
	RR triangular index	-0.1840	0.4649
	STDHR (bpm)	0.0049	0.9847
	RMSSD (msec)	-0.1872	0.4570
	HF (ms^2)	-0.1911	0.4475
	LF (ms^2)	-0.2204	0.3794
	HF (nu)	0.2030	0.4193
	LF (nu)	-0.2030	0.4193
	LF/HF	-0.2693	0.2799
	SD1 (msec)	-0.1868	0.4579
	SD2 (msec)	-0.0820	0.7464

No statistically significant relationships were found.

Table 3-92: Correlations between baseline theta/SMR ratios and baseline HRV parameters in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Stimulant-free ADHD children	Mean HR (bpm)	0.0351	0.8866
	STDRR (sec)	-0.1921	0.4307
	RR triangular index	-0.1528	0.5323
	STDHR (bpm)	-0.2230	0.3587
	RMSSD (msec)	-0.1572	0.5203
	HF (ms^2)	-0.1184	0.6293
	LF (ms^2)	-0.2010	0.4093
	HF (nu)	-0.0551	0.8229
	LF (nu)	0.0551	0.8229
	LF/HF	-0.0367	0.8814
	SD1 (msec)	-0.1572	0.5204
	SD2 (msec)	-0.1952	0.4233

No statistically significant relationships were found.

Table 3-93: Correlations between baseline theta/SMR ratios and baseline HRV parameters in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
ADHD children on stimulants	Mean HR (bpm)	-0.3205	0.1810
	STDRR (sec)	0.5054	0.0273
	RR triangular index	0.2487	0.3045
	STDHR (bpm)	0.3750	0.1137
	RMSSD (msec)	0.4561	0.0497
	HF (ms^2)	0.5458	0.0156
	LF (ms^2)	0.4085	0.0825
	HF (nu)	0.1410	0.5648
	LF (nu)	-0.1410	0.5648
	LF/HF	-0.1675	0.4930
	SD1 (msec)	0.4569	0.0492
	SD2 (msec)	0.4647	0.0450

No statistically significant relationships were found.

3.7.2 Link between baseline theta/SMR ratios and HRV parameters during focussed attention

Baseline theta/SMR ratios were compared to HRV parameters during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-94 for the controls, Table 3-95 for the stimulant-free ADHD children and Table 3-96 for the ADHD children on stimulant medication.

Table 3-94: Correlations between baseline theta/SMR ratios and HRV parameters during focussed attention in controls

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Controls	Mean HR (bpm)	0.1014	0.6889
	STDRR (sec)	-0.1093	0.6660
	RR triangular index	-0.2105	0.4018
	STDHR (bpm)	0.1248	0.6217
	RMSSD (msec)	-0.1157	0.6475
	HF (ms^2)	-0.2051	0.4142
	LF (ms^2)	-0.2560	0.3051
	HF (nu)	0.0311	0.9026
	LF (nu)	-0.0311	0.9026
	LF/HF	-0.1644	0.5144
	SD1 (msec)	-0.1112	0.6604
	SD2 (msec)	-0.1473	0.5597

No statistically significant relationships were found.

Table 3-95: Correlations between baseline theta/SMR ratios and HRV parameters during focussed attention in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Stimulant-free ADHD children	Mean HR (bpm)	0.0608	0.8049
	STDRR (sec)	-0.2869	0.2336
	RR triangular index	-0.2341	0.3348
	STDHR (bpm)	-0.3290	0.1690
	RMSSD (msec)	-0.2390	0.3245
	HF (ms^2)	-0.2944	0.2212
	LF (ms^2)	-0.3619	0.1279
	HF (nu)	0.0085	0.9723
	LF (nu)	-0.0085	0.9723
	LF/HF	0.0615	0.8027
	SD1 (msec)	-0.2392	0.3239
	SD2 (msec)	-0.2714	0.2610

No statistically significant relationships were found.

Table 3-96: Correlations between baseline theta/SMR ratios and HRV parameters during focussed attention in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
ADHD children on stimulants	Mean HR (bpm)	-0.4182	0.0747
	STDRR (sec)	0.5153	0.0239
	RR triangular index	0.4661	0.0443
	STDHR (bpm)	0.4367	0.0615
	RMSSD (msec)	0.5008	0.0290
	HF (ms^2)	0.5474	0.0153
	LF (ms^2)	0.4520	0.0520
	HF (nu)	-0.0181	0.9415
	LF (nu)	0.0181	0.9415
	LF/HF	0.0676	0.7833
	SD1 (msec)	0.5008	0.0290
	SD2 (msec)	0.5189	0.0228

No statistically significant relationships were found.

3.7.3 Link between baseline theta/SMR ratios and skin conductivity

Baseline theta/SMR ratios were compared to baseline skin conductivity values and skin conductivity values during focussed attention in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-97.

Table 3-97: **Correlations between baseline theta/SMR ratios and skin conductivity in controls, stimulant-free ADHD children and ADHD children on stimulant medication**

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Controls	**Baseline SC (µMhos)**	-0.1964	0.4346
	SC during focussed attention (µMhos)	-0.1485	0.5564
Stimulant-free ADHD children	**Baseline SC (µMhos)**	0.0551	0.8227
	SC during focussed attention (µMhos)	-0.0203	0.9343
ADHD children on stimulants	**Baseline SC (µMhos)**	-0.2339	0.3351
	SC during focussed attention (µMhos)	-0.1773	0.4676

No statistically significant relationships were found.

3.7.4 Link between baseline theta/SMR ratios and blood pressure

Baseline theta/SMR ratios were compared to systolic and diastolic blood pressure values in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-98.

Table 3-98: Correlations between baseline theta/SMR ratios and systolic and diastolic blood pressure in controls, stimulant-free ADHD children and ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/SMR ratio	
		r-value	p-value
Controls	**Systolic blood pressure (mmHg)**	0.3689	0.1320
	Diastolic blood pressure (mmHg)	0.4412	0.0668
Stimulant-free ADHD children	**Systolic blood pressure (mmHg)**	-0.1268	0.6048
	Diastolic blood pressure (mmHg)	-0.1647	0.5004
ADHD children on stimulants	**Systolic blood pressure (mmHg)**	-0.0043	0.9860
	Diastolic blood pressure (mmHg)	-0.2532	0.2955

No statistically significant relationships were found.

3.7.5 Link between baseline theta/SMR ratios and ECG parameters

Baseline theta/SMR ratios were compared to ECG parameters in controls, stimulant-free ADHD children and ADHD children on stimulant medication, to determine whether a link existed between them. The results obtained are presented in Table 3-99 for controls, Table 3-100 for stimulant-free ADHD children and Table 3-101 for ADHD children on stimulant medication.

Table 3-99: Correlations between baseline theta/SMR ratios and ECG parameters in controls

	Indicator (unit)	Baseline theta/SMR ratios	
		r-value	p-value
Controls	RR (sec)	-0.2012	0.4234
	HR (bpm)	0.1642	0.5151
	QT (msec)	-0.4059	0.0946
	JT (msec)	-0.1596	0.5269
	QTc (data-derived) (msec)	-0.4800	0.0438
	JTc (data-derived) (msec)	-0.0774	0.7601
	QTc (Bazett) (msec)	-0.4111	0.0901
	JTc (Bazett) (msec)	-0.0329	0.8970
	QTd (msec)	-0.0161	0.9495
	JTd (msec)	-0.4854	0.0411
	QTcd (msec)	-0.0254	0.9204
	JTcd (msec)	-0.4671	0.0507

No statistically significant relationships were found.

Table 3-100: Correlations between baseline theta/SMR ratios and ECG parameters in stimulant-free ADHD children

	Indicator (unit)	Baseline theta/SMR ratios	
		r-value	p-value
Stimulant-free ADHD children	RR (sec)	0.1030	0.6748
	HR (bpm)	-0.1052	0.6683
	QT (msec)	0.2252	0.3540
	JT (msec)	0.3128	0.1923
	QTc (data-derived) (msec)	0.1504	0.5387
	JTc (data-derived) (msec)	0.1878	0.4413
	QTc (Bazett) (msec)	0.1009	0.6811
	JTc (Bazett) (msec)	0.1427	0.5600
	QTd (msec)	-0.2702	0.2632
	JTd (msec)	0.0683	0.7812
	QTcd (msec)	-0.2656	0.2718
	JTcd (msec)	0.0558	0.8206

No statistically significant relationships were found.

Table 3-101: Correlations between baseline theta/SMR ratios and ECG parameters in ADHD children on stimulant medication

	Indicator (unit)	Baseline theta/SMR ratios	
		r-value	p-value
ADHD children on stimulants	RR (sec)	0.3545	0.1364
	HR (bpm)	-0.2118	0.3841
	QT (msec)	0.3397	0.1547
	JT (msec)	0.2015	0.4081
	QTc (data-derived) (msec)	0.0506	0.8371
	JTc (data-derived) (msec)	-0.1554	0.5253
	QTc (Bazett) (msec)	-0.0741	0.7631
	JTc (Bazett) (msec)	-0.2532	0.2956
	QTd (msec)	-0.2792	0.2470
	JTd (msec)	-0.1904	0.4349
	QTcd (msec)	-0.3195	0.1824
	JTcd (msec)	-0.2173	0.3715

No statistically significant relationships were found.

3.8 References

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Chapter 4

Discussion

Indications are that sympathetic under-arousal exists in children with ADHD (1,2,3,4). Published results are, however, controversial. Most studies use only one measure as an index of sympathetic nervous system activity, very few studies measure sympathetic nervous system functioning while participants are both on stimulants and stimulant-free, and the majority of research is conducted without examining the relationship between autonomic nervous system functioning and focussed attention. The latter is a major oversight as the inability to focus attention represents one of the major problems of ADHD. In addition, very little is known about parasympathetic nervous system functioning in ADHD. While Crowell *et al* (1) found that children with ADHD do not differ from controls with regards to parasympathetic nervous system activity, results from the study by Shibagaki and Furuya (5) suggested that children with ADHD display a level of parasympathetic under-arousal. It is, however, not merely enough to look at sympathetic functioning, parasympathetic functioning or even both. As the effects of the autonomic nervous system are, in many organs, dependent on the sympathovagal balance, it is evident that assessing this balance as well as shifts in this balance would be of interest.

Due to indications of sympathetic under-arousal in ADHD, patients with the disorder are treated with noradrenergic stimulants such as Ritalin (methylphenidate). These medications all have stimulatory effects on the sympathetic nervous system and therefore all have the potential to influence cardiac function. Controversy about the cardiovascular

risks of these stimulants exists, with recent increases in FDA warnings causing increased concern (6). However, the prescription of stimulant medication to children with ADHD occurs without any prior physiological testing such as an electrocardiogram.

In this study the main questions addressed were firstly a) whether the functioning of the autonomic nervous system of children with ADHD differs from that of normal children and whether the autonomic nervous system response during focussed attention is different from that of normal children, and b) whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic nervous system functioning in children with ADHD. Secondly, in view of the fact that the medication prescribed is a noradrenergic stimulant, the question was asked whether it has a significant effect on the heart. Lastly, due to the inattention and hyperactivity experienced by children with ADHD, the question was asked whether children with ADHD and normal children can be distinguished on the basis of EEG values and, furthermore, whether methylphenidate has any effect on the EEGs of children with ADHD.

Regarding the children with ADHD, each child was tested while they were stimulant-free and during a period in which they were on stimulant medication. Therefore, each child served as their own control in order to assess the effects of stimulant medication. The stimulant used in this study was long-acting Ritalin (methylphenidate). Eighteen of the children with ADHD were on a long-acting 10 mg Ritalin tablet, while one was on a long-acting 20 mg Ritalin tablet. Since the half-life of long-acting Ritalin in children has

been shown to be 2.5 hours, with a range of 1.5 to 5 hours (7), the wash-out period of three weeks used in this study was considered more than sufficient.

The study protocol was submitted to and approved by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, clearance number S30/2007. The protocol was, furthermore, submitted to and approved by the Department of Health, DOH trial number DOH-27-0808-1816.

The results obtained in this study will be discussed in the following order:

- Comparison of the physical characteristics of children with ADHD and age- and gender-matched controls
- Comparison of baseline autonomic nervous system functioning, as derived from analyses of heart rate variability and skin conductivity, between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls
    - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of autonomic nervous system functioning during focussed attention, as derived from analyses of heart rate variability and skin conductivity, between:
    - Stimulant-free ADHD children and controls
    - ADHD children on stimulant medication and controls

- ADHD children on stimulant medication and stimulant-free ADHD children

- Assessment of the effect of focussed attention on the autonomic nervous system, as derived by analyses of heart rate variability and skin conductivity, in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of blood pressure and ECG values between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls
  - ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of QTc, JTc, QTd and JTd prolongation in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of baseline theta/beta and theta/SMR ratios between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls
  - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of theta/beta and theta/SMR ratios during focussed attention between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls

- ADHD children on stimulant medication and stimulant-free ADHD children

- Assessment of the effect of focussed attention on theta/beta and theta/SMR ratios in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Comparison of theta/beta and theta/SMR ratio delta values of focussed attention minus baseline between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls
  - ADHD children on stimulant medication and stimulant-free ADHD children
- Comparison of baseline alpha values between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls
- Comparison of alpha values during focussed attention between:
  - Stimulant-free ADHD children and controls
  - ADHD children on stimulant medication and controls
  - ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of the effect of focussed attention on alpha values in controls, stimulant-free ADHD children and ADHD children on stimulant medication

- Comparison of alpha power delta values of focussed attention minus baseline between:
    - ❖ Stimulant-free ADHD children and controls
    - ❖ ADHD children on stimulant medication and controls
    - ❖ ADHD children on stimulant medication and stimulant-free ADHD children
- Assessment of a possible link between baseline theta/beta ratios and autonomic nervous system functioning, either at baseline or during focussed attention, in controls, stimulant-free ADHD children and ADHD children on stimulant medication
- Assessment of a possible link between baseline theta/SMR ratios and autonomic nervous system functioning, either at baseline or during focussed attention, in controls, stimulant-free ADHD children and ADHD children on stimulant medication

4.1 Physical characteristics

Studies have shown that stimulant usage is associated with inhibitory effects on both height and weight growth (8,9,10), with the largest effect occurring during the first six months of stimulant treatment (11,12). Although some studies have indicated that stimulant treatment does not adversely affect growth (13,14), an extensive analysis of available literature by Dr A Poulton (11) argues that there is clear evidence of an

association between stimulant treatment and attenuated growth in good quality studies, while those with poorer quality methodology fail to uncover the association.

In this study, where the children with ADHD were on long-acting Ritalin at dosages of 10 mg (eighteen children) and 20 mg (one child) for a mean period of 17.89 months, no statistically significant differences in the means and standard deviations of height (1.41 ± 0.13 m *vs.* 1.41 ± 0.09 m), weight (37.07 ± 10.18 kg *vs.* 37.37 ± 11.48 kg) or waist-to-hip ratios (0.88 ± 0.06 *vs.* 0.89 ± 0.07) were found between children with ADHD and controls. This indicates that, in this study, ADHD children were not found to differ from normal children with regards to height, weight and waist-to-hip ratios. In fact, with regards to physical size, the control group can be considered well-matched to the experimental group. Since the ADHD children were on Ritalin for a mean period of 17.89 months, we should have been able to pick up at least a moderate suppressive effect on height and weight growth. This study can, therefore, not support the results from Swanson *et al* (8), the Multimodal Treatment Study of ADHD cooperative group (10) and Swanson *et al* (9), which suggest that stimulant usage is associated with an inhibitory effect on both height and weight growth; but is in agreement with the findings of Spencer *et al* (13) and Bereket *et al* (14), which indicate that stimulant usage does not adversely affect growth. However, to come to any absolute conclusion on the effect of stimulant usage on growth in children with ADHD will require a longitudinal study.

4.2 Autonomic nervous system functioning

4.2.1 Baseline autonomic nervous system functioning

Few studies have assessed the baseline autonomic nervous system functioning in subjects with ADHD. Moreover, methods used to assess autonomic nervous system functioning in these studies differ, and results are sometimes contradictory. Crowell *et al* (1) found a sympathetic under-arousal in preschool stimulant-free children with ADHD, as assessed by means of electrodermal responses and cardiac pre-ejection periods. However, the children in their study did not differ from age-matched controls with regards to parasympathetic nervous system activity, as assessed by means of respiratory sinus arrhythmia (1). Beauchaine *et al* (2) similarly found sympathetic under-activity in stimulant-free children with ADHD, as assessed by means of electrodermal responses. The part of their study that assessed parasympathetic nervous system functioning is not applicable since it included children with conduct disorder. Shibagaki and Furuya (5), however, found an under-activity of the parasympathetic nervous system, as assessed by means of respiratory sinus arrhythmia, when comparing children with ADHD to controls.

Regarding the effect of stimulant treatment on baseline autonomic nervous system activity, studies have indicated that stimulant medication results in an increase in heart rate (15,16,17,18,19,20,21), increase in skin conductivity (19,20,22) and a possible decrease in heart rate variability (23,24), when compared to placebo. In contrast, Spring *et al* (25) found no differences in skin conductivity pre- and post-medication administration.

In the present study, two methods were used to assess autonomic nervous system functioning at baseline and during focussed attention, namely heart rate variability analyses and skin conductivity.

4.2.1.1 Baseline heart rate variability parameters

Tachograms were analysed by means of time-domain, frequency-domain and Poincaré analyses. The time-domain indicators used in this study included mean heart rate, which is an indicator of sympathovagal balance; STDRR, which is an indication of global heart rate variability (26); HRV triangular index, which is also an indication of global heart rate variability (26); STDHR, which is a measure of the long-term components of heart rate variability (26); and RMSSD, which is an indicator of parasympathetic nervous system activity (27). The frequency-domain indicators used included the high frequency component (HF), the low frequency component (LF) and the LF/HF ratio. HF is an indication of parasympathetic nervous system activity (28,29,30,31), while the autonomic contributions to the LF component are still being investigated and no consensus currently exists. The LF component is said to provide information on sympathetic activity but with notable influences from the parasympathetic nervous system, baroreceptor feedback and brainstem rhythms (32). However, some believe that in most instances, with the exception of conditions such as heart failure and strenuous exercise, the LF component is indeed an indicator of predominantly sympathetic activity (33,34). Furthermore, the LF component is considered by some a definite marker of sympathetic activity when expressed in normalized units (26,35). Therefore, in this study both HF and LF were measured in absolute power (ms^2) and normalized units (nu). The LF/HF ratio was

investigated as a measure of sympathovagal balance (28,29,30,31,32,33), whereby an increase in the LF/HF ratio indicates a predominance of sympathetic activity and a decrease in the LF/HF ratio indicates parasympathetic predominance (27). The Poincaré plot indicators used included SD1, which is an indicator of short term variability in heart rate, representing parasympathetic nervous system activity on the sinus node (36); and SD2, which reflects global heart rate variability as an inverse function of sympathetic modulation (32). In other words, SD2 is believed to be an inverse measure of sympathetic activity (32), whereby an increase in SD2 represents an increase in global heart rate variability which, in turn, reflects a decrease in sympathetic activity. Therefore, an increase in SD2 represents a decrease in sympathetic nervous system activity and *vice versa*.

4.2.1.1.1 Baseline HRV parameters for stimulant-free ADHD children versus controls

In the present study, statistically significant differences in baseline HRV parameters between stimulant-free ADHD children and controls were found for HR (p=0.0245), STDRR (p=0.0082), RR triangular index (p=0.0020), STDHR (p=0.0193), RMSSD (p=0.0157), LF (p=0.0193), SD1 (p=0.0157) and SD2 (p=0.0057). A marginally statistically significant difference was found for HF (p=0.0596). HR was significantly lower (87.67 ± 7.75 bpm *vs.* 93.77 ± 9.90 bpm), while STDRR (0.052 ± 0.020 sec *vs.* 0.036 ± 0.021 sec), RR triangular index (0.10 ± 0.031 *vs.* 0.070 ± 0.035), STDHR (6.75 ± 2.06 bpm *vs.* 5.26 ± 2.05 bpm), RMSSD (52.51 ± 21.95 msec *vs.* 35.99 ± 26.38 msec), HF (659.16 ± 505.75 ms^2 *vs.* 435.67 ± 595.03 ms^2), LF (667.00 ± 755.66 ms^2 *vs.* 372.39 ±

541.41 ms^2), SD1 (37.36 ± 15.59 msec *vs.* 25.63 ± 18.77 msec) and SD2 (76.28 ± 26.86 msec *vs.* 53.43 ± 27.95 msec) were significantly higher in the stimulant-free ADHD children. The lower HR in the stimulant-free ADHD children indicates that these children demonstrate a parasympathetic dominance of the sympathovagal balance when compared to controls. The higher RMSSD, SD1 and HF in the stimulant-free ADHD children suggest that these children exhibit a higher parasympathetic tone than controls, supporting the finding of a lower HR in these children. Normalised LF units did not show a difference in sympathetic activity between stimulant-free ADHD children and controls. However, the higher SD2 in the stimulant-free ADHD children indicates that these children display a lower level of sympathetic nervous system activity than controls. The higher values for STDRR, RR triangular index, STDHR and SD2 indicate a higher overall heart rate variability in the stimulant-free ADHD children. Therefore, at baseline the stimulant-free ADHD children displayed an over-activity of the parasympathetic nervous system, an under-activity of the sympathetic nervous system, and a higher level of overall heart rate variability, when compared to controls. Since it is known that a shift in the sympathovagal balance towards the parasympathetic nervous system leads to an increase in heart rate variability (37), the higher level of overall heart rate variability found in the stimulant-free ADHD children can be accounted for by their parasympathetic over-arousal as well as their sympathetic under-arousal. These results can, therefore, not support the parasympathetic nervous system findings from Crowell *et al* (1), which indicate that stimulant-free children with ADHD do not differ from age-matched controls with regard to parasympathetic nervous system activity; or the results from Shibagaki and Furuya (5), which suggest that children with ADHD display an

under-activity of the parasympathetic nervous system when compared to controls. However, these results support the sympathetic nervous system findings of Crowell *et al* (1), which found sympathetic under-arousal in stimulant-free ADHD children, as assessed by electrodermal responses and cardiac pre-ejection periods; and that of Beauchaine *et al* (2), which similarly found sympathetic under-arousal in stimulant-free children with ADHD, as assessed by means of electrodermal responses.

4.2.1.1.2 Baseline HRV parameters for ADHD children on stimulant medication versus controls

A statistically significant difference in baseline HRV parameters between ADHD children on stimulant medication and controls was found for SD2 (p=0.0388). A marginally statistically significant difference was found for STDHR (p=0.0833). Both SD2 (68.83 ± 28.22 msec *vs.* 53.43 ± 27.95 msec) and STDHR (6.29 ± 2.09 bpm *vs.* 5.26 ± 2.05 bpm) were found to be significantly higher in the ADHD children on stimulant medication. The higher SD2 in the ADHD children on stimulant medication suggests that these children still display an under-activity of the sympathetic nervous system when compared to controls. The higher STDHR and higher SD2 indicate that the ADHD children on stimulant medication demonstrated a higher level of overall heart rate variability when compared to controls. Since it is known that a shift in the sympathovagal balance towards the parasympathetic nervous system causes an increase in heart rate variability, the increased HRV in ADHD children on stimulant medication can be explained by the sympathetic under-activity found in these children.

4.2.1.1.3 Baseline HRV parameters for ADHD children on stimulant medication versus stimulant-free ADHD children

When comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, statistically significant differences in baseline HRV parameters were found for mean HR (p=0.0033), STDRR (p=0.0421) and RR triangular index (p=0.0033), while a marginally statistically significant difference was found for LF (p=0.0766). Mean HR was higher in ADHD children while they were on stimulant medication (95.41 ± 11.03 bpm *vs.* 87.67 ± 7.75 bpm), while STDRR (0.044 ± 0.021 sec *vs.* 0.052 ± 0.020 sec), RR triangular index (0.074 ± 0.035 *vs.* 0.100 ± 0.031) and LF (541.47 ± 689.72 ms^2 *vs.* 667.00 ± 755.66 ms^2) were higher in ADHD children while they were stimulant-free. The higher HR found in ADHD children on stimulant medication indicates that these children exhibit a sympathetic dominance of the sympathovagal balance when compared to stimulant-free ADHD children. These results are in agreement with the findings of Spencer *et al* (15), Biederman *et al* (16), Biederman *et al* (17), Wernicke *et al* (18), Zahn *et al* (19), Ballard *et al* (21) and Zahn *et al* (20), which indicated that stimulant usage is associated with an increase in heart rate. The lower values for STDRR and RR triangular index indicate a lower level of overall heart rate variability in ADHD children on stimulant medication. These results are in agreement with the findings of Porges *et al* (23) and DuPaul *et al* (24), which suggest that stimulant usage is associated with a decrease in heart rate variability. LF values were not supported by a significantly lower LF in normalised units and no conclusion could thus be derived from LF values. In summary, the use of methylphenidate results in a shift in the sympathovagal balance towards the sympathetic

nervous system and a decrease in heart rate variability at baseline. The decrease in heart rate variability caused by methylphenidate is of great significance since a decreased heart rate variability is believed to be a marker of both physiological and psychological distress (38).

4.2.1.2 Baseline skin conductivity

Skin conductivity is the measurement of the electrical conductance of the skin as a result of eccrine sweat gland activity (39). Since the eccrine sweat glands are innervated by the sympathetic nervous system exclusively, with no parasympathetic input, skin conductivity is believed to be an indicator of sympathetic nervous system activity (2).

4.2.1.2.1 Baseline skin conductivity for stimulant-free ADHD children versus controls

A marginally statistically significant difference in baseline skin conductivity (p=0.0754) was found between stimulant-free ADHD children and controls, with skin conductivity found to be lower in stimulant-free ADHD children (1.35 ± 0.83 µMhos *vs.* 1.96 ± 1.00 µMhos). This indicates that the stimulant-free ADHD children demonstrated a lower level of sympathetic tone than controls, suggesting a level of sympathetic under-arousal in children with ADHD. These results support the HRV findings which suggested that stimulant-free ADHD children display sympathetic under-activity at baseline, relative to controls. Furthermore, these results support the previous findings of Crowell *et al* (1) and that of Beauchaine *et al* (2), which found sympathetic under-arousal in stimulant-free

children with ADHD, as assessed by electrodermal responses and cardiac pre-ejection periods.

4.2.1.2.2 Baseline skin conductivity for ADHD children on stimulant medication versus controls

No statistically significant difference in baseline skin conductivity between ADHD children on stimulant medication and controls was found. These results suggest that, while taking stimulant medication, ADHD children demonstrate a baseline sympathetic tone similar to that demonstrated by normal children. However, since the HRV analysis revealed that ADHD children on stimulant medication display a baseline sympathetic under-activity relative to controls, it can be assumed that methylphenidate usage shifts the autonomic balance of children with ADHD towards normal levels; however, a normal autonomic balance is not reached.

4.2.1.2.3 Baseline skin conductivity for ADHD children on stimulant medication versus stimulant-free ADHD children

A statistically significant difference in baseline skin conductivity ($p=0.0055$) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free. These results indicate that baseline skin conductivity is higher in ADHD children while they are on stimulant medication (2.21 ± 1.14 µMhos *vs.* 1.35 ± 0.83 µMhos). These results support the findings of Zahn *et al* (19), Cohen *et al* (22) and Zahn *et al* (20), which suggest that stimulant usage is associated with an increase in sympathetic tone, as assessed by skin

conductivity. Although findings by Spring *et al* (25) indicated that there are no differences in skin conductivity levels pre- and post-medication administration, the majority of findings suggest, and are confirmed by the results of the present study, that skin conductivity is increased with methylphenidate usage. These results support the HRV findings, which suggested that ADHD children on stimulant medication display a sympathetic dominance of the sympathovagal balance when compared to stimulant-free ADHD children.

4.2.1.3 Summary of baseline autonomic nervous system functioning

At baseline, stimulant-free children with ADHD demonstrate an over-activity of the parasympathetic nervous system when compared to controls. Methylphenidate usage appears to normalise this parasympathetic over-activity since ADHD children on stimulant medication display no difference in parasympathetic tone relative to controls. Stimulant-free children with ADHD, furthermore, display baseline under-activity of the sympathetic nervous system when compared to controls. Although methylphenidate usage attempts to normalise the sympathetic under-activity, the level of sympathetic arousal found in ADHD children on stimulant medication is still lower than that found in controls. Methylphenidate usage, therefore, results in a shift in the sympathovagal balance towards the sympathetic nervous system and a decrease in global heart rate variability at baseline. The observation that heart rate variability decreases with the usage of methylphenidate, but still remains higher than that of the control group, supports the assumption that the autonomic balance is only partially corrected by methylphenidate medication.

4.2.2 Autonomic nervous system functioning during focussed attention

No studies which assessed the functioning of the autonomic nervous system during focussed attention in children with ADHD could be found. However, Crowell *et al* (1) measured the autonomic nervous system of children with ADHD while they played a game used to elicit the psychological response pattern found during reward. Their results suggested that, during a reward situation, non-medicated children with ADHD exhibit an attenuation of the sympathetic nervous system, as assessed by electrodermal responses and cardiac pre-ejection periods, when compared to controls (1). Furthermore, the children with ADHD did not differ from controls with regards to parasympathetic nervous system activity during a reward situation, as assessed by means of respiratory sinus arrhythmia (1). Broyd *et al* (3) measured the sympathetic nervous system activity of non-medicated children with ADHD while they performed a GO/NOGO task, which investigates motor inhibition. Their results indicated that, during a GO/NOGO task, non-medicated children with ADHD exhibit an attenuation of the sympathetic nervous system, as assessed by skin conductivity, relative to controls (3). Interestingly, when the ADHD children were on stimulant medication, no differences in sympathetic nervous system activity between these children and controls were found during the GO/NOGO task (3). O'Connell *et al* (4) found that non-medicated children with ADHD display an attenuation of the sympathetic nervous system, as assessed by skin conductivity levels, specifically during error making.

4.2.2.1 Heart rate variability parameters during focussed attention

Heart rate variability parameters measured during focussed attention were those determined at baseline, mentioned and discussed in Chapter 4 (4.2.1.1).

4.2.2.1.1 HRV parameters during focussed attention for stimulant-free ADHD children versus controls

Statistically significant differences in HRV parameters during focussed attention between stimulant-free ADHD children and controls were found for STDRR (p=0.0082), RR triangular index (p=0.0019), STDHR (p=0.0082), RMSSD (p=0.0193), HF (p=0.0133), LF (p=0.0011), SD1 (p=0.0185) and SD2 (p=0.0047). All these values were found to be significantly higher in the stimulant-free ADHD children relative to controls: STDRR (0.047 ± 0.016 sec *vs.* 0.034 ± 0.019 sec), RR triangular index (0.092 ± 0.026 *vs.* 0.066 ± 0.032), STDHR (6.68 ± 1.84 bpm *vs.* 5.35 ± 2.74 bpm), RMSSD (45.04 ± 18.24 msec *vs.* 34.21 ± 25.39 msec), HF (512.37 ± 411.62 ms^2 *vs.* 275.17 ± 410.86 ms^2), LF (607.16 ± 539.96 ms^2 *vs.* 228.78 ± 238.17 ms^2), SD1 (32.07 ± 12.95 msec *vs.* 24.40 ± 18.13 msec) and SD2 (72.17 ± 20.38 msec *vs.* 49.86 ± 23.29 msec). The higher values for RMSSD, SD1 and HF in the stimulant-free ADHD children point towards a higher parasympathetic tone during focussed attention in these children relative to controls. Although the higher LF is, once again, inconclusive, the higher SD2 values indicate a sympathetic under-arousal during focussed attention in stimulant-free ADHD children relative to controls. The higher STDRR, RR triangular index, STDHR and SD2 indicate a higher level of overall heart rate variability during focussed attention in the stimulant-free ADHD children relative to controls. Therefore, during focussed attention, the

stimulant-free ADHD children demonstrated a higher parasympathetic tone, lower sympathetic tone and higher level of overall heart rate variability relative to controls. The higher level of overall heart rate variability can, once again, be accounted for by the higher level of parasympathetic nervous system activity and lower level of sympathetic nervous system activity found in these children. These results do not support the parasympathetic nervous system findings by Crowell *et al* (1), which indicate that during reward, ADHD children display the same level of parasympathetic nervous system activity as controls. They do, however, support the findings by Broyd *et al* (3), which indicate that stimulant-free ADHD children exhibit an attenuated sympathetic tone, as assessed by means of skin conductivity, during a GO/NOGO task; and the sympathetic nervous system findings by Crowell *et al* (1), which suggest that stimulant-free ADHD children demonstrate an under-activity of the sympathetic nervous system, as assessed by means of electrodermal responses and cardiac pre-ejection periods, during reward; as well as the findings by O'Connell *et al* (4), which indicate that ADHD children display an attenuated sympathetic tone, as assessed by means of skin conductivity, during error making.

4.2.2.1.2 HRV parameters during focussed attention for ADHD children on stimulant medication versus controls

Statistically significant differences in HRV parameters during focussed attention between ADHD children on stimulant medication and controls were found for LF (p=0.0417) and SD2 (p=0.0417). Both LF (916.79 ± 1998.11 ms^2 *vs.* 228.78 ± 238.17 ms^2) and SD2 (69.78 ± 38.15 msec *vs.* 49.86 ± 23.29 msec) were significantly higher in the ADHD

children on stimulant medication. The higher LF is not supported by a significantly higher LF in normalised units and therefore remains inconclusive. The higher SD2 indicates an under-activity of the sympathetic nervous system as well as a higher level of overall heart rate variability during focussed attention in ADHD children on stimulant medication, relative to controls. The higher level of HRV during focussed attention in the ADHD children on stimulant medication can be explained by the sympathetic under-arousal exhibited by these children relative to controls.

4.2.2.1.3 HRV parameters during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

When comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, statistically significant differences in HRV parameters during focussed attention were found for mean HR ($p=0.0329$) and RR triangular index ($p=0.0176$). Mean HR was higher in ADHD children while they were on stimulant medication (96.22 ± 9.98 bpm *vs.* 90.43 ± 8.84 bpm), while RR triangular index was higher in ADHD children while they were stimulant-free (0.071 ± 0.034 *vs.* 0.092 ± 0.026). The higher HR found while the ADHD children were on stimulant medication, indicates a shift in the sympathovagal balance towards the sympathetic nervous system with the usage of stimulant medication. The lower RR triangular index found while the ADHD children were on stimulant medication, indicates a decrease in global heart rate variability with the use of stimulant medication. The decrease in HRV can, however, be accounted for by the shift in the sympathovagal balance towards the sympathetic nervous system. These results suggest

that methylphenidate usage results in an increase in sympathetic nervous system activity and a decrease in global heart rate variability during focussed attention in children with ADHD.

4.2.2.2 Skin conductivity during focussed attention

4.2.2.2.1 Skin conductivity during focussed attention for stimulant-free ADHD children versus controls

A marginally statistically significant difference in skin conductivity during focussed attention ($p=0.0556$) between stimulant-free ADHD children and controls was found, with skin conductivity during focussed attention found to be lower in stimulant-free ADHD children (1.68 ± 1.08 µMhos *vs.* 2.43 ± 1.27 µMhos). These results suggest that the stimulant-free ADHD children demonstrated a lower level of sympathetic tone during focussed attention than controls. These results support the HRV findings which suggested that stimulant-free ADHD children display an attenuation of the sympathetic nervous system during focussed attention relative to controls. These results, furthermore, support the findings by Broyd *et al* (3), which indicated that stimulant-free ADHD children exhibit an attenuated sympathetic tone, as assessed by means of skin conductivity, during a GO/NOGO task; and Crowell *et al* (1), which suggest that stimulant-free ADHD children demonstrate an under-activity of the sympathetic nervous system, as assessed by means of electrodermal responses and cardiac pre-ejection periods, during reward; as well as the findings by O'Connell *et al* (4), which indicate that ADHD children exhibit an attenuated sympathetic tone, as assessed by means of skin conductivity, during error making.

4.2.2.2.2 Skin conductivity during focussed attention for ADHD children on stimulant medication versus controls

No statistically significant difference in skin conductivity during focussed attention between ADHD children on stimulant medication and controls was found. These results support the findings by Broyd *et al* (3), which suggest that while ADHD children are on stimulant medication they exhibit no difference in sympathetic nervous system activity, as assessed by skin conductivity, during a GO/NOGO task, when compared to controls. These results suggest that, while on stimulant medication, ADHD children demonstrate a level of sympathetic tone similar to that demonstrated by controls, suggesting that methylphenidate usage normalizes the usually attenuated activity of the sympathetic nervous system during focussed attention in children with ADHD. However, since HRV analyses have indicated that ADHD children on stimulant medication display a sympathetic under-activity during focussed attention relative to controls, it can be assumed that methylphenidate usage shifts the autonomic balance of children with ADHD towards normal levels; however, a normal autonomic balance is not reached.

4.2.2.2.3 Skin conductivity during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

A statistically significant difference in skin conductivity during focussed attention ($p=0.0126$) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free. These values indicate that, during focussed attention, skin conductivity is higher in ADHD children while they are on stimulant medication (2.40 ± 1.08 µMhos *vs.* 1.68 ± 1.08

μMhos). Methylphenidate usage therefore results in an increase in sympathetic nervous system activity during focussed attention in children with ADHD. These results support the HRV findings, which suggested that ADHD children on stimulant medication demonstrate a shift in the sympathovagal balance towards the sympathetic nervous system during focussed attention relative to stimulant-free ADHD children.

4.2.2.3 Summary of autonomic nervous system functioning during focussed attention

During focussed attention, stimulant-free children with ADHD demonstrate an over-activity of the parasympathetic nervous system when compared to controls. Methylphenidate usage appears to normalise this parasympathetic over-activity since ADHD children on stimulant medication display no difference in parasympathetic tone during focussed attention when compared to controls. Stimulant-free children with ADHD, furthermore, display under-activity of the sympathetic nervous system during focussed attention relative to controls. Although methylphenidate usage attempts to normalise the sympathetic under-activity, the level of sympathetic arousal during focussed attention found in ADHD children on stimulant medication is still lower than that found in controls. Methylphenidate usage results in a shift in the sympathovagal balance towards the sympathetic nervous system and a decrease in global heart rate variability during focussed attention in children with ADHD.

4.2.3 The effect of focussed attention on the autonomic nervous system

No studies on the effect of focussed attention on the autonomic nervous system in children with ADHD could be found. However, Crowell *et al* (1) found that during reward, heart rate values increase in non-medicated children with ADHD. Furthermore, this increase in heart rate was said to be mediated exclusively by parasympathetic withdrawal, with no independent sympathetic contribution (1). Beauchaine *et al* (2) found that while watching a videotaped peer conflict, non-medicated ADHD children demonstrated a vagal withdrawal characterised by a decrease in respiratory sinus arrhythmia.

4.2.3.1 Effect of focussed attention on heart rate variability parameters

4.2.3.1.1 Effect of focussed attention on HRV parameters in controls

Regarding the controls, a statistically significant difference between baseline and focussed attention was found for HF (p=0.0347), while marginally statistically significant differences were found for LF (p=0.0611) and the LF/HF ratio (p=0.0777). Both HF (435.67 ± 595.03 ms^2 *vs.* 275.17 ± 410.86 ms^2) and LF (372.39 ± 541.41 ms^2 *vs.* 228.78 ± 238.17 ms^2) decreased from baseline to focussed attention, while the LF/HF ratio (1.02 ± 0.67 *vs.* 1.31 ± 1.00) increased from baseline to focussed attention. The decrease in HF indicates a decrease in parasympathetic activity from baseline to focussed attention in controls. However, due to the lack of complete understanding of the autonomic contributions to the LF component, and since it is not supported by a statistically significant decrease in the normalised units of LF, we cannot conclude that the decrease in LF indicates a decrease in sympathetic activity from baseline to focussed attention.

However, since the LF/HF ratio increased, we can assume that the sympathovagal balance shifted towards the sympathetic nervous system from baseline to focussed attention in controls, which is the expected reactivity of the autonomic nervous system to a psychological stressor (36).

4.2.3.1.2 Effect of focussed attention on HRV parameters in stimulant-free ADHD children

When tested while they were stimulant-free, the ADHD children displayed statistically significant differences between baseline and focussed attention for mean HR (p=0.0006), STDRR (p=0.0483), RMSSD (p=0.0035), HF (p=0.0112), HFnu (p=0.0329), LFnu (p=0.0329) and SD1 (p=0.0035). Marginally statistically significant differences between baseline and focussed attention were also found for RR triangular index (p=0.0909) and LF/HF (p=0.0534). Mean HR (87.67 ± 7.75 bpm *vs.* 90.43 ± 8.84 bpm), LFnu (48.06 ± 16.82 nu *vs.* 55.78 ± 16.80 nu) and LF/HF (1.22 ± 1.01 *vs.* 1.67 ± 1.26) increased from baseline to focussed attention, while STDRR (0.052 ± 0.020 sec *vs.* 0.047 ± 0.016 sec), RR triangular index (0.100 ± 0.031 *vs.* 0.092 ± 0.026), RMSSD (52.51 ± 21.95 msec *vs.* 45.04 ± 18.24 msec), HF (659.16 ± 505.75 ms^2 *vs.* 512.37 ± 411.62 ms^2), HFnu (51.94 ± 16.82 nu *vs.* 44.22 ± 16.80 nu) and SD1 (37.36 ± 15.59 msec *vs.* 32.07 ± 12.95 msec) decreased from baseline to focussed attention. The increase in LFnu suggests an increase in sympathetic tone from baseline to focussed attention, while the decrease in RMSSD, SD1, HF and HFnu indicate a decrease in parasympathetic tone from baseline to focussed attention. This is supported by an increase in mean HR and an increase in the LF/HF ratio, which both indicate a shift in the sympathovagal balance towards the sympathetic

nervous system. As previously mentioned, a shift in the sympathovagal balance towards the sympathetic nervous system is the expected reactivity of the autonomic nervous system to a psychological stressor (36). The decrease in STDRR and RR triangular index indicate a decrease in overall heart rate variability from baseline to focussed attention. It has been shown that mental stress is associated with a decrease in heart rate variability due to its associated increase in sympathetic activity (37); therefore the decrease in heart rate variability from baseline to focussed attention is expected. Stimulant-free ADHD children, therefore, display a shift in the sympathovagal balance towards the sympathetic nervous system and a decrease in heart rate variability from baseline to focussed attention. These findings support the findings by Crowell *et al* (1) and Beauchaine *et al* (2) which show that parasympathetic nervous system activity, as assessed by means of heart rate and respiratory sinus arrhythmia, decreases during reward or while watching a videotaped peer conflict, respectively. However, the finding of an increase in sympathetic tone from baseline to focussed attention does not support the findings by Crowell *et al* (1), which suggest that the increase in heart rate during reward is mediated exclusively by vagal withdrawal with no contribution from the sympathetic nervous system.

Furthermore, when comparing the delta values (Δ = focussed attention - baseline) of HRV parameters from the stimulant-free ADHD children to those of controls, statistically significant differences were found for RMSSD Δ ($p=0.0298$) and SD1 Δ ($p=0.0245$). The magnitude of the decrease in RMSSD (-7.47 ± 10.42 msec *vs.* -1.78 ± 15.38 msec) and SD1 (-5.29 ± 7.40 msec *vs.* -1.23 ± 10.95 msec) between baseline and focussed attention

was greater in the stimulant-free ADHD children than in the controls. These results indicate that the decrease in parasympathetic tone from baseline to focussed attention was greater in stimulant-free ADHD children than in controls. Since our previous results have suggested a baseline parasympathetic over-arousal in children with ADHD, it does appear reasonable that this would result in a greater change in parasympathetic activity from baseline to focussed attention. A marginally statistically significant difference in delta values of HRV parameters between stimulant-free ADHD children and controls was also found regarding HR Δ ($p=0.0500$), with the change in HR between baseline and focussed attention found to be greater in the stimulant-free ADHD children (2.76 ± 2.69 bpm *vs.* 0.95 ± 4.28 bpm). This finding can, however, be explained by the larger decrease in parasympathetic tone demonstrated by the stimulant-free ADHD children.

4.2.3.1.3 Effect of focussed attention on HRV parameters in ADHD children on stimulant medication

When the ADHD children were tested while they were on stimulant medication, only marginally statistically significant differences between baseline and focussed attention were found regarding the normalized units of HF ($p=0.0942$) and LF ($p=0.0942$), using the paired t-test. HFnu decreased (51.47 ± 17.14 nu *vs.* 44.04 ± 17.11 nu) and LFnu increased (48.53 ± 17.14 nu *vs.* 55.96 ± 17.11 nu) from baseline to focussed attention. With the Wilcoxon signed-rank test no statistically significant differences between baseline and focussed attention were found. These results indicate that the usual autonomic reactivity from baseline to focussed attention, i.e. a shift in the sympathovagal

balance towards the sympathetic nervous system, is abolished by methylphenidate medication.

4.2.3.2 Effect of focussed attention on skin conductivity

4.2.3.2.1 Effect of focussed attention on skin conductivity in controls

Regarding the controls, a statistically significant difference between skin conductivity at baseline and during focussed attention was found using both the paired t-test (p=0.0049) and Wilcoxon signed-rank test (p=0.0033), with skin conductivity increasing from baseline to focussed attention (1.96 ± 1.00 µMhos *vs.* 2.43 ± 1.27 µMhos). These results suggest that the controls demonstrated a significant increase in sympathetic tone from baseline to focussed attention, as is expected. These results support our HRV findings which suggested that controls exhibit a shift in the sympathovagal balance towards the sympathetic nervous system from baseline to focussed attention.

4.2.3.2.2 Effect of focussed attention on skin conductivity in stimulant-free ADHD children

When the ADHD children were tested while stimulant-free, a statistically significant difference between skin conductivity at baseline and during focussed attention was found using both the paired t-test (p=0.0065) and Wilcoxon signed-rank test (p=0.0025), with skin conductivity increasing from baseline to focussed attention (1.35 ± 0.83 µMhos *vs.* 1.68 ± 1.08 µMhos). These findings indicate that stimulant-free ADHD children display a significant increase in sympathetic tone from baseline to focussed attention. These results support the HRV findings which suggested that stimulant-free ADHD children

demonstrate a shift in the sympathovagal balance towards the sympathetic nervous system, caused by an increase in sympathetic tone and a decrease in parasympathetic tone, from baseline to focussed attention. These results do not support the findings by Crowell *et al* (1), which imply that the increase in heart rate in children with ADHD, found during reward, is mediated exclusively by vagal withdrawal with no contribution from the sympathetic nervous system.

4.2.3.2.3 Effect of focussed attention on skin conductivity in ADHD children on stimulant medication

When the ADHD children were tested while on stimulant medication, only a marginally statistically significant difference between skin conductivity at baseline and during focussed attention was found using the Wilcoxon signed-rank test (p=0.0989), with skin conductivity increasing from baseline to focussed attention (2.21 ± 1.14 µMhos *vs.* 2.40 ± 1.08 µMhos). No statistically significant difference was found using the paired t-test. This finding suggests that the usual reactivity of the autonomic nervous system to a psychological stressor is abolished by the use of methylphenidate stimulant medication, and therefore supports the HRV findings.

4.2.3.3 Summary of the effect of focussed attention on the autonomic nervous system

The normal response of the autonomic nervous system to a psychological or cognitive stressor is a shift in the sympathovagal balance towards the sympathetic nervous system. As is expected, the response from baseline to focussed attention in controls was a shift in

the sympathovagal balance towards the sympathetic nervous system. Similarly, stimulant-free ADHD children demonstrated a shift in the sympathovagal balance towards the sympathetic nervous system and a decrease in heart rate variability from baseline to focussed attention. The shift in the sympathovagal balance towards the sympathetic nervous system, in both controls and stimulant-free ADHD children, was due to an increase in sympathetic tone, as well as a decrease in parasympathetic tone. The decrease in parasympathetic tone demonstrated by the stimulant-free ADHD children was greater than the decrease in parasympathetic tone demonstrated by the controls, possibly due to the baseline parasympathetic over-activity found in the children with ADHD. Methylphenidate usage, however, abolishes the reactivity of the autonomic nervous system from baseline to focussed attention, possibly due to its activation of the sympathetic nervous system.

4.3 Cardiac functioning

4.3.1 Comparison of cardiac functioning between experimental and control groups

4.3.1.1 Blood pressure

Most systemic arterioles are innervated by sympathetic neurons, with tonic noradrenaline discharge maintaining myogenic tone (40). Noradrenaline released by the sympathetic nervous system binds to α-1 receptors on the smooth muscle causing vasoconstriction (40). If sympathetic tone increases, arterioles constrict, resulting in an increase in blood

pressure. On the other hand, if sympathetic tone decreases, the arterioles will dilate, causing blood pressure to decrease. Furthermore, noradrenaline released by the sympathetic nervous system can bind to β_1 receptors in the heart, resulting in, amongst others, an increase in the force of cardiac contraction (41). This increase in cardiac contractility results in an increase in cardiac output and thereby causes an increase in blood pressure.

Stimulants commonly used to treat ADHD have been shown to cause significant increases in blood pressure as compared to placebo (16,17,18), with methylphenidate specifically shown by Ballard *et al* (21) to cause significant increases in both systolic and diastolic blood pressure.

4.3.1.1.1 Blood pressure values for stimulant-free ADHD children versus controls

No statistically significant difference in systolic blood pressure (95.00 ± 7.64 mmHg *vs.* 97.17 ± 9.97 mmHg) was found between stimulant-free ADHD children and controls. However, a marginally statistically significant difference was found between stimulant-free ADHD children and controls regarding diastolic blood pressure (p=0.0767), with diastolic blood pressure found to be lower in stimulant-free ADHD children (65.95 ± 5.97 mmHg *vs.* 70.39 ± 8.51 mmHg). These results suggest that the stimulant-free ADHD children demonstrated a lower level of sympathetic activity than controls. These results support the HRV and skin conductivity findings which indicated that stimulant-free ADHD children demonstrate an attenuation of the sympathetic nervous system at baseline relative to controls.

4.3.1.1.2 Blood pressure values for ADHD children on stimulant medication versus controls

No statistically significant difference in diastolic blood pressure (69.74 ± 8.77 mmHg *vs.* 70.39 ± 8.51 mmHg) between ADHD children on stimulant medication and controls was found. However, a statistically significant difference in systolic blood pressure ($p=0.0003$) between ADHD children on stimulant medication and controls was found, with systolic blood pressure found to be higher in ADHD children on stimulant medication (111.53 ± 7.93 mmHg *vs.* 97.17 ± 9.97 mmHg). At first glance these results would appear to suggest that medicated children with ADHD exhibit a higher level of sympathetic tone than controls. However, sympathetic activation has a significant influence on peripheral resistance and a higher diastolic blood pressure was not found for ADHD children on stimulant medication. In addition, various factors may have contributed to the higher systolic blood pressure, including the fact that a higher systolic blood pressure, as opposed to higher diastolic blood pressure, is primarily influenced by vagal activity. The vagus nerve inhibits the cardiac pacemaker, atrial myocardium and AV conduction system, but perhaps more relevant here, depresses ventricular contractility. This negative inotropic effect will cause a decrease in cardiac output and thereby decrease systolic blood pressure. Earlier in this discussion it was shown, by the HRV results, that a significantly higher parasympathetic activity is present in stimulant-free ADHD children relative to controls, while no statistically significant differences in parasympathetic tone could be detected between ADHD children on stimulant medication and controls. This suggests that methylphenidate usage lowers the parasympathetic over-activity of children with ADHD. The increase in systolic blood pressure found in the

ADHD children on stimulant medication can therefore, most probably be ascribed to the decrease in vagal activity caused by methylphenidate.

4.3.1.1.3 Blood pressure values for ADHD children on stimulant medication versus stimulant-free ADHD children

Statistically significant differences in systolic (p=0.0003) and diastolic (p=0.0235) blood pressure were found between ADHD children on stimulant medication and stimulant-free ADHD children. While they were on stimulant medication, the ADHD children had significantly higher values for both systolic (111.53 ± 7.93 mmHg *vs.* 95.00 ± 7.64 mmHg) and diastolic blood pressure (69.74 ± 8.77 mmHg *vs.* 65.95 ± 5.97 mmHg). These results support the findings by Biederman *et al* (17), Wernicke *et al* (18), Biederman *et al* (16) and Ballard *et al* (21), which indicate that stimulant usage is associated with increases in both systolic and diastolic blood pressure. These results, furthermore, support the HRV and skin conductivity findings, which suggested that methylphenidate usage is associated with an activation of the sympathetic nervous system, a decrease in the activity of the parasympathetic nervous system and, therefore, a shift in the sympathovagal balance towards the sympathetic nervous system.

4.3.1.1.4 Summary of blood pressure values

Stimulant-free children with ADHD showed a significantly lower diastolic blood pressure than controls, suggesting a level of sympathetic under-activity in non-medicated children with ADHD. Although ADHD children on stimulant medication displayed higher systolic blood pressure than controls, this can most probably be ascribed to the decrease

in vagal activity caused by methylphenidate usage. Methylphenidate usage increased both systolic and diastolic blood pressure. These results confirm the sympathomimetic properties of stimulant medications. The clinical implication for the use of adrenergic stimulants in individuals with hypertension is self-evident.

4.3.1.2 ECG parameters

ECG parameters measured in our study included RR, HR, QT and JT intervals, and heart rate corrected QTc and JTc intervals. QT and JT intervals were corrected for heart rate using a data-derived formula published by Wernicke *et al* (42) as well as Bazett's formula (43,44,45). Other measures included QT and JT dispersion and heart rate corrected QTcd and JTcd, which were, once again, corrected for heart rate using a data-derived formula published by Wernicke *et al* (42) as well as Bazett's formula (43,44,45).

Stimulants commonly used to treat ADHD have been shown to cause increases in HR (16,17,18), with methylphenidate specifically shown by Ballard *et al* (21) and Spencer *et al* (15) to cause increases in HR values. Studies on the effect of stimulant medication on QT and QTc intervals are controversial with some studies indicating a small but insignificant increase in QT (46) and QTc values (46,47), and others indicating no changes in QT intervals (18,48,49) with the usage of stimulant medication. Furthermore, results by Biederman *et al* (16) indicate a decrease in QT intervals with the usage of stimulant medication. Regarding the effect of stimulant medication on QT dispersion values, some studies have indicated a decrease in QTd (50), while others report no changes in QTd values with the usage of stimulant medication (18). Methylphenidate

specifically, has been shown to cause no changes in ECG parameters by both Ballard *et al* (21) and Spencer *et al* (15). No studies which examined the effect of methylphenidate on JTc and JTd values could be found.

4.3.1.2.1 ECG parameters for stimulant-free ADHD children versus controls

Statistically significant differences between ECG parameters of stimulant-free ADHD children and control subjects were found for RR (p=0.0227) and HR (p=0.0386). HR was lower (74.32 ± 8.53 bpm *vs.* 80.67 ± 10.17 bpm), while RR intervals were larger (0.81 ± 0.11 sec *vs.* 0.74 ± 0.08 sec) in ADHD children while they were stimulant-free. A marginally statistically significant difference was found for JT (p=0.0703), with JT intervals found to be larger in ADHD children while they were stimulant-free (305.44 ± 13.11 msec *vs.* 293.96 ± 22.97 msec). These results point towards a parasympathetic dominance of the sympathovagal balance in stimulant-free ADHD children when compared to controls. These results support our previous findings of attenuated baseline sympathetic activity, as indicated by HRV, skin conductivity and blood pressure findings, and over-active baseline parasympathetic activity, as indicated by HRV findings, in non-medicated children with ADHD.

4.3.1.2.2 ECG parameters for ADHD children on stimulant medication versus controls

No statistically significant differences between ECG parameters of ADHD children on stimulant medication and control subjects were found. Marginally statistically significant differences were, however, found for QT (p=0.0593) and JT (p=0.0943), with both QT

(358.25 ± 23.96 msec *vs.* 372.83 ± 21.63 msec) and JT intervals (282.89 ± 18.25 msec *vs.* 293.96 ± 22.97 msec) found to be smaller in the ADHD children on stimulant medication.

4.3.1.2.3 ECG parameters for ADHD children on stimulant medication versus stimulant-free ADHD children

Statistically significant differences between ECG parameters of ADHD children on stimulant medication and stimulant-free ADHD children were obtained for RR (p=0.0025), HR (p=0.0070), QT (p=0.0002) and JT (p=0.0002). HR were higher in ADHD children while they were on stimulant medication (83.95 ± 15.22 bpm *vs.* 74.32 ± 8.53 bpm), while RR (0.70 ± 0.10 sec *vs.* 0.81 ± 0.11 sec), QT (358.25 ± 23.96 msec *vs.* 383.95 ±18.46 msec) and JT intervals (282.89 ± 18.25 msec *vs.* 305.44 ± 13.11 msec) were larger in ADHD children while they were stimulant-free. These results support previous findings by Ballard *et al* (21) and Spencer *et al* (15), which indicate that methylphenidate usage is associated with an increase in heart rate. Furthermore, these results indicate that stimulant usage results in a shift in the sympathovagal balance towards the sympathetic nervous system, supporting our HRV, skin conductivity and blood pressure findings. Based on the HRV and SC results, it can be assumed that the shift in the sympathovagal balance towards the sympathetic nervous system as a result of methylphenidate usage is due to both an increase in sympathetic activity and decrease in parasympathetic activity. A marginally statistically significant difference was found for the data-derived JTc (p=0.0536), with JTc values found to be larger in ADHD children while they were stimulant-free (324.24 ± 16.58 msec *vs.* 331.83 ± 17.68 msec). These

results suggest that methylphenidate usage leads to a significant shortening of the JTc interval and not a JTc prolongation. Therefore, these results cannot support the findings by Ballard *et al* (21) and Spencer *et al* (15), which indicate that methylphenidate usage does not affect any ECG parameters.

4.3.1.2.4 Summary of ECG parameters

Stimulant-free children with ADHD demonstrated a parasympathetic dominance of the sympathovagal balance when compared to controls, confirming our HRV, skin conductivity and blood pressure findings. Methylphenidate usage results in an increase in HR and decreases in the lengths of the RR, QT, JT and JTc intervals. The shortening of the QT and JT intervals is expected due to the increase in heart rate caused by methylphenidate usage, however, the shortening of the JTc interval is puzzling.

4.3.2 Prolongation of ECG parameters

Prolonged QTc and JTc intervals are associated with an increased risk of ventricular arrhythmias (47,51) and an increased probability of morbidity and mortality (52). Prolonged QTd and JTd values are a sign of cardiac instability and point towards an increased risk for ventricular arrhythmias (53).

4.3.2.1 Prolongation of the QTc interval based on the Moss and Robinson criteria

Based on the Moss and Robinson criteria of QTc prolongation (54), two of the controls, three of the stimulant-free ADHD children and two of the ADHD children taking stimulant medication demonstrated a prolongation of the Bazett-corrected QTc interval.

Since the degree of QTc prolongation found in our ADHD children is comparable to the degree of QTc prolongation found in our controls, we can either assume that the Moss and Robinson criteria for QTc prolongation is too stringent for our population and therefore does not effectively reveal which individuals have an increased risk for ventricular arrhythmias, or that the two controls indeed have prolonged QTc intervals. Whatever the case, the results are in agreement with those authors (15,21) that did not support a general prolongation of the QTc interval by methylphenidate.

4.3.2.2 Within-patient QTc prolongation

A regulatory definition of QTc prolongation is a within-patient medication-related change in the Bazett-corrected QTc of more than 30 ms (47). Only one child demonstrated a within-patient increase of 30 msec or more with the usage of stimulant medication. These results suggest that methylphenidate, in general, is not likely to increase QTc length and adversely affect cardiac depolarization and repolarization duration. However, the finding of an increase of 30 msec or more in the one individual does suggest that methylphenidate usage may result in a prolongation of the QTc interval in susceptible individuals.

4.3.2.3 JTc prolongation

Twelve of the controls, eight of the stimulant-free ADHD children and ten of the ADHD children on stimulant medication demonstrated a prolongation of the Bazett-corrected JTc interval based on the criteria established by Berul *et al* (52). Since the degree of JTc prolongation found in our ADHD children is comparable to the degree of JTc

prolongation found in our controls, we can assume that the criteria for JTc prolongation established by Berul *et al* (52) is too stringent for our population and therefore does not effectively reveal which individuals have an increased risk for ventricular arrhythmias. However, in four of our ADHD children, the use of methylphenidate was associated with a prolongation of the JTc interval, suggesting that methylphenidate may result in a prolongation of the JTc interval in susceptible individuals.

4.3.2.4 QTd and JTd prolongation

Shah *et al* (55) found that a QTd or JTd value equal to or greater than 55 msec is associated with an increased risk of critical ventricular arrhythmias such as ventricular tachycardia, torsades de pointes and cardiac arrest. However, in the present study none of the controls and none of the ADHD children displayed a QTd or JTd equal to or greater than 55 msec. Since QTd and JTd are non-invasive markers of the underlying inhomogeneity of myocardial repolarization, these results indicate that none of the children in this study had an increased risk for critical ventricular arrhythmias, according to QTd and JTd values. The results furthermore suggest that methylphenidate is not likely to adversely affect ECG dispersion values.

4.3.2.5 Summary of prolongation of ECG parameters

Methylphenidate usage does not affect QT or JT dispersion values. Moreover, methylphenidate usage, in general, is not likely to result in QTc and JTc prolongation; however, it may cause QTc and JTc prolongation in susceptible individuals. The reason

behind the prolongation of QTc and JTc in some individuals should be further investigated as it is important to know when the use of methylphenidate poses a risk.

4.4 Theta/beta and theta/SMR ratios

The diagnosis of ADHD can, in many cases, be problematic. In some circles it is believed that EEGs, especially QEEGs, may be of assistance in the diagnosis of the disorder. However, there is still considerable controversy regarding this possibility. Preliminary observations on EEG values made during this study are presented in the following paragraphs. Based on reported findings of those who support the notion of QEEGs as a diagnostic tool for ADHD, we set and tested a number of relevant hypotheses. This part of the study is considered exploratory as we are aware of the fact that more technologically advanced equipment may be able to detect differences not registered here.

Monastra *et al* (56) defined the theta/beta ratio of an individual as an attentional index, which is suggested to be a "biological" measure of attention. Since individuals with ADHD are said to display higher theta/beta ratios than normal individuals (57,58,59), the determination of the attentional index of an individual is suggested to allow for the assessment of the presence and severity of ADHD, by comparison to that of a normative sample (60). SMR 13-15 Hz activity is believed to be increased with the inhibition of movement and a decrease in muscle tone and is, furthermore, believed to play a role in attention (61). In line with this reasoning, an increase in SMR will therefore indicate a decrease in impulsivity and fidgetiness and an increase in relaxed focus and attention. It is therefore feasible to assume that individuals with ADHD should exhibit a decrease in

SMR activity due to their impulsivity and fidgetiness, relative to controls. Since there are indications that individuals with ADHD display an increased theta activity (58,62), and since it is feasible to assume that these individuals exhibit a decreased SMR, we hypothesized that individuals with ADHD should exhibit higher theta/SMR ratios when compared to normal individuals. It is important to note that certain authors have doubts that the theta/beta and theta/SMR ratios are reflections of attention and restlessness in an individual and are, therefore, of the opinion that they cannot differentiate between children with ADHD and normal children (63).

4.4.1 Baseline theta/beta and theta/SMR ratios

No statistically significant differences in baseline theta/beta or theta/SMR ratios were found between any of our groups.

4.4.2 Theta/beta and theta/SMR ratios during focussed attention

Since the theta/beta ratio is said to be a "biological" measure of attention (56) and the theta/SMR ratio can be described as a "biological" measure of hyperactivity, we predicted that children with ADHD should have higher theta/beta and theta/SMR ratios than controls during focussed attention. Furthermore, since stimulant medication is believed to reduce the level of inattention and impulsivity of an individual, we hypothesized that methylphenidate usage should result in decreases in both the theta/beta and theta/SMR ratios.

However, no statistically significant differences in theta/beta or theta/SMR ratios during focussed attention were found between any of our groups.

4.4.3 Effect of focussed attention on theta/beta and theta/SMR ratios

Focussed attention is usually associated with a decrease in theta power and an increase in beta power (64), and therefore a decrease in the theta/beta ratio. Since SMR is said to be increased with the inhibition of movement and a decrease in muscle tone, a decrease in the theta/SMR ratio during focussed attention should reflect a decrease in restlessness and fidgeting. However, since children with ADHD are known to be restless and hyperactive, we predicted a possible increase in the theta/SMR ratio during focussed attention in these individuals due to a possible increase in SMR power.

However, no statistically significant differences between baseline and focussed attention were found for the theta/beta or theta/SMR ratios in any of our groups.

4.4.4 Comparison of delta values (change) of theta/beta and theta/SMR ratios

4.4.4.1 Delta values (change) of theta/beta and theta/SMR ratios for stimulant-free ADHD children versus controls

No statistically significant differences between the delta values (focussed attention minus baseline) were found regarding the theta/beta and theta/SMR ratios of the stimulant-free ADHD children and the controls.

4.4.4.2 Delta values (change) of theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus controls

No statistically significant differences between the delta values (focussed attention minus baseline) were found regarding the theta/beta and theta/SMR ratios of the ADHD children on stimulant medication and the controls.

4.4.4.3 Delta values (change) of theta/beta and theta/SMR ratios for ADHD children on stimulant medication versus stimulant-free ADHD children

No statistically significant difference between the delta values (focussed attention minus baseline) of theta/beta ratios of ADHD children on stimulant medication and stimulant-free ADHD children was found. A statistically significant difference was, however, found between the delta values of the theta/SMR ratios ($p=0.0485$). The difference was found to be statistically significant with the paired t-test ($p=0.0485$) and marginally significant with the Wilcoxon signed-rank test ($p=0.0836$). The mean delta value of focussed attention minus baseline for the theta/SMR ratio in ADHD children on stimulant medication was positive (1.91 ± 6.65), indicating an increase in the theta/SMR ratio from baseline to focussed attention, while the mean delta value for the theta/SMR ratio in stimulant-free ADHD children was negative (-2.52 ± 6.34), indicating a decrease in the theta/SMR ratio from baseline to focussed attention. These results suggest that the ADHD children on stimulant medication were more restless and fidgety during focussed attention than the stimulant-free ADHD children. As this is definitely not the case, it can be suggested that the theta/SMR ratio does not reflect the level of restlessness in an individual.

4.4.5 Summary of theta/beta and theta/SMR ratios

The results indicated that, within the limitations of the equipment used in this study, the theta/beta and theta/SMR ratios cannot differentiate between children with ADHD and normal children. Furthermore, theta/beta and theta/SMR ratios do not appear to reflect the level of attention and restlessness, respectively, in an individual. These results question the validity of the theta/beta and theta/SMR ratios as determinants of attention and restlessness, respectively.

4.5 Alpha power

One of the primary electrophysiological differences identified by QEEG analysis of patients with ADHD includes a reduction in alpha power (65). Alpha power (8-13 Hz) is believed to be characterised by an awake, relaxed state associated with receptiveness (66). Alpha power measured in this study included thalpha (6-10 Hz), low alpha (8-10 Hz) and high alpha (11-12 Hz). It is said that low alpha power represents an inner awareness of self, while high alpha power represents centering (67).

4.5.1 Baseline alpha power

4.5.1.1 Baseline alpha power for stimulant-free ADHD children versus controls

No statistically significant differences in baseline alpha power between stimulant-free ADHD children and control subjects were found.

4.5.1.2 Baseline alpha power for ADHD children on stimulant medication versus controls

No statistically significant differences in baseline alpha power between ADHD children on stimulant medication and control subjects were found.

4.5.1.3 Summary of baseline alpha power

Our results suggest that baseline alpha values cannot differentiate between children with ADHD and normal children.

4.5.2 Alpha power during focussed attention

4.5.2.1 Alpha power during focussed attention for stimulant-free ADHD children versus controls

No statistically significant differences in alpha power during focussed attention between stimulant-free ADHD children and control subjects were found.

4.5.2.2 Alpha power during focussed attention for ADHD children on stimulant medication versus controls

Statistically significant differences in low alpha power during focussed attention ($p=0.0418$) and high alpha power during focussed attention ($p=0.0164$) were found between ADHD children on stimulant medication and control subjects, with low alpha power during focussed attention found to be lower (-0.96 ± 2.18 µV *vs.* 0.67 ± 5.05 µV) and high alpha power during focussed attention found to be higher (-0.09 ± 1.38 µV *vs.*

-4.82 ± 11.88 μV) in ADHD children on stimulant medication. These results suggest that ADHD children on stimulant medication exhibit a higher level of high alpha power and a lower level of low alpha power when compared to controls. As it is said that low alpha power represents an inner awareness of self, while high alpha power represents centering (67), the results suggest that methylphenidate increases centering but decreases inner awareness of self during focussed attention in children with ADHD.

4.5.2.3 Alpha power during focussed attention for ADHD children on stimulant medication versus stimulant-free ADHD children

A statistically significant difference in high alpha power during focussed attention ($p=0.0486$) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained while they were stimulant-free, with high alpha power during focussed attention found to be higher in ADHD children on stimulant medication (-0.09 ± 1.38 μV *vs.* -1.04 ± 1.74 μV). These results confirm our previous suggestions that methylphenidate usage causes an increase in high alpha power, and therefore an increase in centering, during focussed attention in children with ADHD.

4.5.2.4 Summary of alpha power during focussed attention

While on stimulant medication, children with ADHD exhibited significantly lower low alpha power and significantly higher high alpha power during focussed attention relative to controls. These results suggest that ADHD children on stimulant medication exhibit a lower degree of inner-awareness of self and a higher degree of centering during focussed attention than controls. Methylphenidate usage caused a statistically significant increase

in high alpha power during focussed attention, suggesting that methylphenidate usage results in a higher degree of centering during focussed attention in children with ADHD.

4.5.3 Effect of focussed attention on alpha power

During a task that requires attention normal children exhibit a decrease in alpha activity known as alpha blocking (66). Since alpha activity is associated with receptiveness and mental idling (66), a decrease in alpha activity indicates that the brain is no longer at rest and no longer as receptive to outside information. This alpha activity is then replaced by beta activity of above 12 Hz, which is generally associated with active concentration (68). Lubar (64) has suggested that children with ADHD do not exhibit an alpha block during a task that requires attention.

4.5.3.1 Effect of focussed attention on alpha power in controls

Regarding controls, a statistically significant difference between baseline and focussed attention was found for high alpha ($p=0.0016$), while a marginally statistically significant difference between baseline and focussed attention was found for thalpha ($p=0.0803$). Both high alpha (1.24 ± 2.76 µV *vs.* -4.82 ± 11.88 µV) and thalpha (2.91 ± 11.72 µV *vs.* -4.94 ± 14.15 µV) decreased from baseline to focussed attention. As was expected, these results indicate that the controls demonstrated an alpha block from baseline to focussed attention.

4.5.3.2 Effect of focussed attention on alpha power in stimulant-free ADHD children

A statistically significant difference in high alpha (p=0.0022) between baseline and focussed attention was found, with high alpha decreasing from baseline to focussed attention (1.03 ± 1.63 μV *vs.* -1.04 ± 1.74 μV). These results suggest that stimulant-free children with ADHD also exhibited an alpha block from baseline to focussed attention. Therefore these results do not support the findings by Lubar (64) which suggested that children with ADHD do not display an alpha block from baseline to focussed attention.

4.5.3.3 Effect of focussed attention on alpha power in ADHD children on stimulant medication

No statistically significant differences between baseline and focussed attention were found for thalpha, low alpha or high alpha regarding the ADHD children on stimulant medication. These results suggest that methylphenidate abolishes the alpha block from baseline to focussed attention in children with ADHD.

4.5.3.4 Summary of the effect of focussed attention on alpha power

Controls demonstrated a statistically significant decrease in high alpha power, as well as a marginally statistically significant decrease in thalpha power, from baseline to focussed attention. Stimulant-free children with ADHD also demonstrated a statistically significant decrease in high alpha power from baseline to focussed attention. These results suggest that both controls and stimulant-free children with ADHD exhibit an alpha block from baseline to focussed attention. However, ADHD children taking stimulant

medication showed no statistically significant differences in alpha power between baseline and focussed attention, suggesting that methylphenidate usage abolishes the alpha block from baseline to focussed attention in children with ADHD.

4.5.4 Comparison of delta values (change) of alpha power

4.5.4.1 Delta values (change) of alpha power for stimulant-free ADHD children versus controls

No statistically significant differences between the delta values (focussed attention minus baseline) were found regarding thalpha, low alpha and high alpha power of the stimulant-free ADHD children and the control subjects. These results suggest that stimulant-free ADHD children and controls do not differ with regard to the magnitude of the difference in alpha power between baseline and focussed attention.

4.5.4.2 Delta values (change) of alpha power for ADHD children on stimulant medication versus controls

A statistically significant difference in delta values of high alpha ($p=0.0127$) and a marginally statistically significant difference in delta values of thalpha ($p=0.0656$) was found between ADHD children on stimulant medication and control subjects, with delta values of high alpha (-0.19 ± 2.23 µV *vs.* -6.06 ± 12.45 µV) and thalpha (0.79 ± 6.12 µV *vs.* -7.85 ± 17.90 µV) found to be smaller in ADHD children on stimulant medication. These results suggest that ADHD children on stimulant medication demonstrate less alpha reactivity from baseline to focussed attention than controls.

4.5.4.3 Delta values (change) of alpha power for ADHD children on stimulant medication versus stimulant-free ADHD children

A statistically significant difference in delta values of high alpha (p=0.0048) and a marginally statistically significant difference in delta values of thalpha (p=0.0990) was found when comparing the values obtained while the ADHD children were on stimulant medication to those obtained when they were stimulant-free. Delta values of high alpha (-0.19 ± 2.23 μV *vs.* -2.08 ± 2.25 μV) and thalpha (0.79 ± 6.12 μV *vs.* -5.58 ± 16.46 μV) were both found to be larger in stimulant-free ADHD children. These results suggest that methylphenidate usage decreases the alpha reactivity from baseline to focussed attention in children with ADHD.

4.5.4.4 Summary of delta values (change) of alpha power

Stimulant-free ADHD children and controls do not appear to differ with regards to the magnitude of the difference in alpha power between baseline and focussed attention. ADHD children on stimulant medication do, however, appear to demonstrate less alpha reactivity from baseline to focussed attention than controls. Methylphenidate usage significantly decreases the alpha reactivity of children with ADHD.

4.6 Summary of EEG parameters, ADHD and methylphenidate

The results suggested that children with ADHD cannot be differentiated from normal children on the basis of certain EEG values. The results do, however, point towards some effects of methylphenidate that may have negative consequences for the psychological

well-being of the individual on this type of medication. It should be stressed that more sophisticated instrumentation for the quantification of EEGs are available than those used in this work and that this section of the study should perhaps be considered a preliminary exploration of the possibilities.

4.7 Baseline theta/beta and theta/SMR ratios and autonomic functioning

In the final analysis we tested for possible relationships between baseline theta/beta ratios and autonomic functioning and baseline theta/SMR ratios and autonomic functioning. No statistically significant relationships were found between baseline theta/beta ratios and HRV parameters, skin conductivity values, blood pressure values and ECG parameters, either at baseline or during focussed attention, in any of the children in this study. Furthermore, no statistically significant relationships were found between baseline theta/SMR ratios and HRV parameters, skin conductivity values, blood pressure values and ECG parameters, either at baseline or during focussed attention, in any of the children in this study.

4.8 Summary of the study

With regards to the heart rate variability (HRV) and skin conductivity analyses the questions we asked were: a) whether baseline autonomic nervous system functioning of stimulant-free children with ADHD differs from that of normal children, b) whether the

stimulant prescribed, namely methylphenidate, has an influence on baseline autonomic nervous system functioning in children with ADHD and c) whether the autonomic nervous system response during focussed attention is different from that of normal children.

When the baseline autonomic nervous system functioning of stimulant-free children with ADHD was examined to see whether it differed from that of normal children it was found that the stimulant-free ADHD children showed a baseline parasympathetic dominance of the autonomic balance when compared to controls. Parasympathetic dominance can occur as result of lower sympathetic nervous system activity, higher parasympathetic nervous system activity, or both. However, in the stimulant-free ADHD children parasympathetic dominance was found to occur as a result of parasympathetic over-activity, as well as sympathetic under-activity. This conclusion was derived from HRV analyses which indicated that stimulant-free ADHD children display parasympathetic over-arousal at baseline when compared to controls and skin conductivity and HRV analyses, which suggested that stimulant-free ADHD children exhibit sympathetic under-activity at baseline relative to controls. The baseline parasympathetic dominance of the autonomic balance in stimulant-free ADHD children, relative to controls, was confirmed by the significantly lower HR and significantly higher levels of HRV found in these children.

When it was examined whether the stimulant prescribed, namely methylphenidate, has an influence on baseline autonomic nervous system functioning in children with ADHD it

was found that methylphenidate shifted the autonomic balance of children with ADHD towards normal levels, but indications were that a normal autonomic balance was not reached. This conclusion was derived since no statistically significant differences in parasympathetic tone between ADHD children on stimulant medication and controls were found, suggesting that methylphenidate usage lowers the parasympathetic over-activity of children with ADHD. Indeed, ADHD children on stimulant medication were found to have lower parasympathetic tone than stimulant-free ADHD children; however, the difference was not statistically significant. Furthermore, sympathetic activity was significantly increased by methylphenidate as can be seen by the significantly higher skin conductivity values found for ADHD children on stimulant medication relative to stimulant-free ADHD children. However, sympathetic activity was not raised to normal levels as can be seen by the significantly higher SD2 values of the Poincaré Plot found for ADHD children on stimulant medication when compared to controls. The shift in the autonomic balance towards normal levels in children with ADHD was reflected by the higher HR and lower HRV found for ADHD children on stimulant medication when compared to stimulant-free ADHD children. However, HRV in ADHD children on stimulant medication was still higher than controls suggesting that a normal autonomic balance was not reached.

With regards to the question of whether the autonomic nervous system response during focussed attention in children with ADHD differs from that of normal children we asked a) whether autonomic nervous system functioning during focussed attention differed between stimulant-free ADHD children and normal children, b) whether the autonomic

nervous system response to focussed attention (difference between baseline and focussed attention) differed between stimulant-free ADHD children and normal children, c) whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic nervous system functioning during focussed attention in children with ADHD and iv) whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic response to focussed attention (difference between baseline and focussed attention) in children with ADHD.

When the autonomic nervous system functioning during focussed attention of stimulant-free ADHD children was examined to see whether it differed from that of normal children it was found that stimulant-free ADHD children showed a parasympathetic dominance of the autonomic balance during focussed attention when compared to controls. This parasympathetic dominance was due to parasympathetic over-activity as well as sympathetic under-activity. This conclusion was derived from HRV analyses which indicated that parasympathetic activity during focussed attention was found to be higher in stimulant-free ADHD relative to controls and HRV and skin conductivity analyses which indicated that sympathetic activity during focussed attention was found to be lower in stimulant-free ADHD children relative to controls. The parasympathetic dominance of the autonomic balance during focussed attention in stimulant-free ADHD children, relative to controls, was confirmed by the significantly higher levels of HRV found in these children.

When the autonomic response to focussed attention (difference between baseline and focussed attention) of stimulant-free ADHD children was examined to see whether it differed from normal children it was found that controls and stimulant-free ADHD children both demonstrated a shift in the sympathovagal balance towards the sympathetic nervous system from baseline to focussed attention. This conclusion was derived from HRV analyses which indicated that parasympathetic activity decreased from baseline to focussed attention in controls and stimulant-free ADHD children. However, the decrease in parasympathetic activity was found to be larger in stimulant-free ADHD children. Furthermore, skin conductivity analyses indicated that sympathetic activity increased from baseline to focussed attention in controls, while HRV and skin conductivity analyses indicated that sympathetic activity increased from baseline to focussed attention in stimulant-free ADHD children. The increase in sympathetic activity did not significantly differ between controls and stimulant-free ADHD children. In controls, the shift in the sympathovagal balance towards the sympathetic nervous system was supported by a significant increase in the LF/HF ratio from baseline to focussed attention. In stimulant-free ADHD children the shift in the sympathovagal balance towards the sympathetic nervous system was supported by a significant increase in HR and the LF/HF ratio as well as a significant decrease in HRV from baseline to focussed attention.

When it was examined whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic nervous system functioning during focussed attention in children with ADHD it was found that methylphenidate shifted the autonomic balance during focussed attention of children with ADHD towards normal levels, but indications are that

a normal autonomic balance was not reached. This conclusion was derived since no statistically significant differences in parasympathetic tone during focussed attention between ADHD children on stimulant medication and controls were found, suggesting that methylphenidate usage lowers the parasympathetic over-activity of children with ADHD. Sympathetic activity during focussed attention was increased by methylphenidate as can be seen by the significantly higher skin conductivity values found for ADHD children on stimulant medication when compared to stimulant-free ADHD children. However, sympathetic activity was not raised to normal levels as can be seen by the significantly lower SD2 values of the Poincaré Plot found for ADHD children on stimulant medication when compared to controls. This shift in the autonomic balance of ADHD children on stimulant medication towards normal levels, relative to stimulant-free ADHD children, was confirmed by the higher HR and lower HRV found for ADHD children on stimulant medication when compared to stimulant-free ADHD children. However, HRV in ADHD children on stimulant medication was still higher than controls suggesting that a normal autonomic balance was not reached in ADHD children on stimulant medication.

When it was examined whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic response to focussed attention (difference between baseline and focussed attention) in children with ADHD it was found that methylphenidate abolished the reactivity of the autonomic nervous system from baseline to focussed attention in children with ADHD. This conclusion was derived from HRV analyses which revealed that no significant difference in parasympathetic activity between baseline and focussed

attention was found in ADHD children on stimulant medication and HRV and skin conductivity analyses which indicated that no significant difference in sympathetic activity between baseline and focussed attention was found in ADHD children on stimulant medication. This was confirmed by the fact that no significant differences in HR, LF/HF and HRV between baseline and focussed attention were found in ADHD children on stimulant medication.

With regards to the cardiac analyses the questions we asked were a) whether the autonomic functioning, as assessed by blood pressure and ECG parameters, of stimulant-free ADHD children differs from that of normal children, b) whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic nervous system functioning, as assessed by blood pressure and ECG parameters, of children with ADHD and c) whether the stimulant prescribed, namely methylphenidate adversely affects QTc, JTc or cardiac dispersion parameters.

When the autonomic functioning, as assessed by blood pressure and ECG parameters, of stimulant-free ADHD children was examined to see whether it differed from that of normal children it was found that stimulant-free ADHD children showed a parasympathetic dominance of the autonomic balance when compared to controls. This conclusion was derived from diastolic blood pressure values which indicated that stimulant-free ADHD children demonstrated an under-activity of the sympathetic nervous system when compared to controls. This parasympathetic dominance of the autonomic balance in stimulant-free ADHD children, relative to controls, was confirmed

by the significantly lower HR and significantly higher RR intervals found in stimulant-free ADHD children relative to controls.

When it was examined whether the stimulant prescribed, namely methylphenidate, has an influence on autonomic nervous system functioning, as assessed by blood pressure and ECG parameters, of children with ADHD it was found that methylphenidate results in an activation of the sympathetic nervous system in children with ADHD. This conclusion was derived from systolic and diastolic blood pressure values which indicated that ADHD children on stimulant medication demonstrated a higher level of sympathetic tone than stimulant-free ADHD children. This sympathetic dominance of the sympathovagal balance in ADHD children on stimulant medication, relative to stimulant-free ADHD children, was confirmed by significantly higher HR and significantly smaller RR, QT and JT intervals found in ADHD children on stimulant medication when compared to stimulant-free ADHD children.

When it was examined whether the stimulant prescribed, namely methylphenidate adversely affects QTc, JTc and cardiac dispersion parameters it was found that methylphenidate usage, in general, is not likely to result in QTc or JTc prolongation; however, it may cause QTc and JTc prolongation in susceptible individuals. Furthermore, methylphenidate usage did not appear to adversely affect cardiac dispersion parameters.

With regards to EEG functioning, the questions we asked were a) whether theta/beta and theta/SMR ratios can differentiate between children with ADHD and normal children, b) whether alpha power can differentiate between children with ADHD and normal children and c) whether the stimulant prescribed, namely methylphenidate, has an influence on EEG functioning of children with ADHD.

EEG results suggested that theta/beta and theta/SMR ratios cannot differentiate between children with ADHD and normal children. Furthermore, theta/beta and theta/SMR ratios do not appear to reflect the level of attention and restlessness in an individual.

Moreover, EEG results suggested that alpha power cannot differentiate between children with ADHD and normal children.

When it was examined whether the stimulant prescribed, namely methylphenidate, can influence EEG functioning of children with ADHD it was found that methylphenidate causes a significant increase in high alpha power during focussed attention in children with ADHD, suggesting that methylphenidate increases the level of centering in these children. Furthermore, methylphenidate abolishes the alpha block from baseline to focussed attention in children with ADHD.

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Chapter 5

Conclusions

With regards to the heart rate variability (HRV) and skin conductivity analyses the questions we asked were:

Does baseline autonomic nervous system functioning of stimulant-free children with ADHD differ from that of normal children?

- Stimulant-free children with ADHD showed a baseline parasympathetic dominance of the autonomic balance when compared to controls. This parasympathetic dominance was found to occur as a result of parasympathetic over-activity as well as sympathetic under-activity.

Does the stimulant prescribed, namely methylphenidate, have an influence on baseline autonomic nervous system functioning of children with ADHD?

- Methylphenidate shifted the autonomic balance of children with ADHD towards normal levels, but indications are that a normal autonomic balance was not reached in these children.

Does autonomic nervous system functioning during focussed attention differ between stimulant-free children with ADHD and normal children?

- Stimulant-free children with ADHD showed a parasympathetic dominance of the autonomic balance during focussed attention when compared to controls.

This parasympathetic dominance was due to parasympathetic over-activity as well as sympathetic under-activity.

Does the autonomic response to focussed attention (difference between baseline and focussed attention) differ between stimulant-free children with ADHD and normal children?

- Controls and stimulant-free children with ADHD both demonstrated a shift in the sympathovagal balance towards the sympathetic nervous system from baseline to focussed attention.

Does the stimulant prescribed, namely methylphenidate, have an influence on autonomic nervous system functioning during focussed attention in children with ADHD?

- Methylphenidate shifted the autonomic balance of children with ADHD towards normal levels, but indications are that a normal autonomic balance was not reached in these children.

Does the stimulant prescribed, namely methylphenidate, have an influence on the autonomic response to focussed attention (difference between baseline and focussed attention) in children with ADHD?

- Methylphenidate abolished the reactivity of the autonomic nervous system from baseline to focussed attention in children with ADHD.

With regards to the cardiac analyses the questions we asked were:

Does the autonomic nervous system functioning as reflected by blood pressure and ECG parameters of stimulant-free children with ADHD differ from that of normal children?

- Stimulant-free children with ADHD showed a parasympathetic dominance of the autonomic balance when compared to controls.

Does the stimulant prescribed, namely methylphenidate, have an influence on autonomic nervous system functioning as reflected by blood pressure and ECG parameters of children with ADHD?

- Methylphenidate results in an activation of the sympathetic nervous system in children with ADHD.

Does the stimulant prescribed, namely methylphenidate, adversely affect QTc, JTc and cardiac dispersion parameters of children with ADHD?

- Methylphenidate usage, in general, is not likely to result in QTc or JTc prolongation; however, it may cause QTc and JTc prolongation in susceptible individuals. Furthermore, methylphenidate usage does not appear to adversely affect cardiac dispersion parameters. These results suggest that methylphenidate does not adversely affect cardiac depolarization and repolarization and does not result in an increased risk of ventricular arrhythmias in children with ADHD.

With regards to EEG functioning, the questions we asked were:

Can theta/beta and theta/SMR ratios differentiate between children with ADHD and normal children?

- Theta/beta and theta/SMR ratios cannot differentiate between children with ADHD and normal children. Furthermore, theta/beta and theta/SMR ratios do not appear to reflect the level of attention and restlessness in an individual.

Can alpha power differentiate between children with ADHD and normal children?

- Alpha power cannot differentiate between children with ADHD and normal children.

Does the stimulant prescribed, namely methylphenidate, influence EEG functioning of children with ADHD?

- Methylphenidate causes a significant increase in high alpha power during focussed attention in children with ADHD, suggesting that methylphenidate increases the level of centering in these children.
- Methylphenidate abolishes the alpha block from baseline to focussed attention in children with ADHD.

Recommendations for future studies:

- Larger groups of children should be used.
- Tests should be performed on children with ADHD prior to their inclusion in the study in order to exclude children with learning disabilities that might have been misdiagnosed as ADHD, as well as children with co-morbidities such as conduct disorder.
- Cardiovascular function of children with ADHD should be assessed at rest and during the exercise stress test. In other words, the effect of methylphenidate on cardiovascular functioning should be assessed during a stress ECG. This is of particular importance as the results of this study suggest that the stress response of children with ADHD is attenuated by methylphenidate.
- In this study it was found that methylphenidate affects cardiovascular function in only a few individuals. It is likely that a larger study group will be able to identify more children whose cardiovascular function is affected by methylphenidate. It would then be important to assess such individuals for the possible presence of channelopathies as indications are that there may be a link between ADHD and cardiac channelopathies.
- Cognitive function and emotional responses should also be tested, both while the ADHD children are stimulant-free and while they are on stimulant medication, so that the effect of the stimulant can be assessed in an objective manner. Although a variety of tests should be used it would be of interest to see whether centering and inner awareness, as well as the alpha block, are indeed influenced by

methylphenidate in the manner suggested by the preliminary EEG results of this study.

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Appendix A

PARTICIPANT HRV EXPERIMENTAL DATA

Controls

Subject 21 Baseline

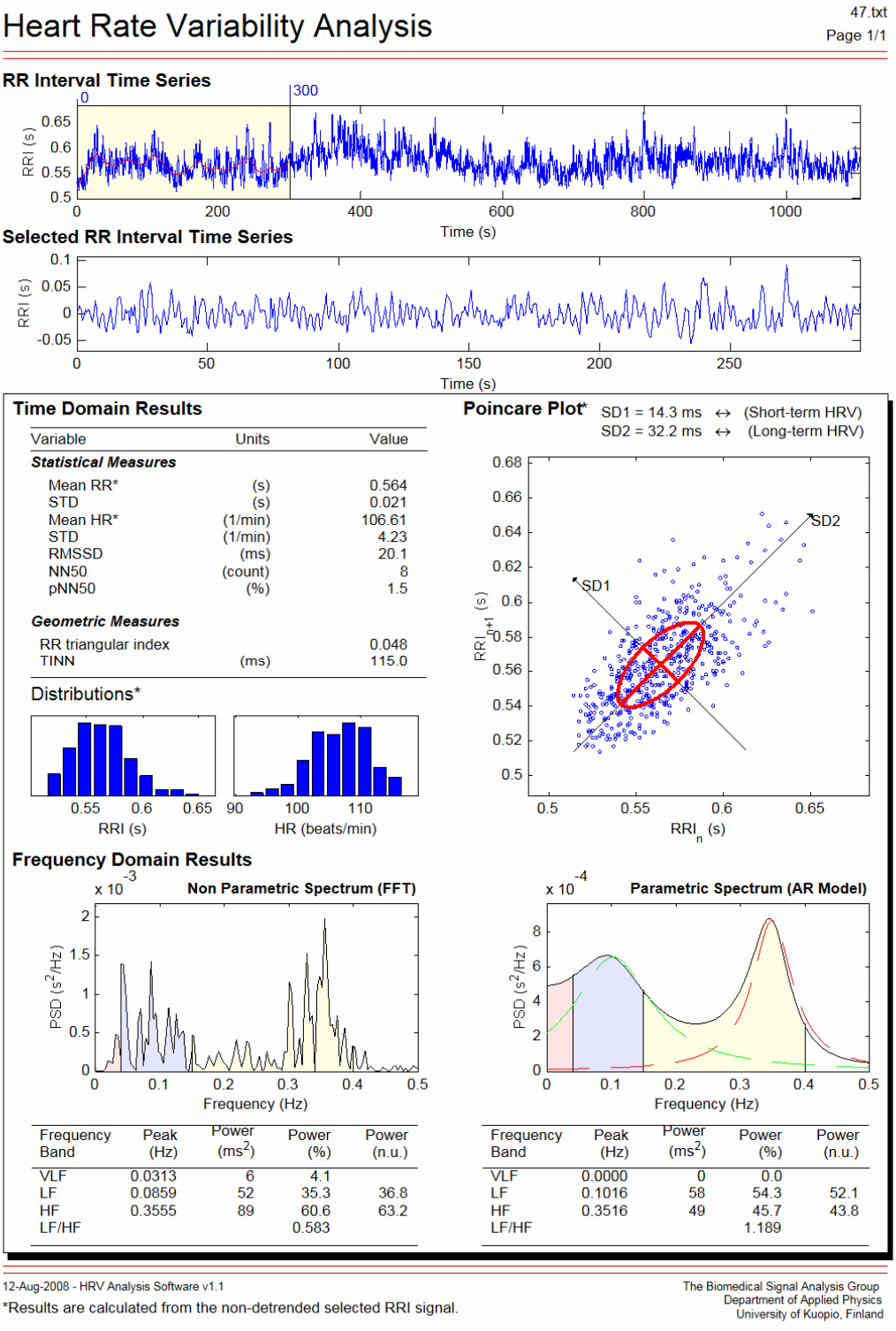

Figure A-1: Baseline HRV data for control subject 21

Subject 21 Focussed attention

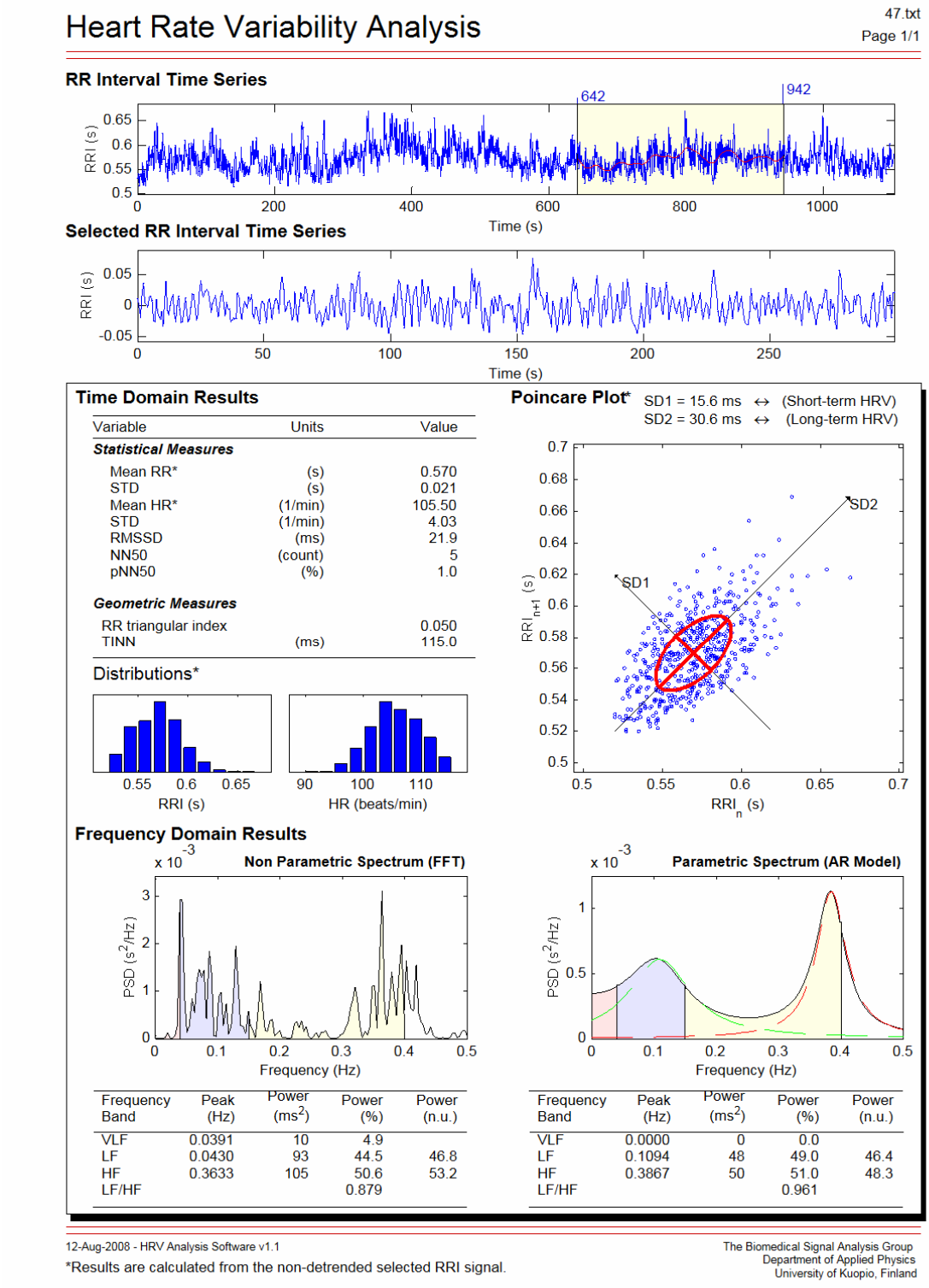

Figure A-2: HRV data during focused attention for control subject 21

Subject 22 Baseline

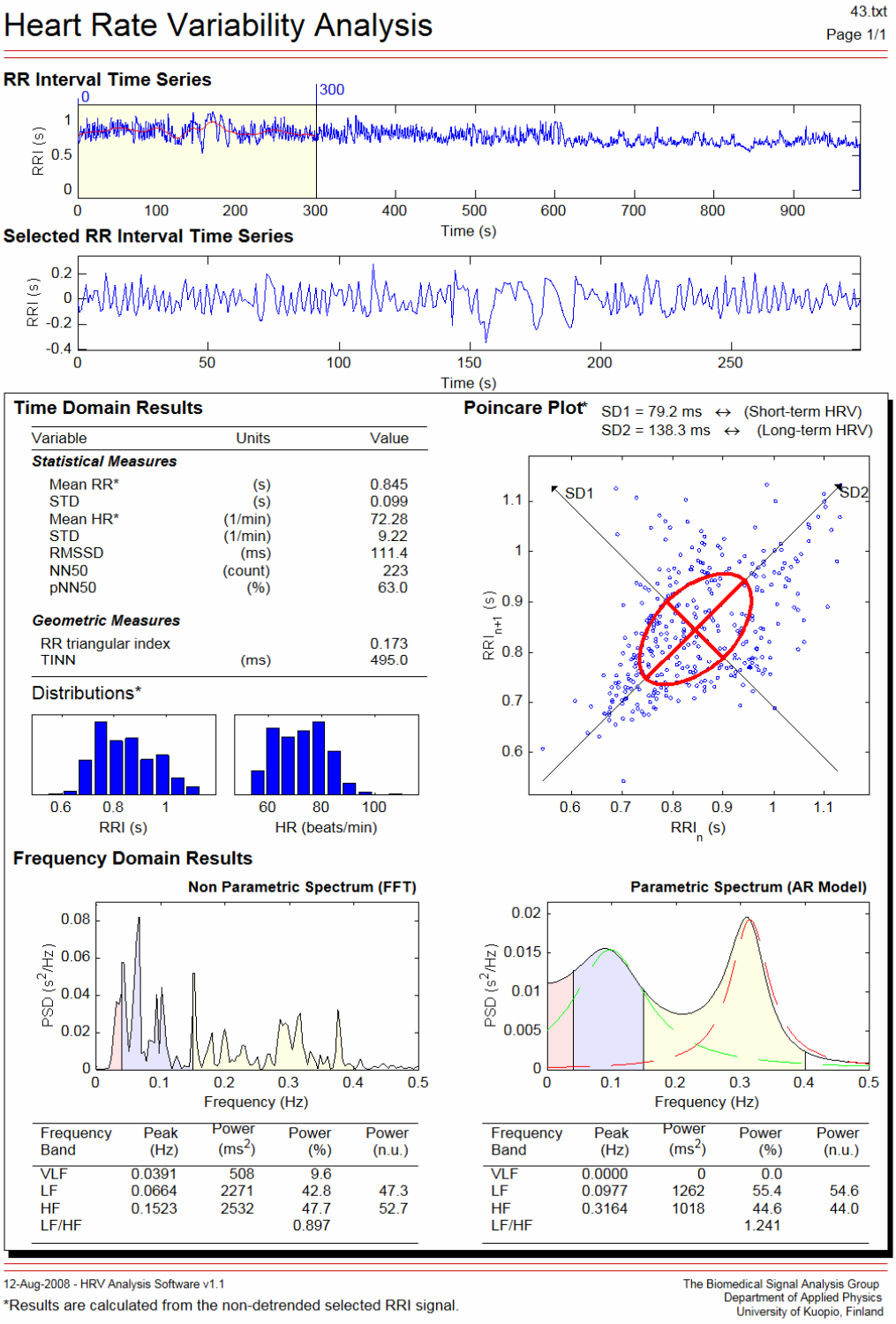

Figure A-3: Baseline HRV for control subject 22

Subject 22 Focussed attention

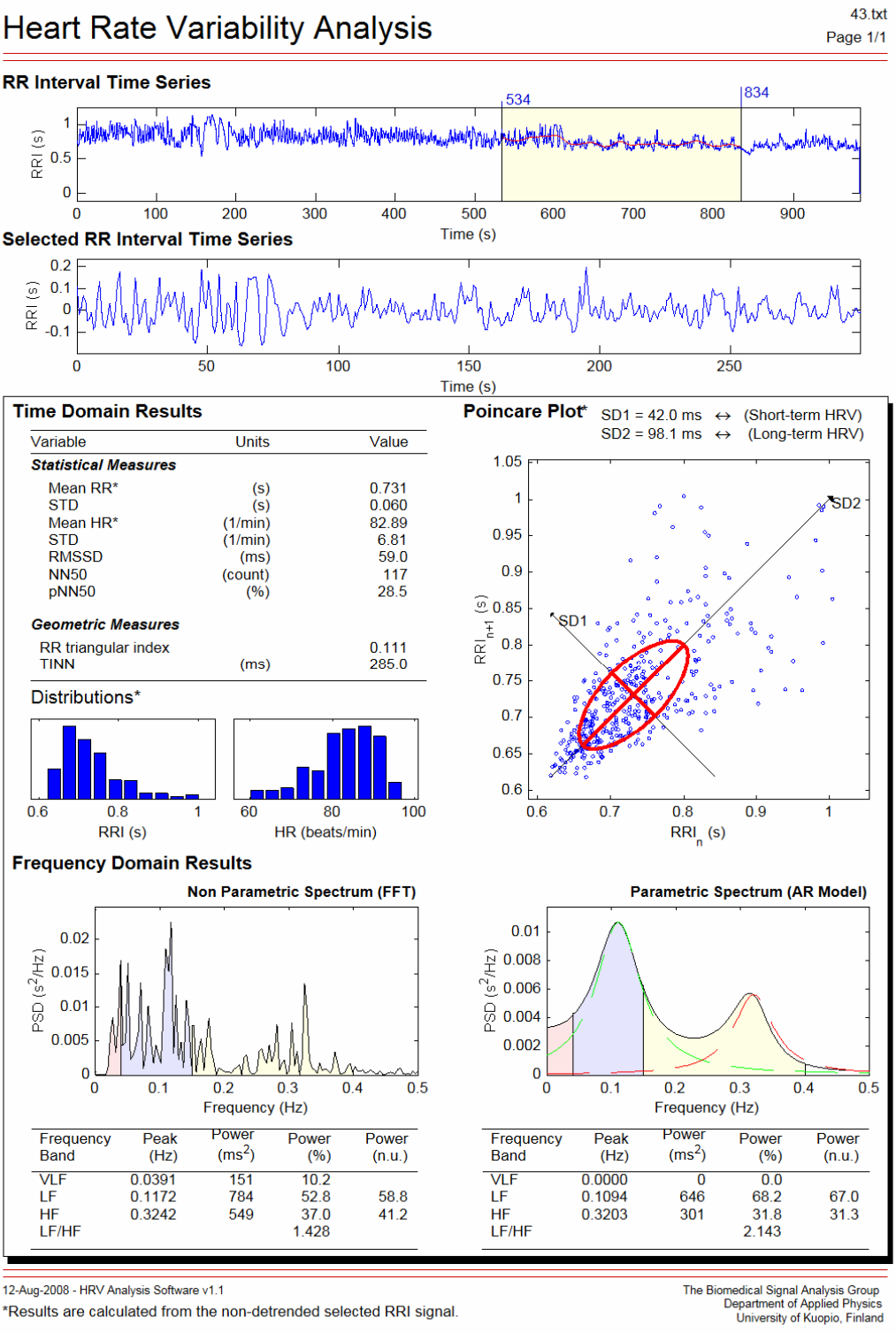

Figure A-4: HRV data during focussed attention for control subject 22

Subject 23 Baseline

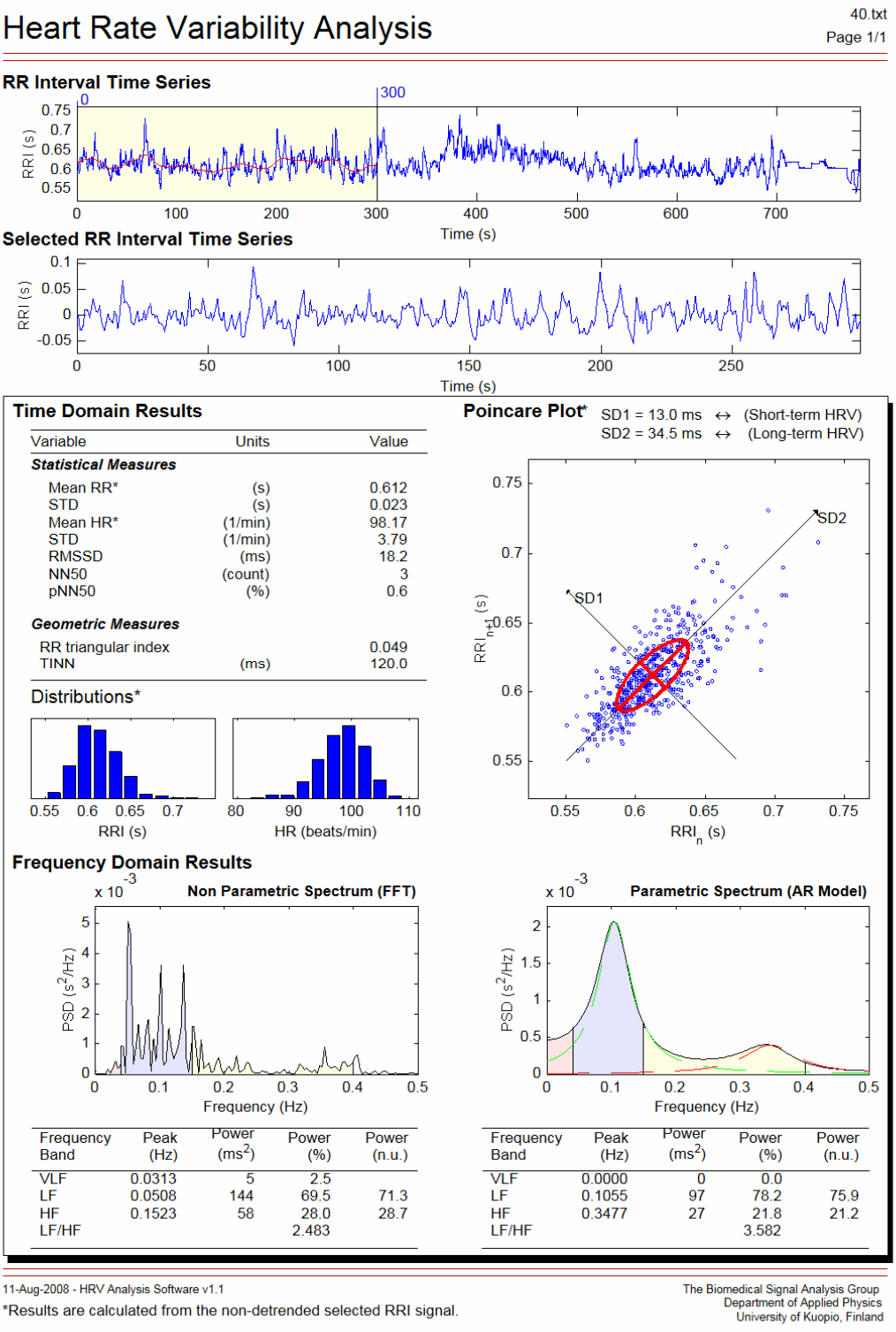

Figure A-5: Baseline HRV data for control subject 23

Subject 23 Focussed attention

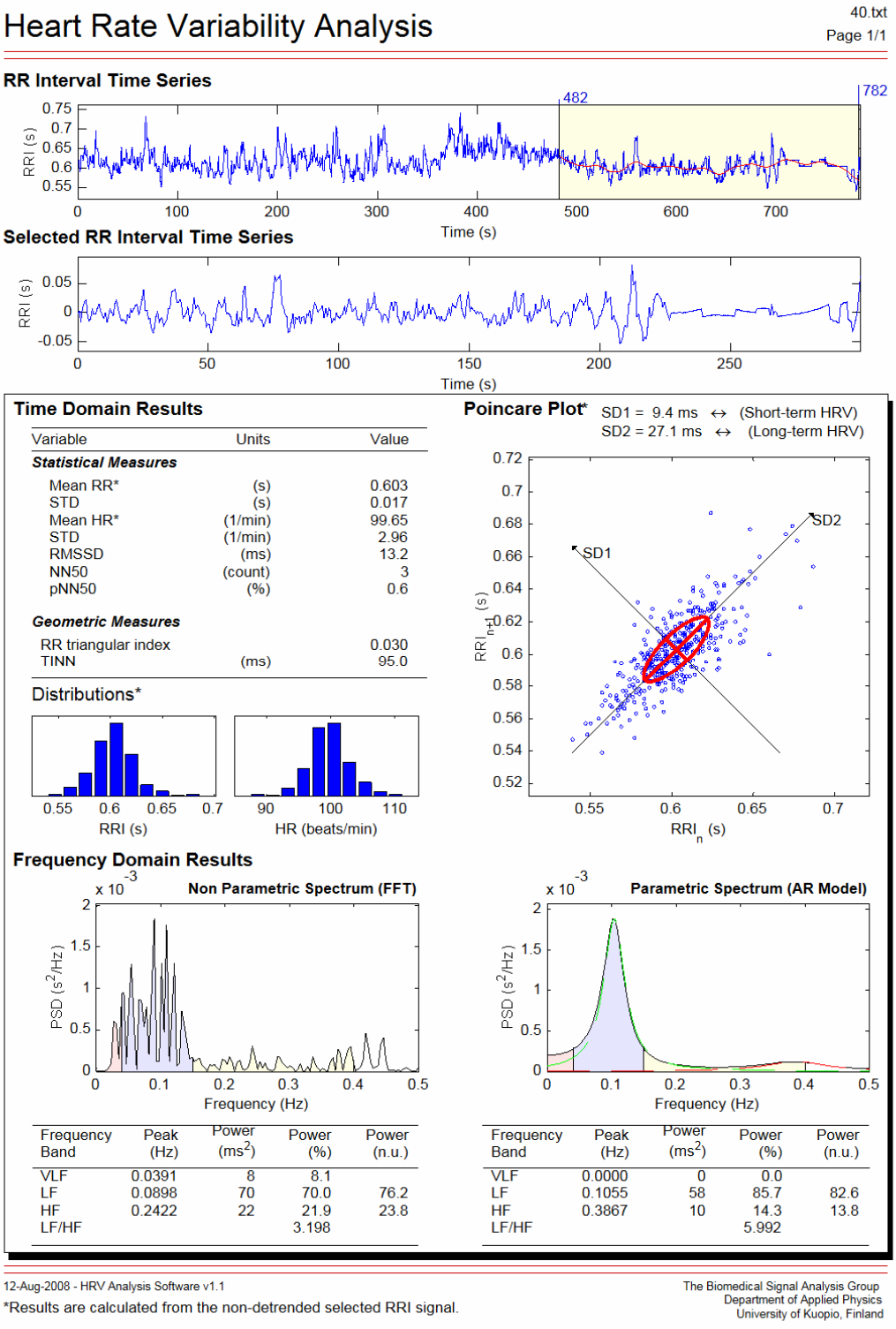

Figure A-6: HRV data during focussed attention for control subject 23

Subject 24 Baseline

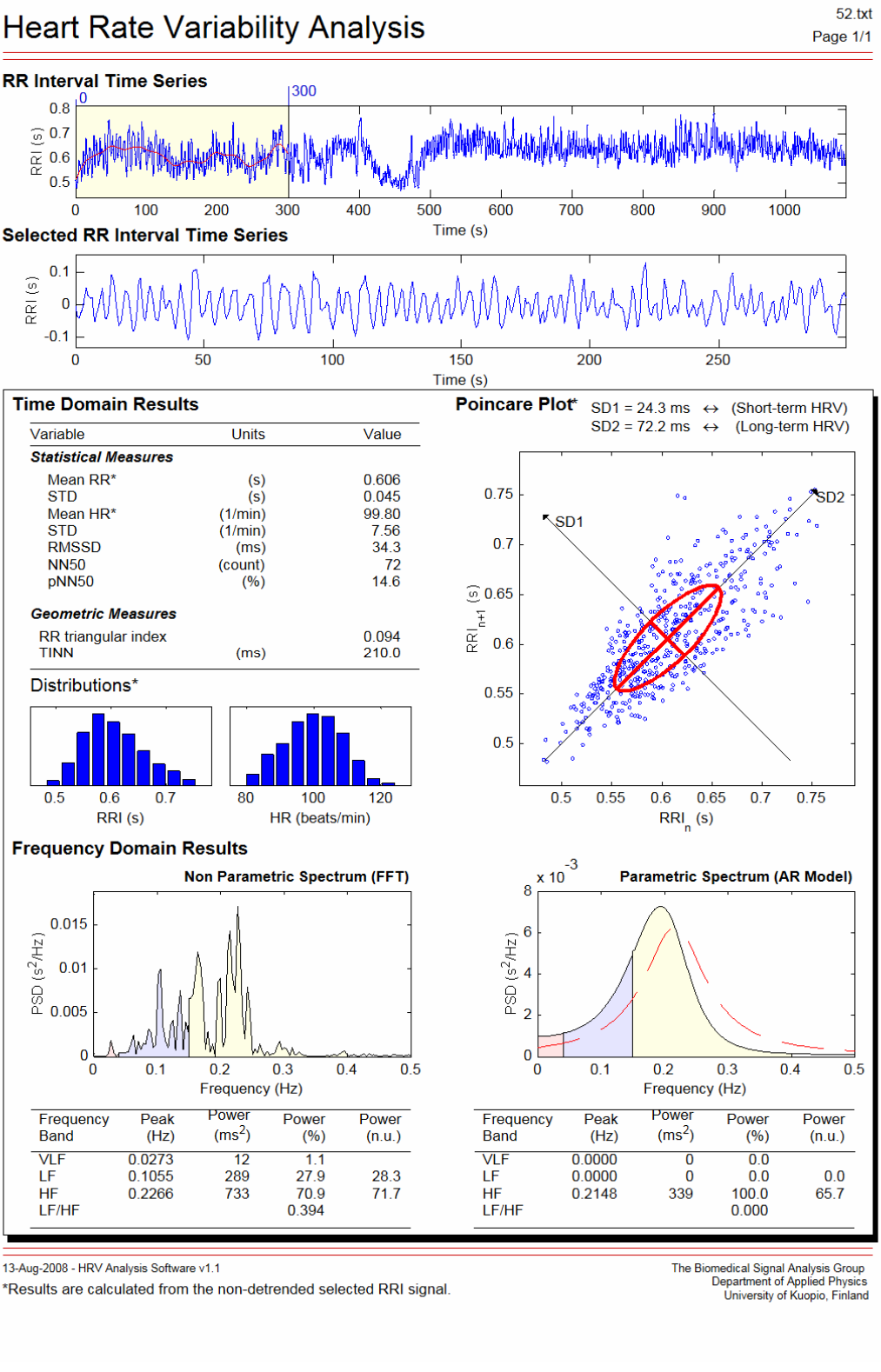

Figure A-7: Baseline HRV data for control subject 24

Subject 24 Focussed attention

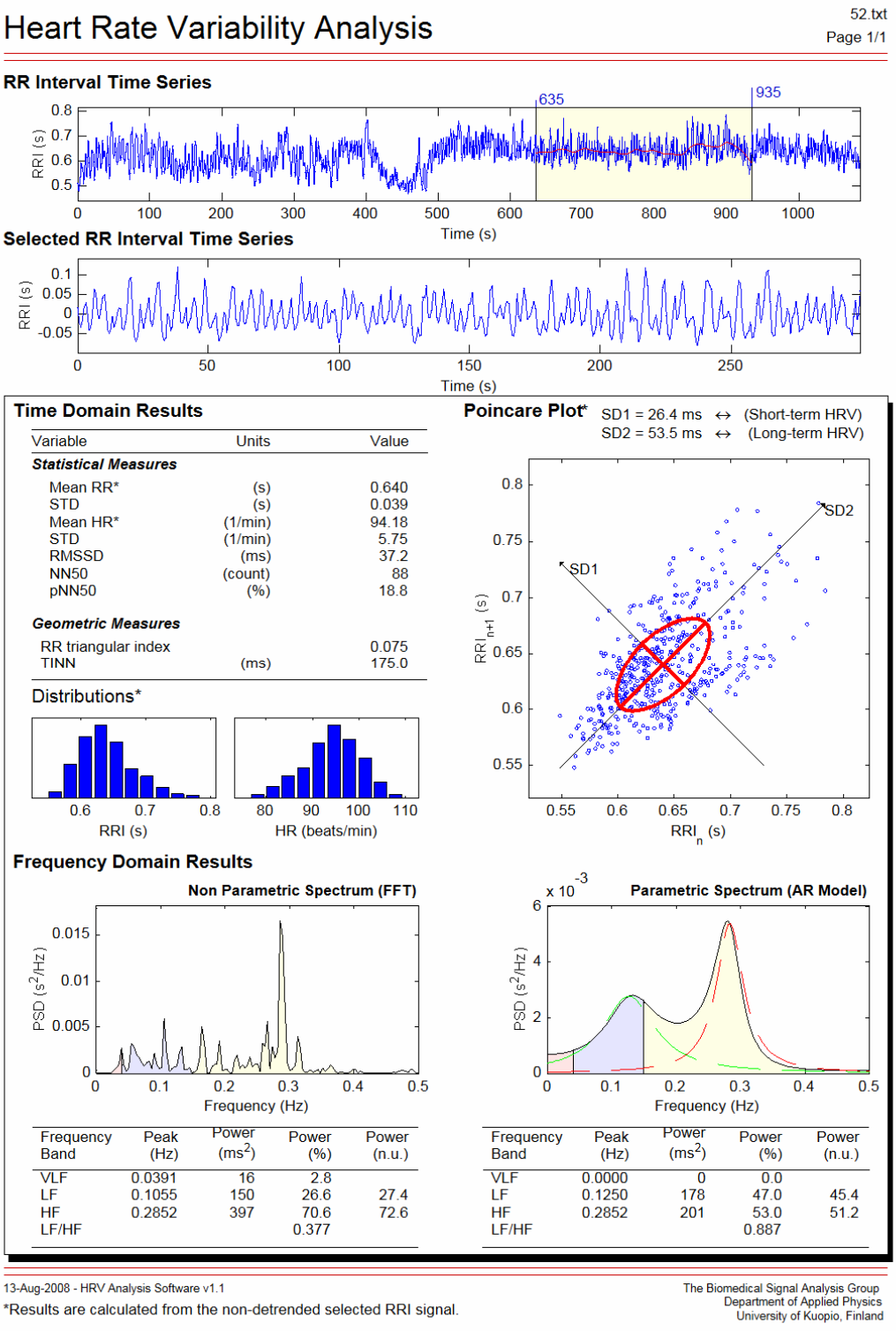

Figure A-8: HRV data during focussed attention for control subject 24

Subject 25 Baseline

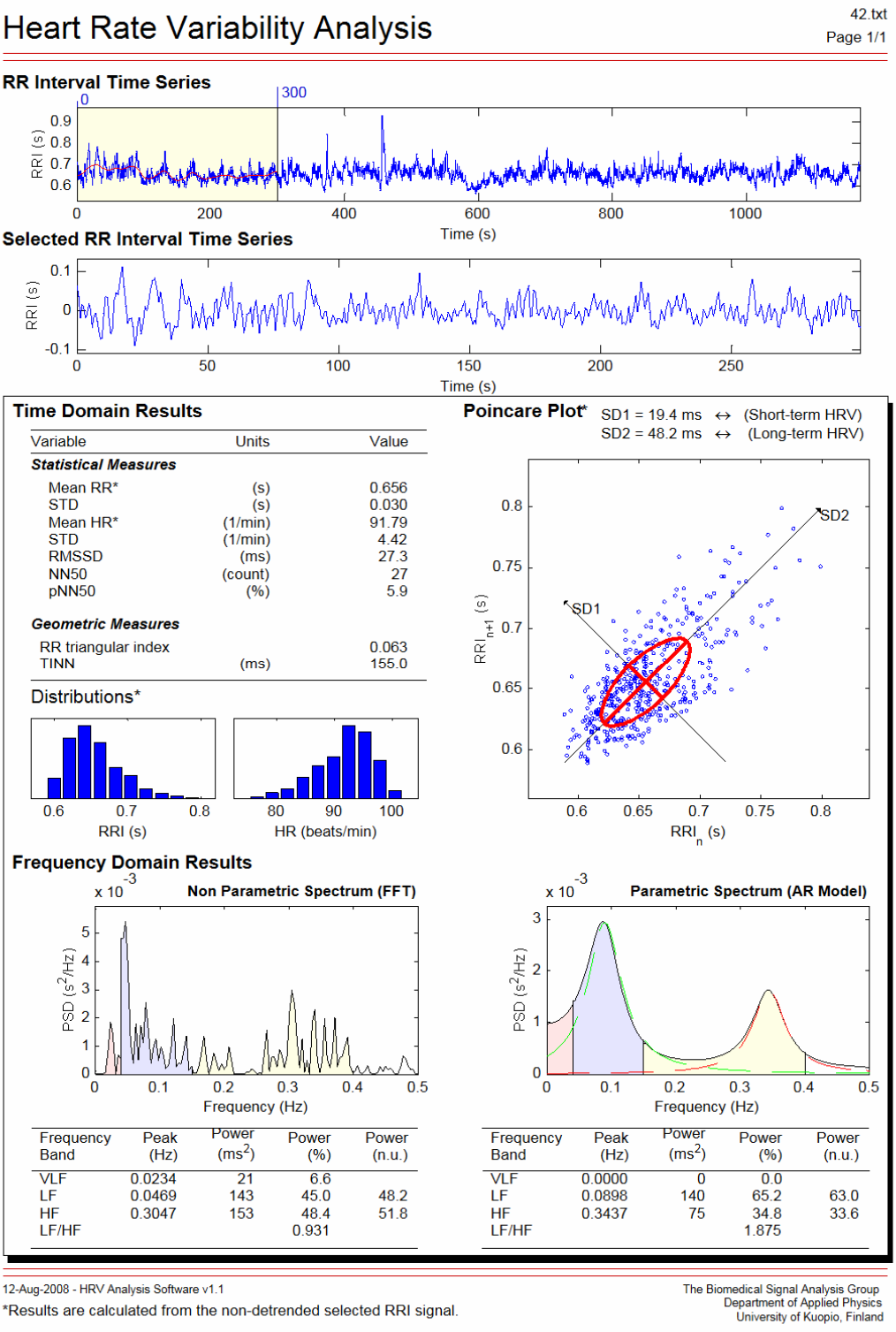

Figure A-9: Baseline HRV data for control subject 25

Subject 25 Focussed attention

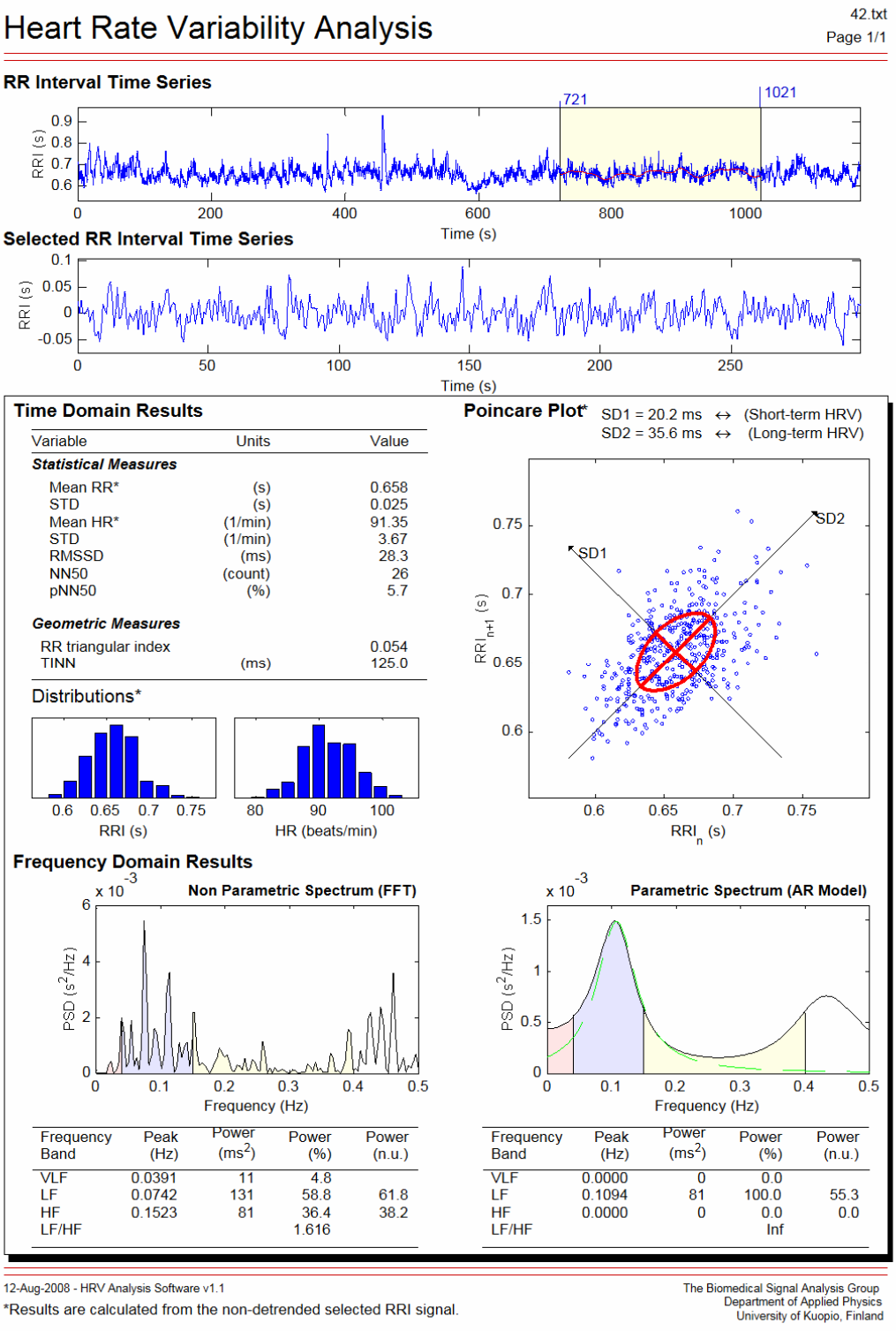

Figure A-10: HRV data during focussed attention for control subject 25

Subject 26 Baseline

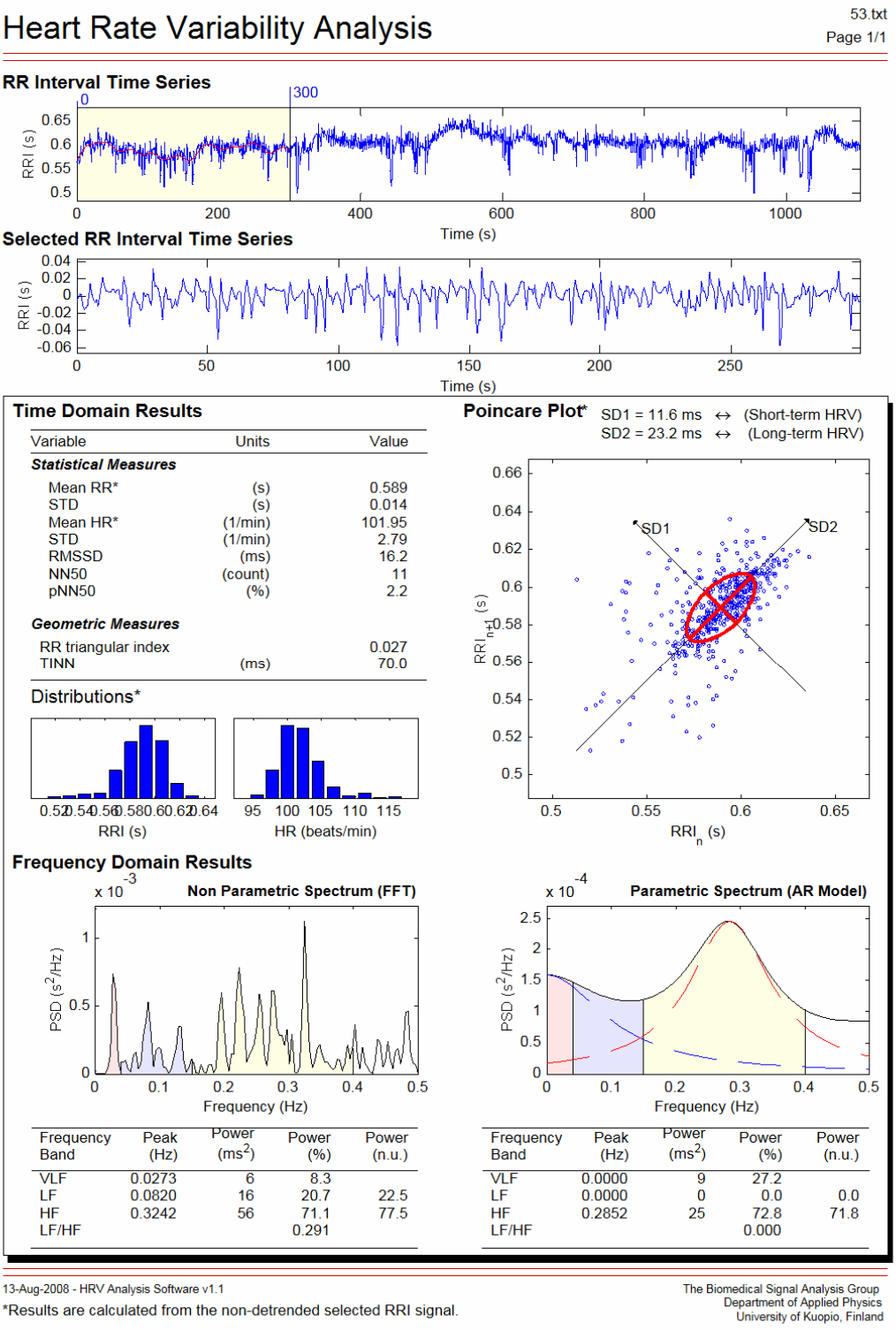

Figure A-11: Baseline HRV data for control subject 26

Subject 26 Focussed attention

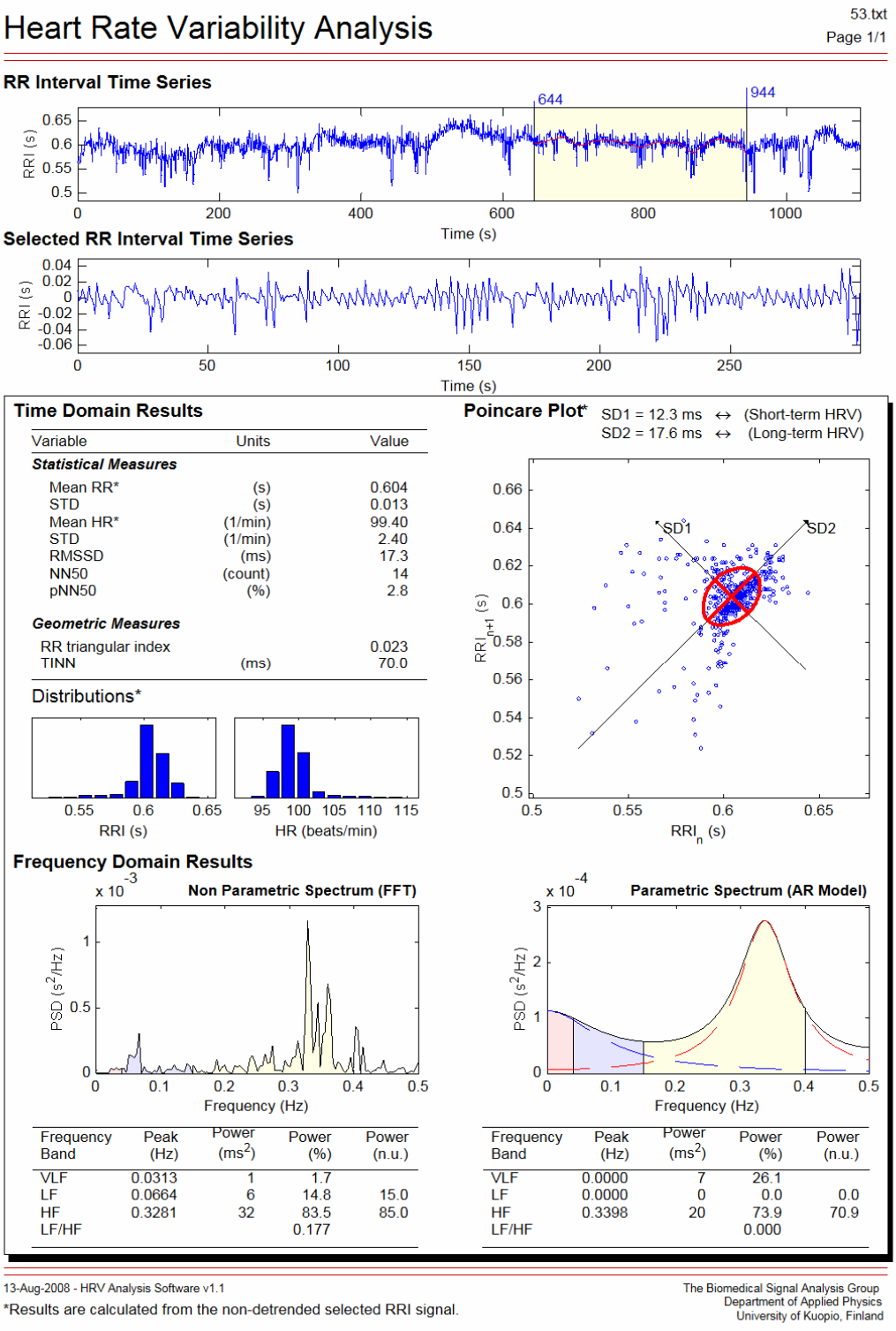

Figure A-12: HRV data during focused attention for control subject 26

Subject 27 Baseline

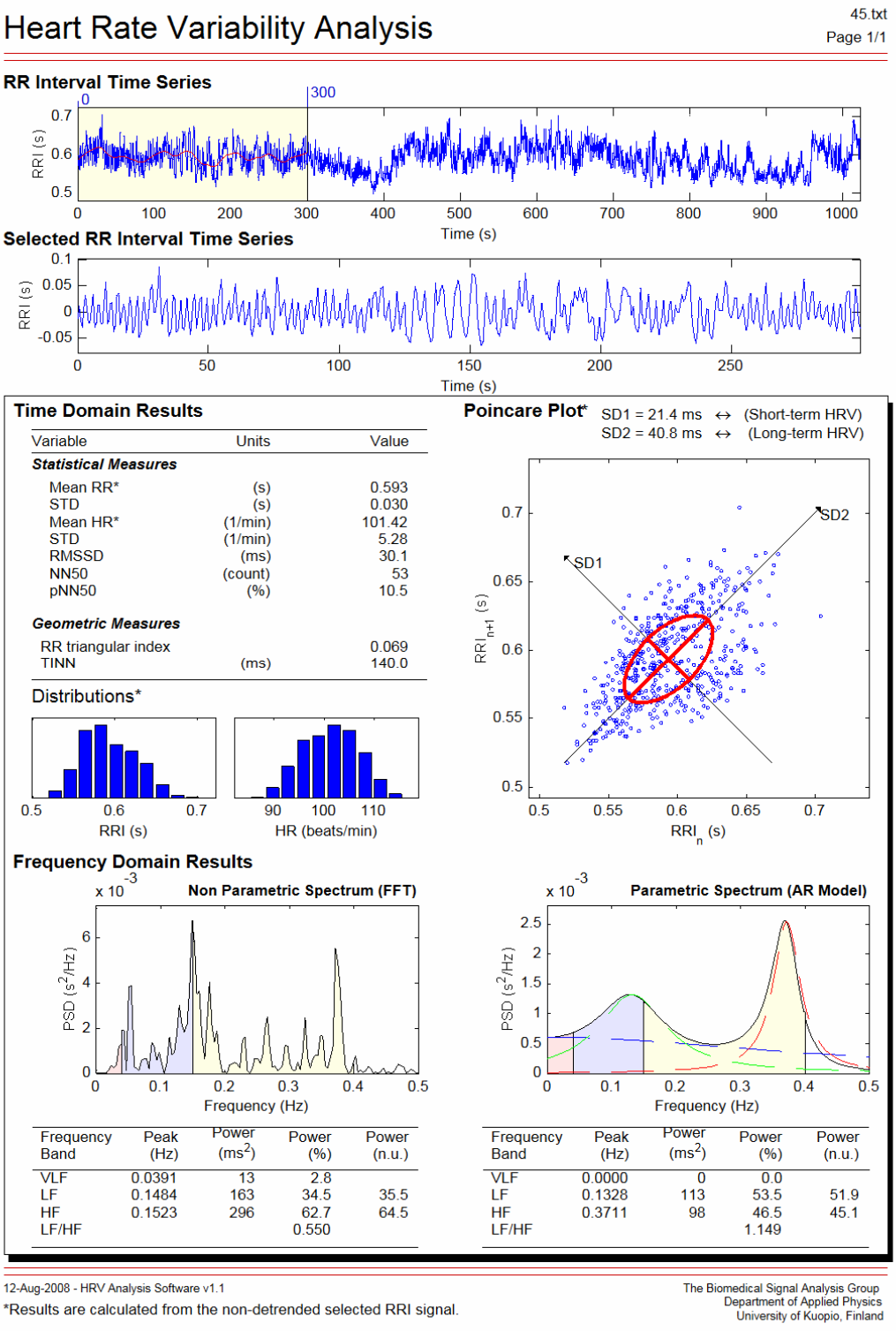

Figure A-13: Baseline HRV data for control subject 27

Subject 27 Focussed attention

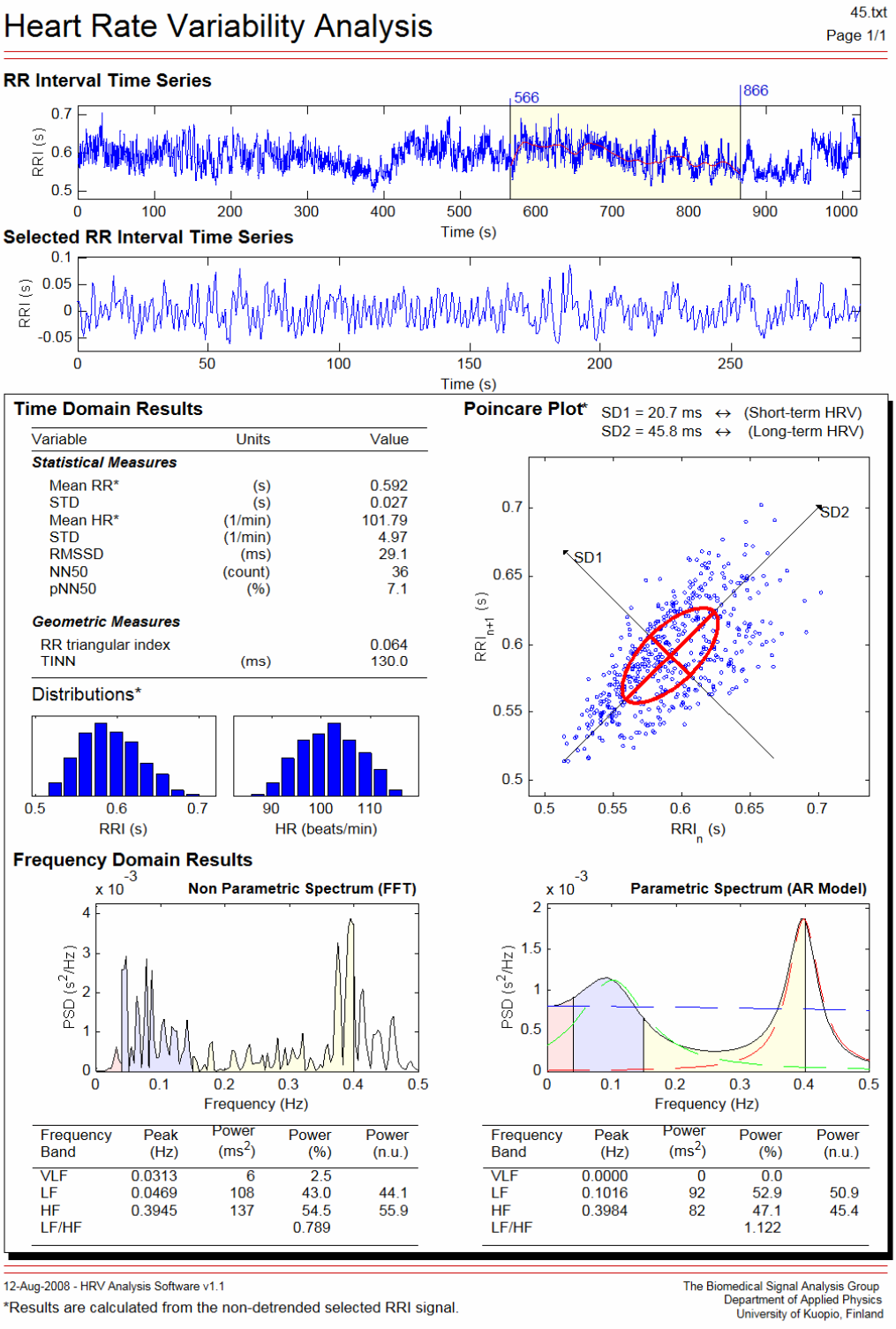

Figure A-14: HRV data during focussed attention for control subject 27

Subject 28 Baseline

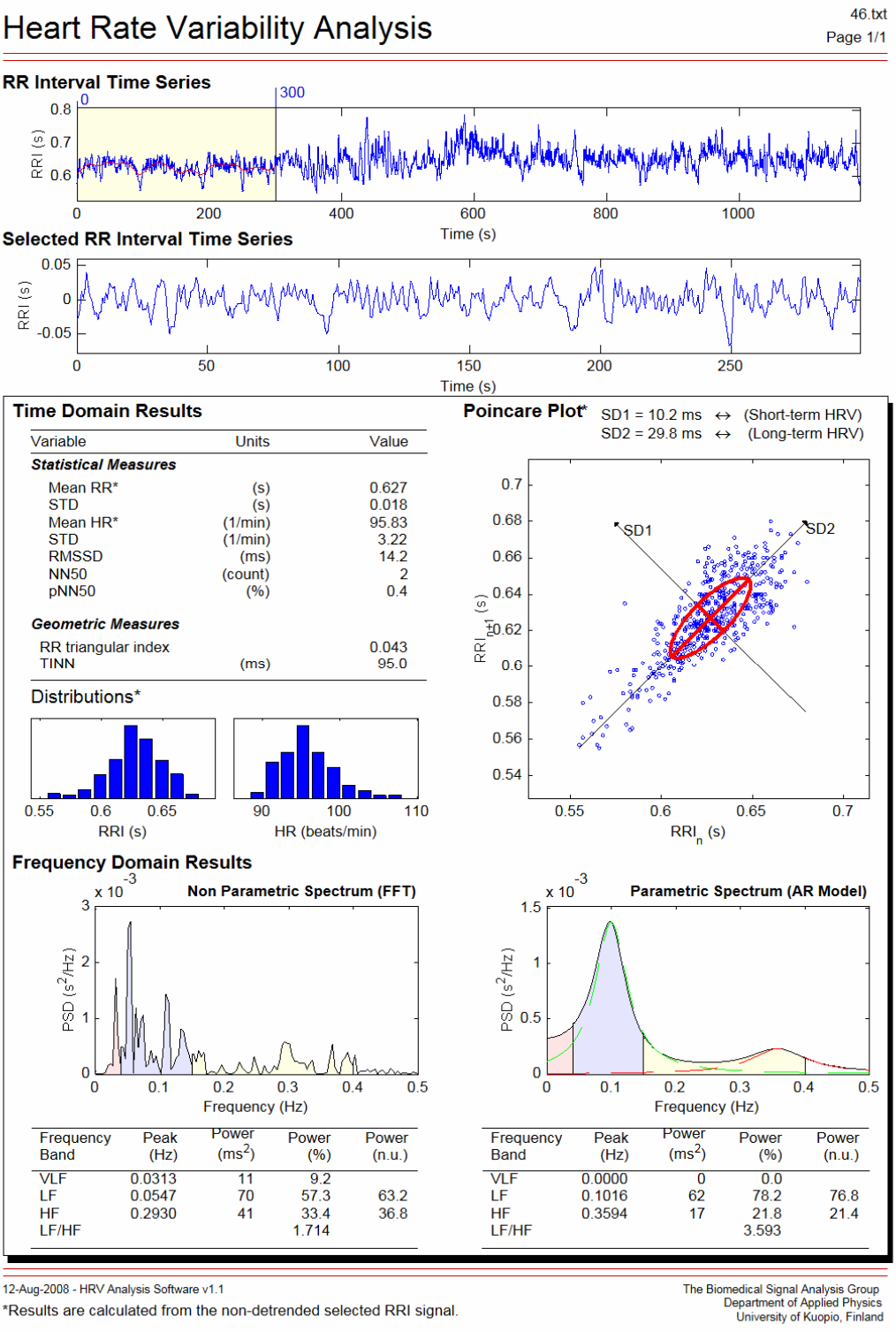

Figure A-15: Baseline HRV data for control subject 28

Subject 28 Focussed attention

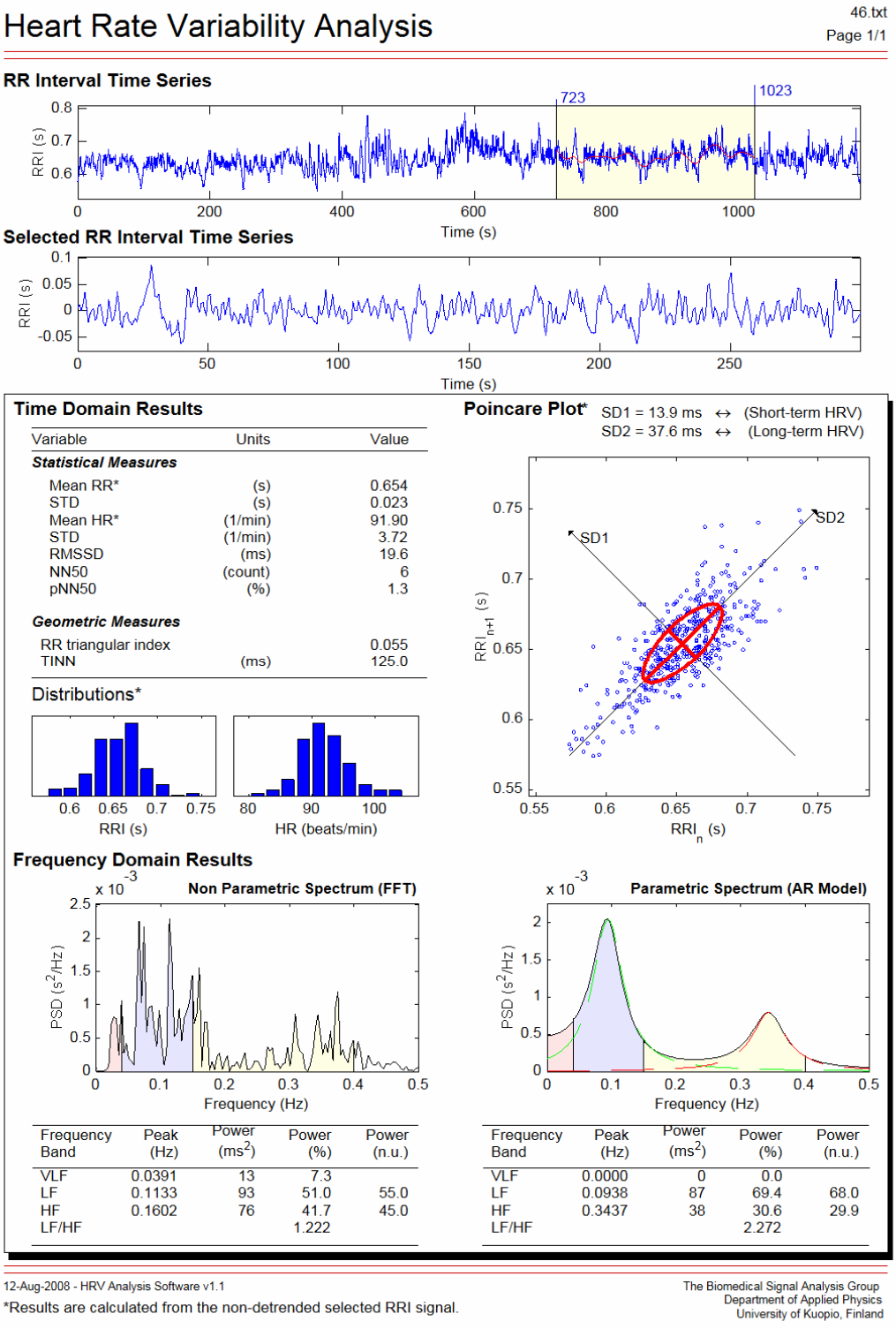

Figure A-16: HRV data during focussed attention for control subject 28

Subject 29 Baseline

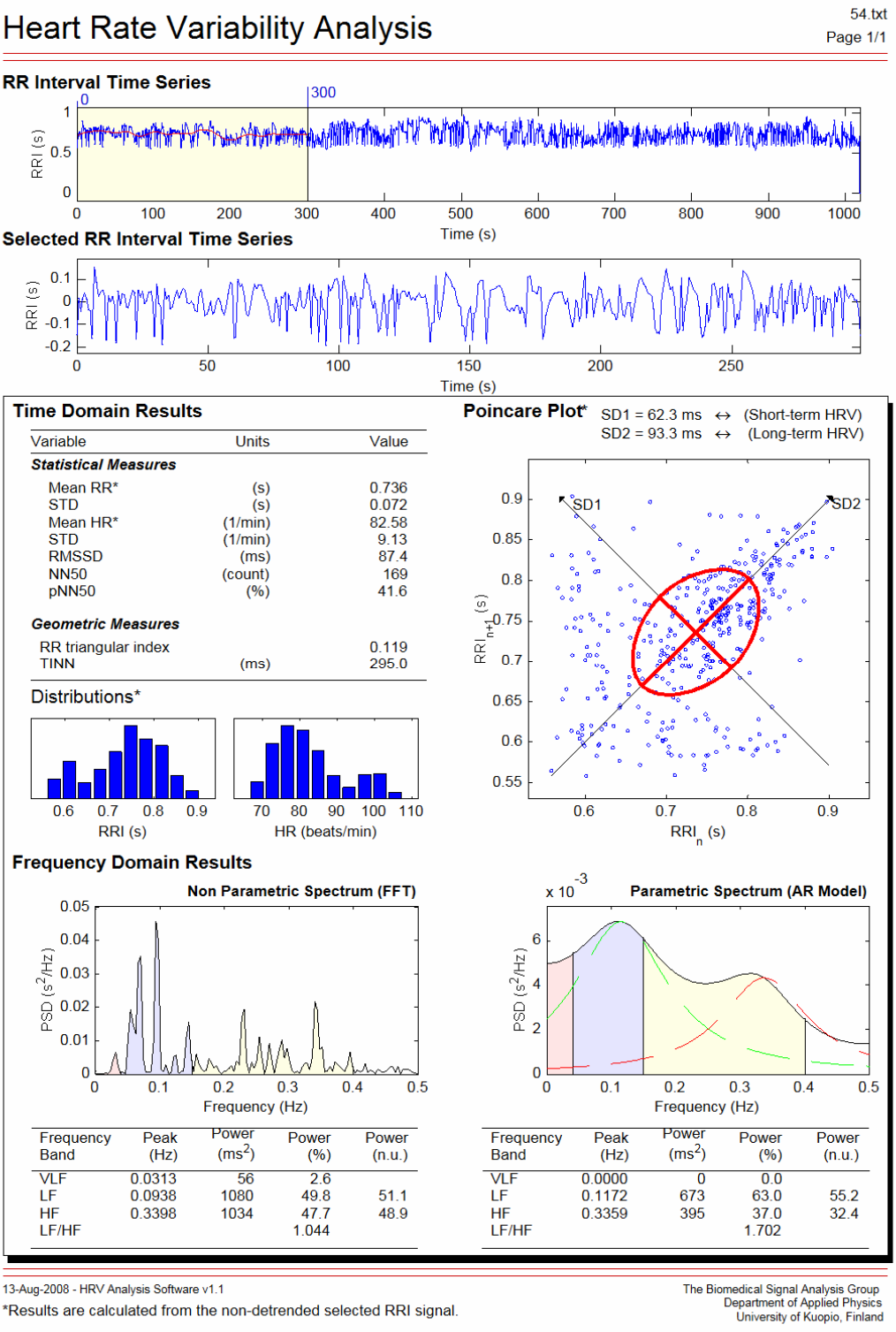

Figure A-17: Baseline HRV data for control subject 29

Subject 29 Focussed attention

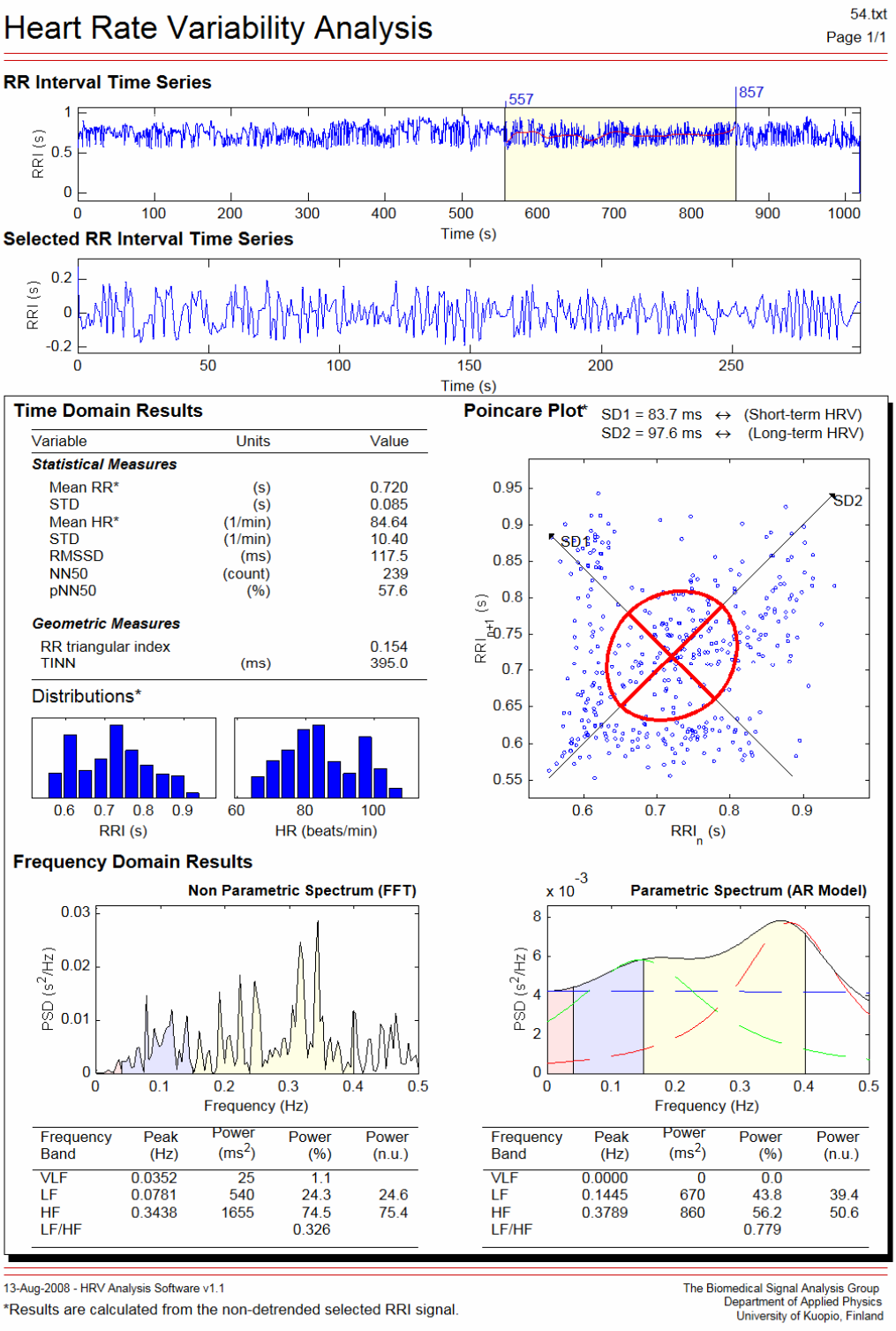

Figure A-18: HRV data during focussed attention for control subject 29

Subject 30 Baseline

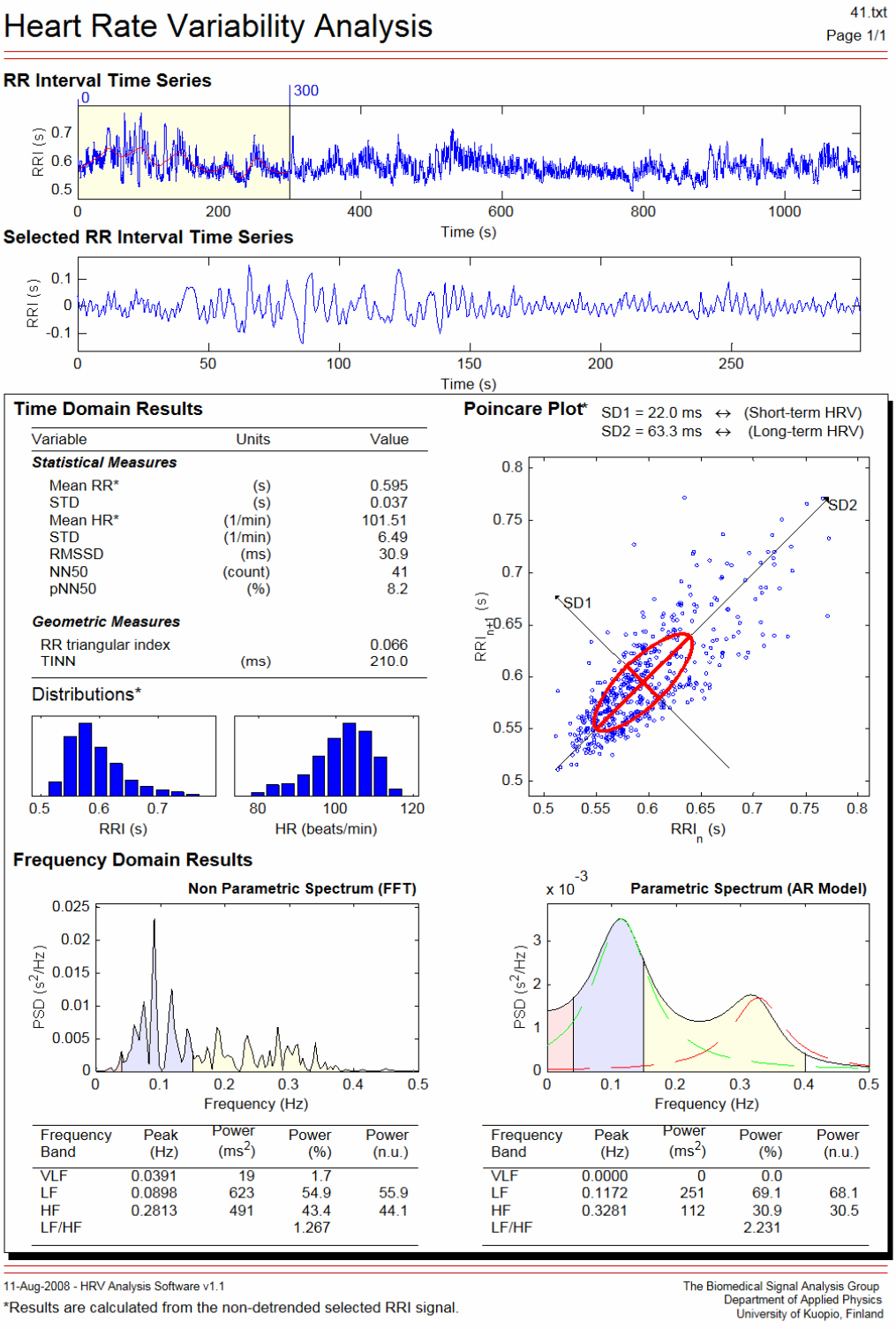

Figure A-19: Baseline HRV data for control subject 30

Subject 30 Focussed attention

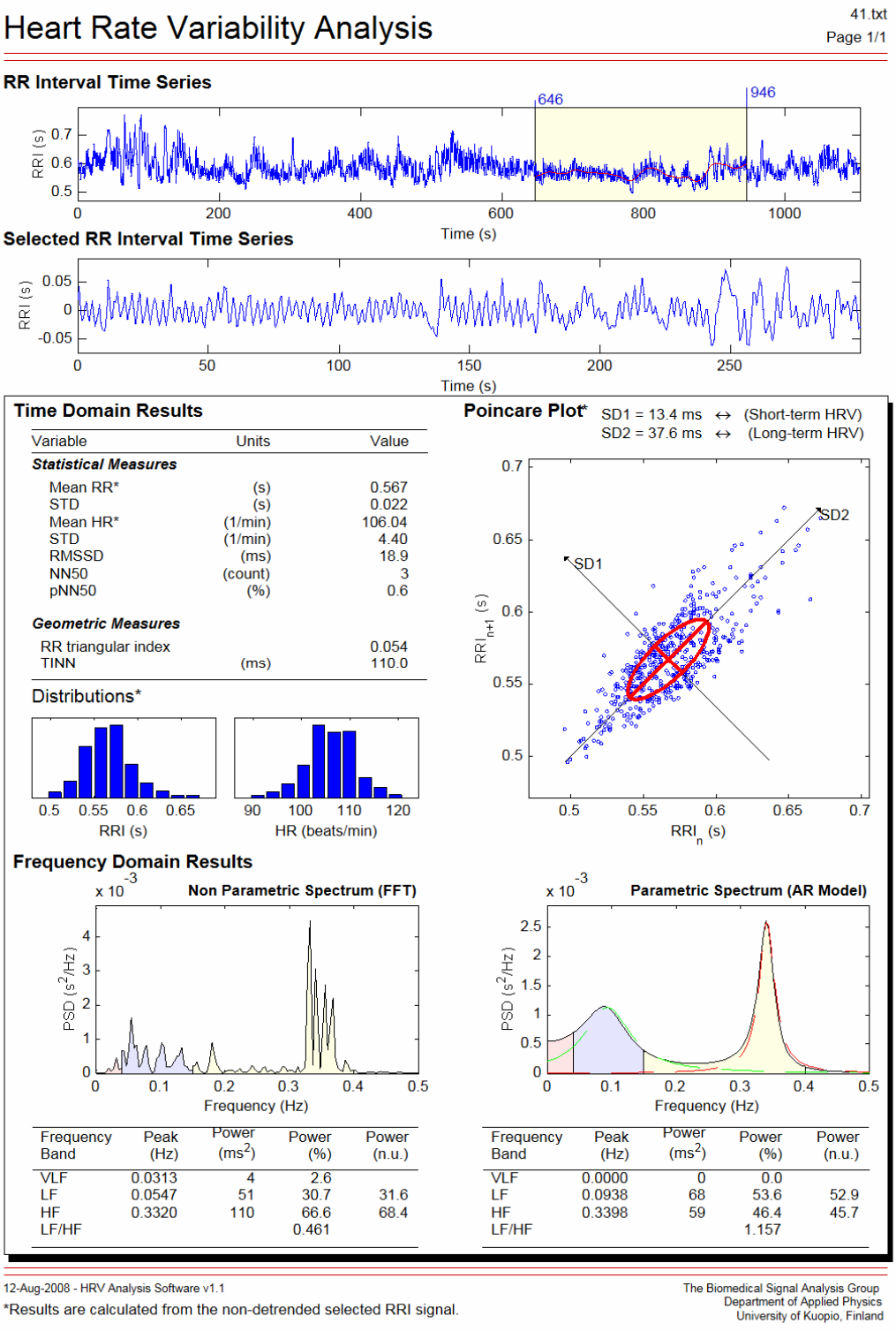

Figure A-20: HRV data during focussed attention for control subject 30

Subject 31 Baseline

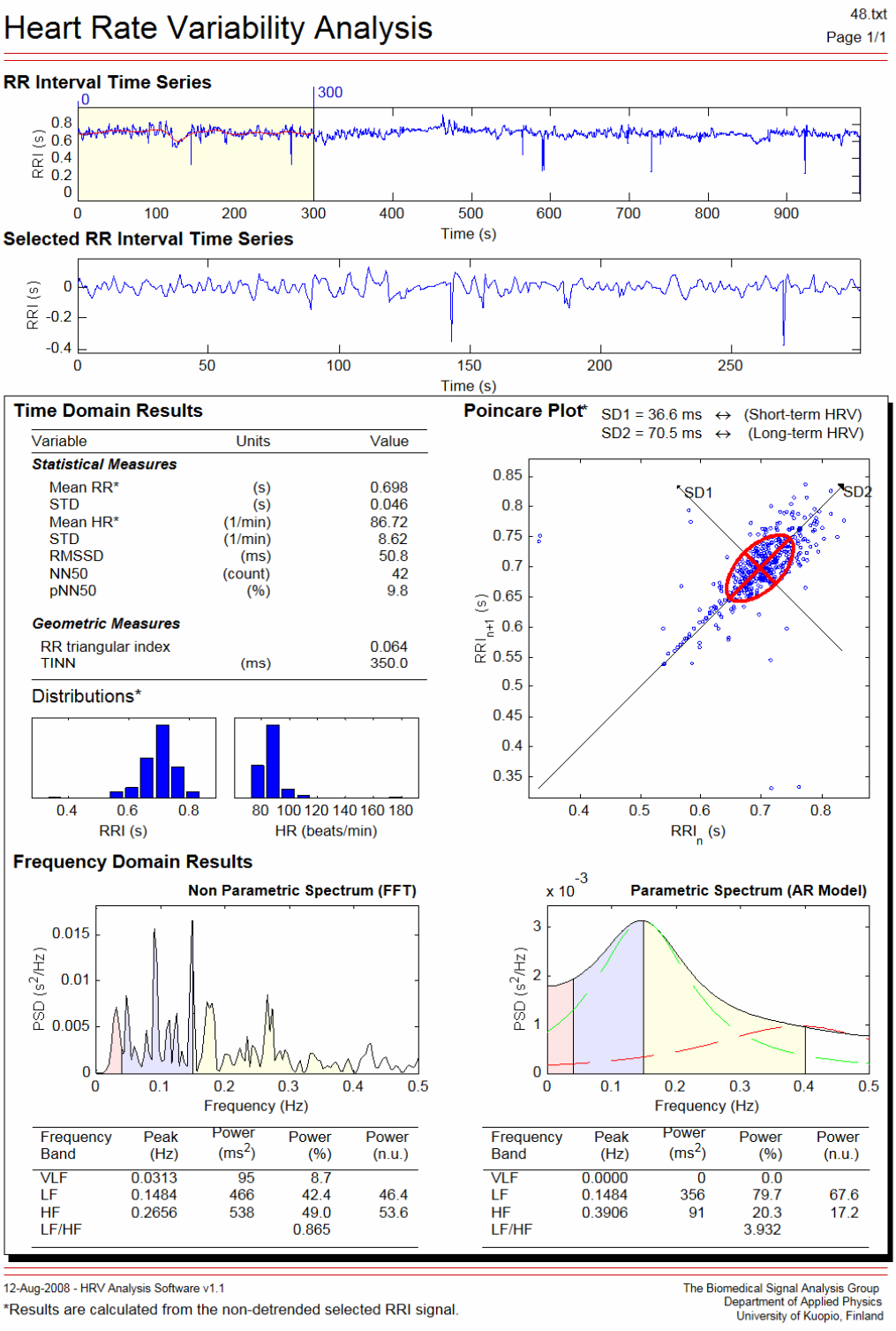

Figure A-21: Baseline HRV data for control subject 31

Subject 31 Focussed attention

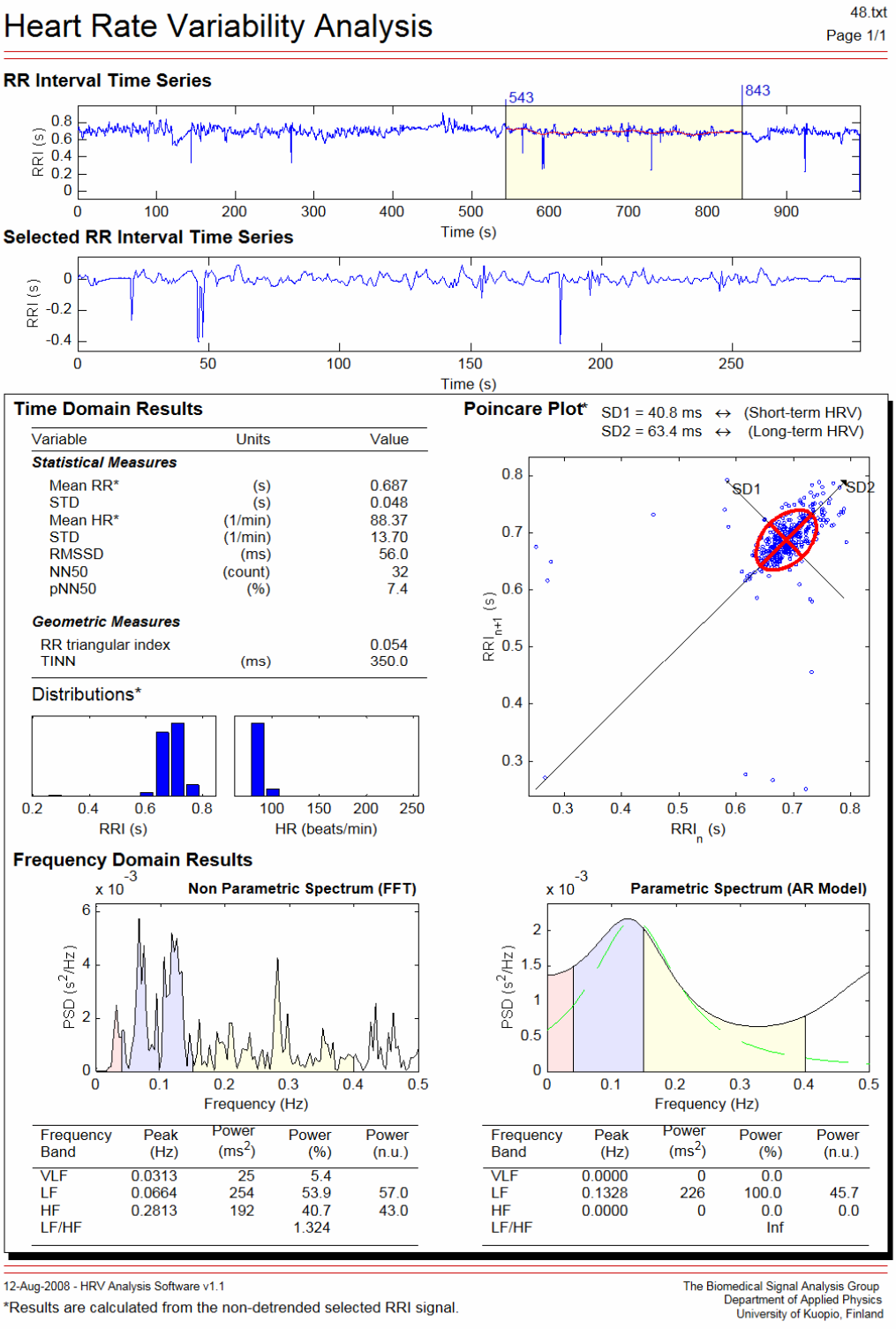

Figure A-22: HRV data during focussed attention for control subject 31

Subject 32 Baseline

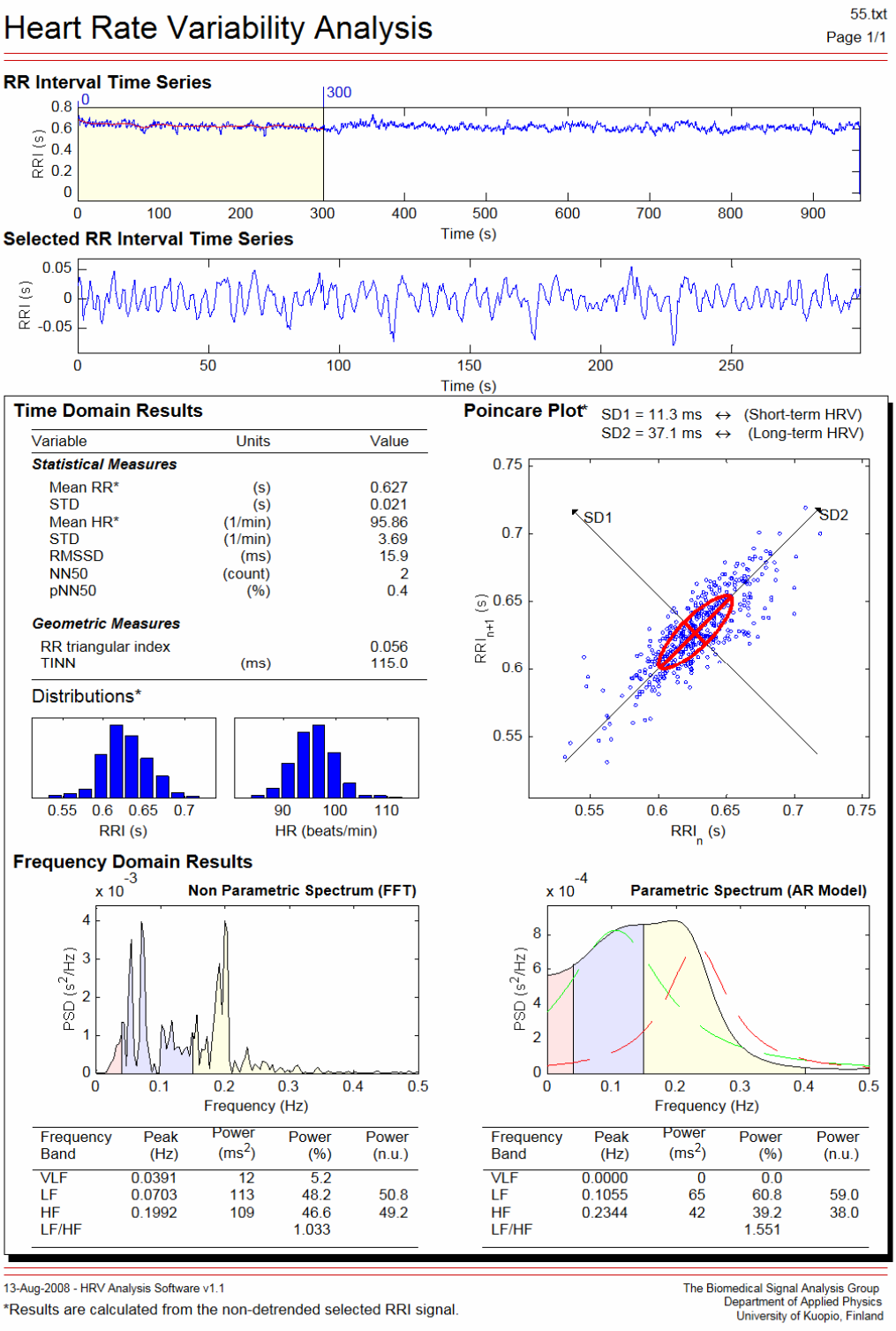

Figure A-23: Baseline HRV data for control subject 32

Subject 32 Focussed attention

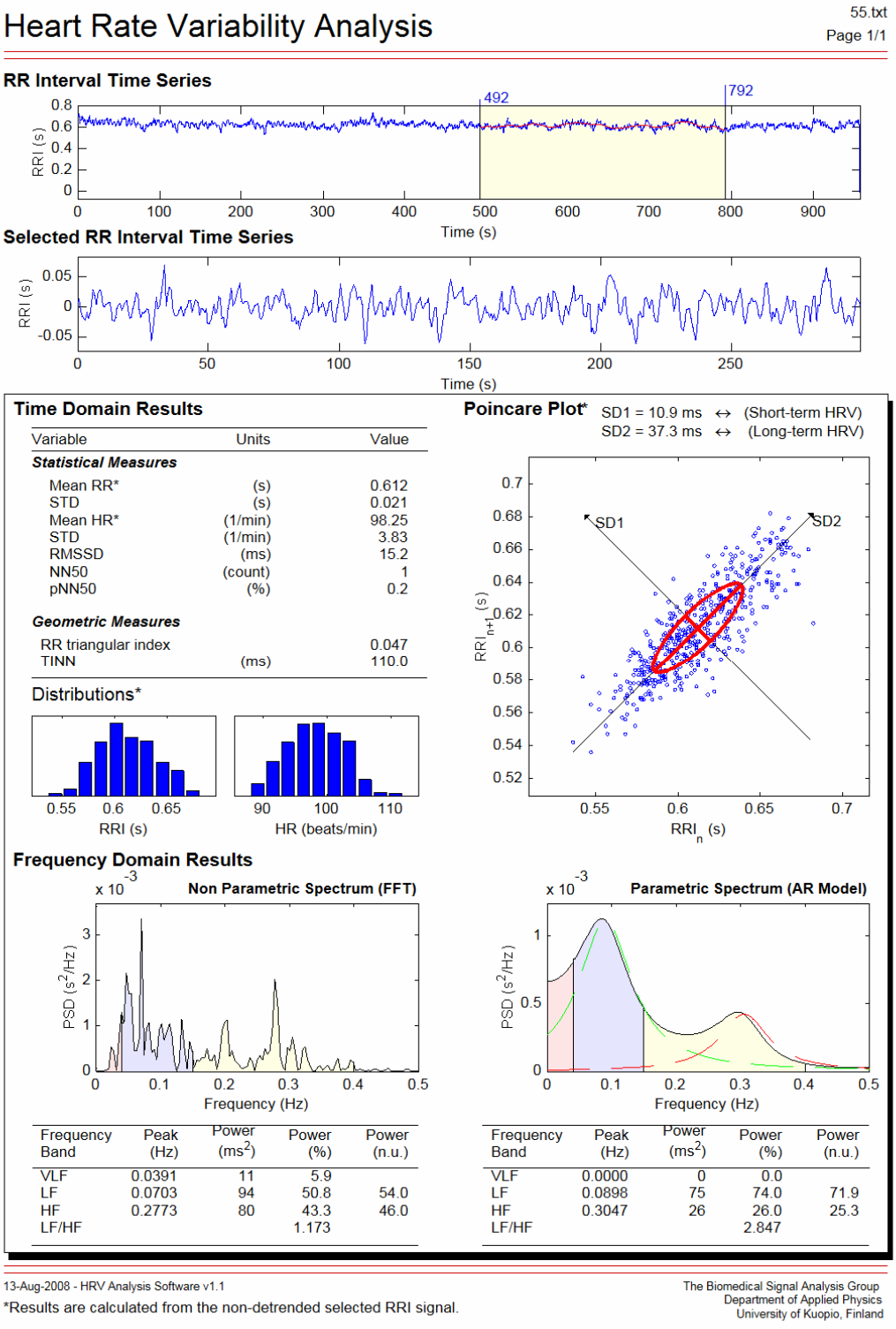

Figure A-24: HRV data during focussed attention for control subject 32

Subject 33 Baseline

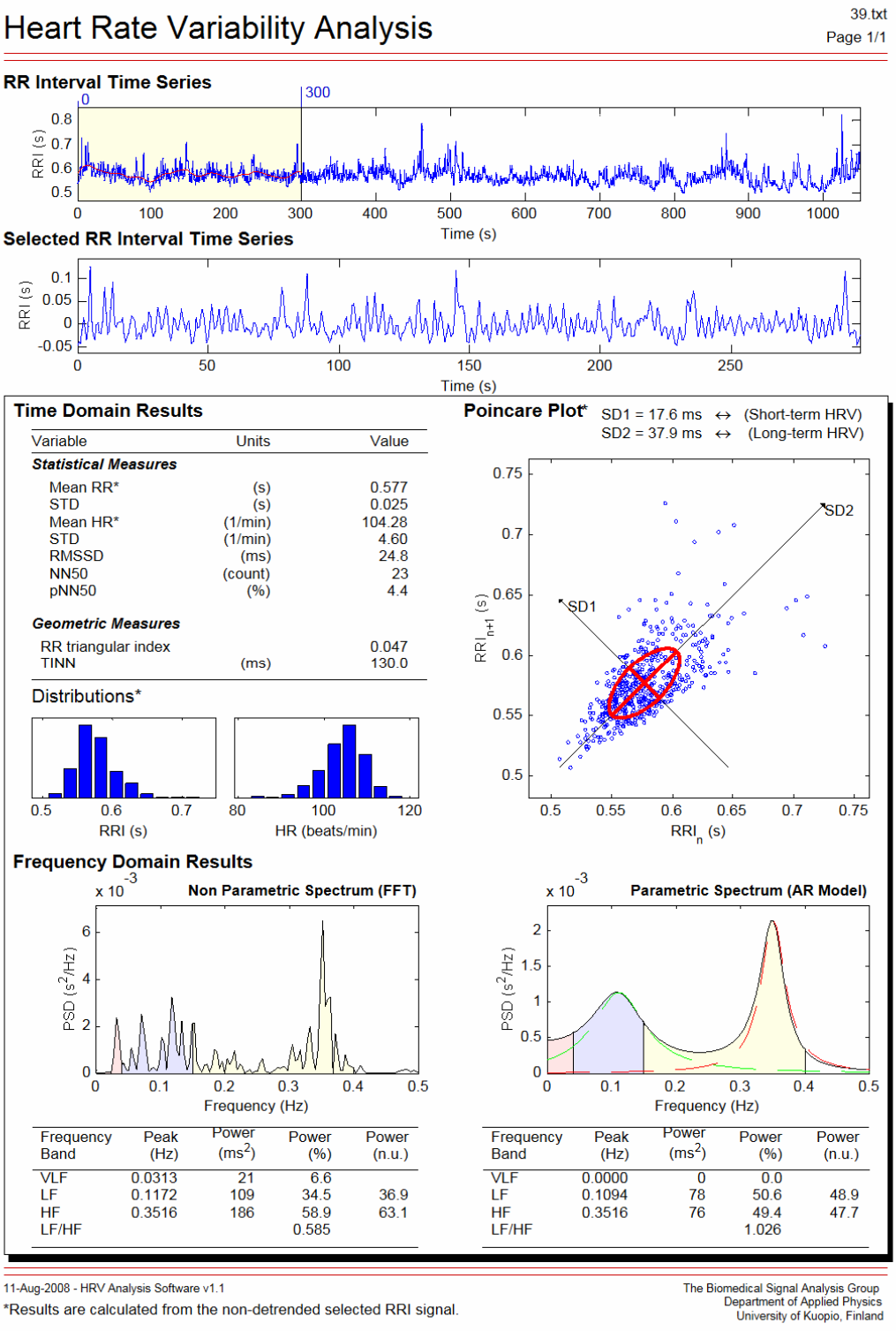

Figure A-25: Baseline HRV data for control subject 33

Subject 33 Focussed attention

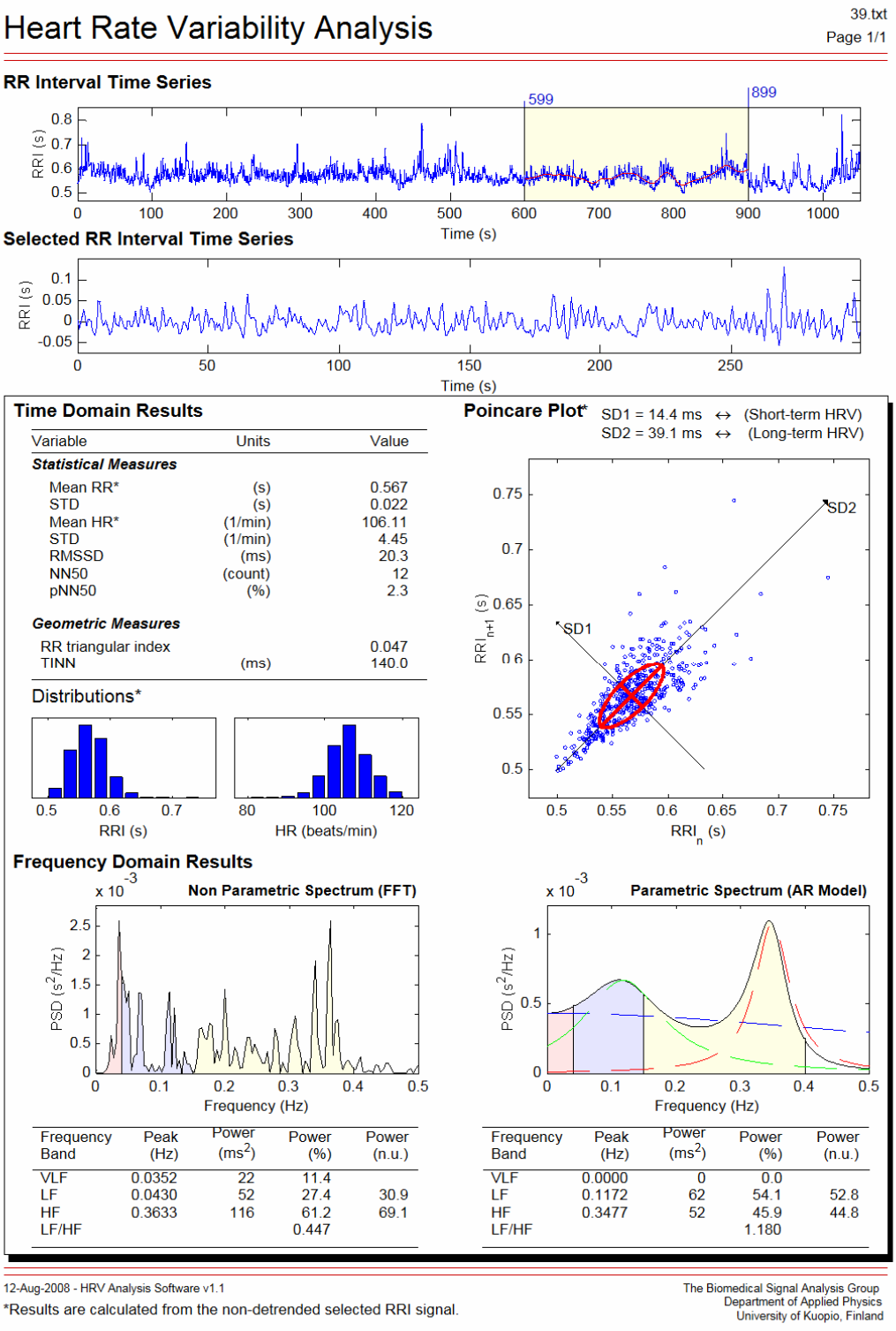

Figure A-26: HRV data during focussed attention for control subject 33

Subject 34 Baseline

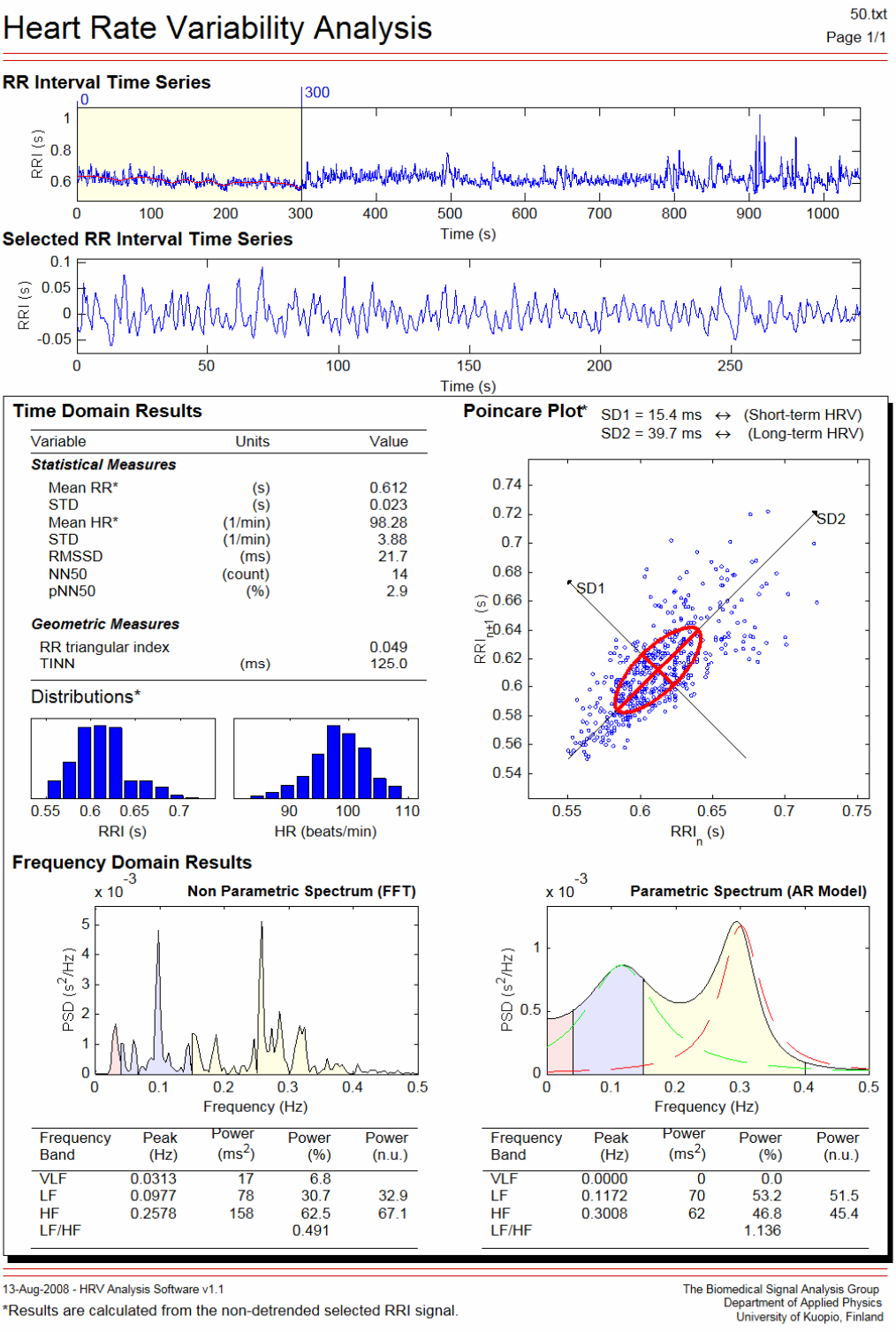

Figure A-27: Baseline HRV data for control subject 34

Subject 34 Focussed attention

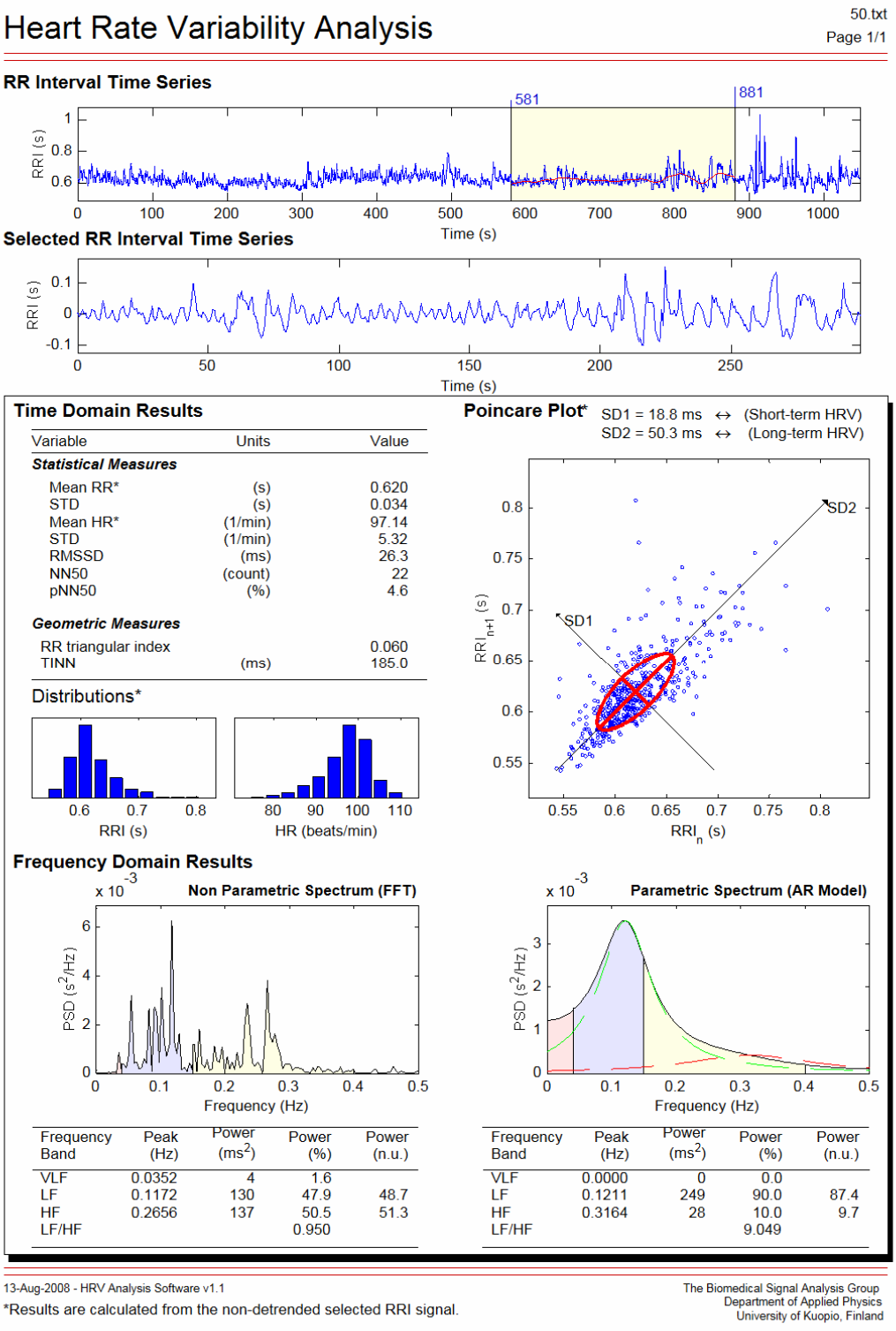

Figure A-28: HRV data during focussed attention for control subject 34

Subject 35 Baseline

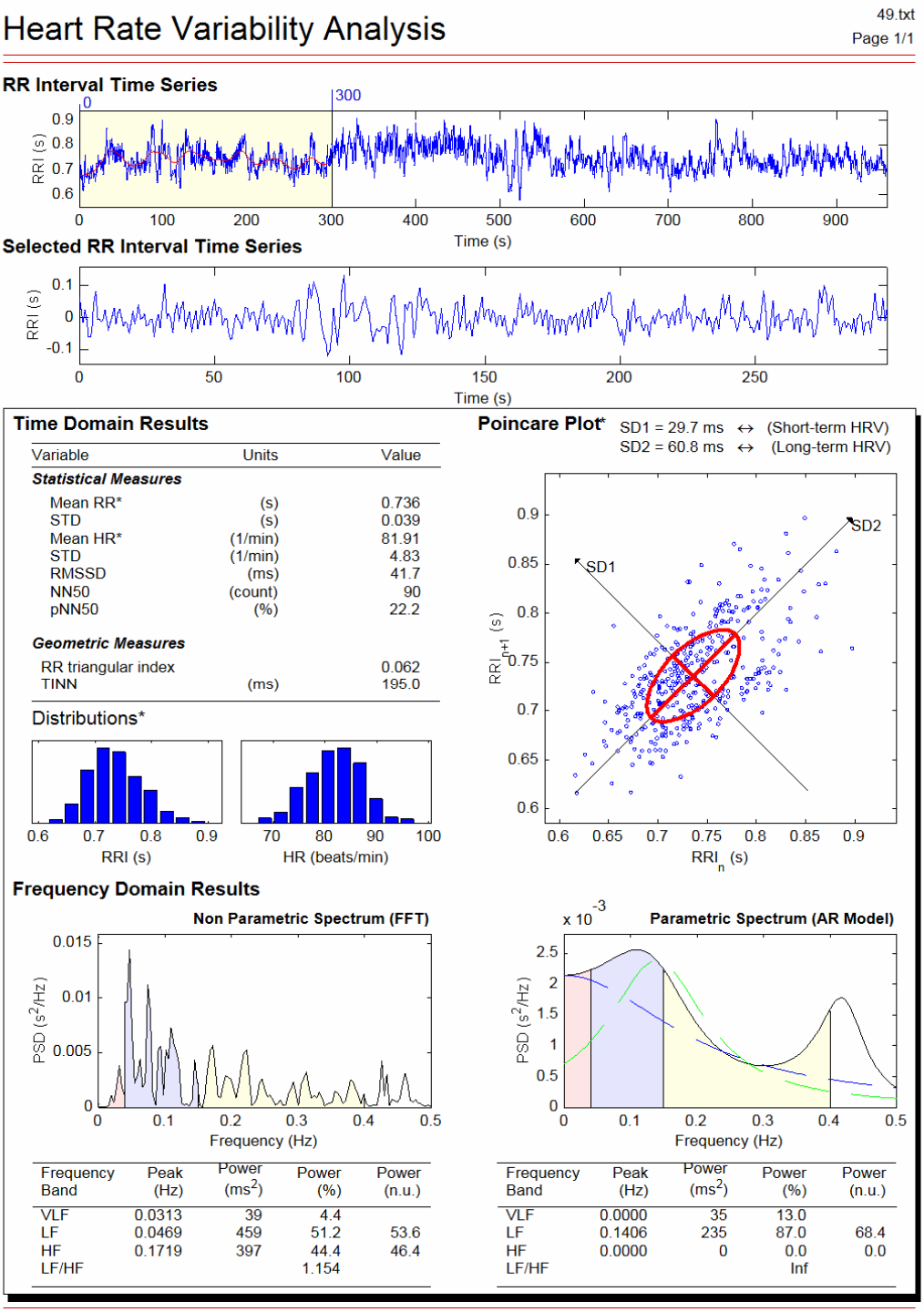

Figure A-29: Baseline HRV data for control subject 35

Subject 35 Focussed attention

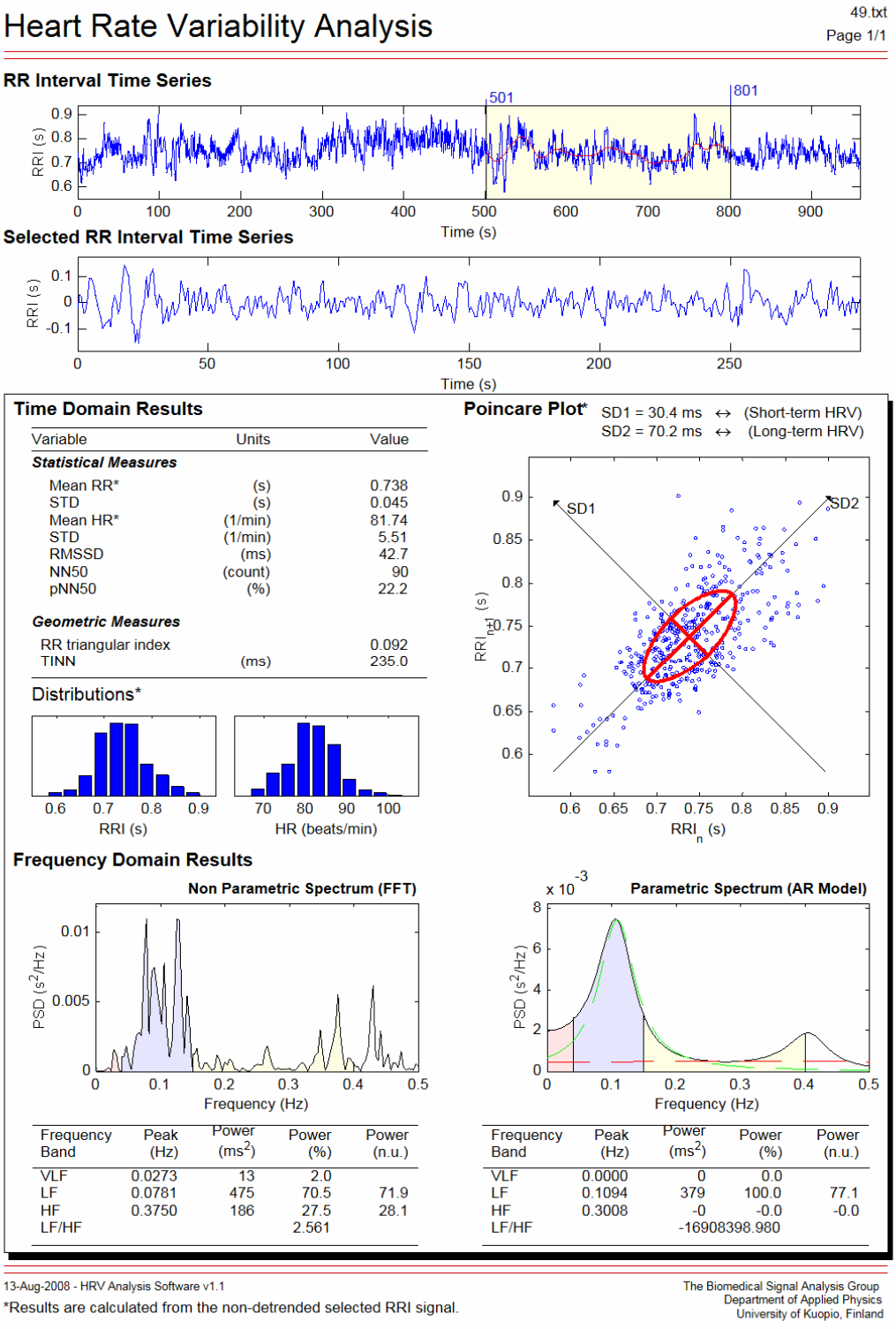

Figure A-30: HRV data during focussed attention for control subject 35

Subject 36 Baseline

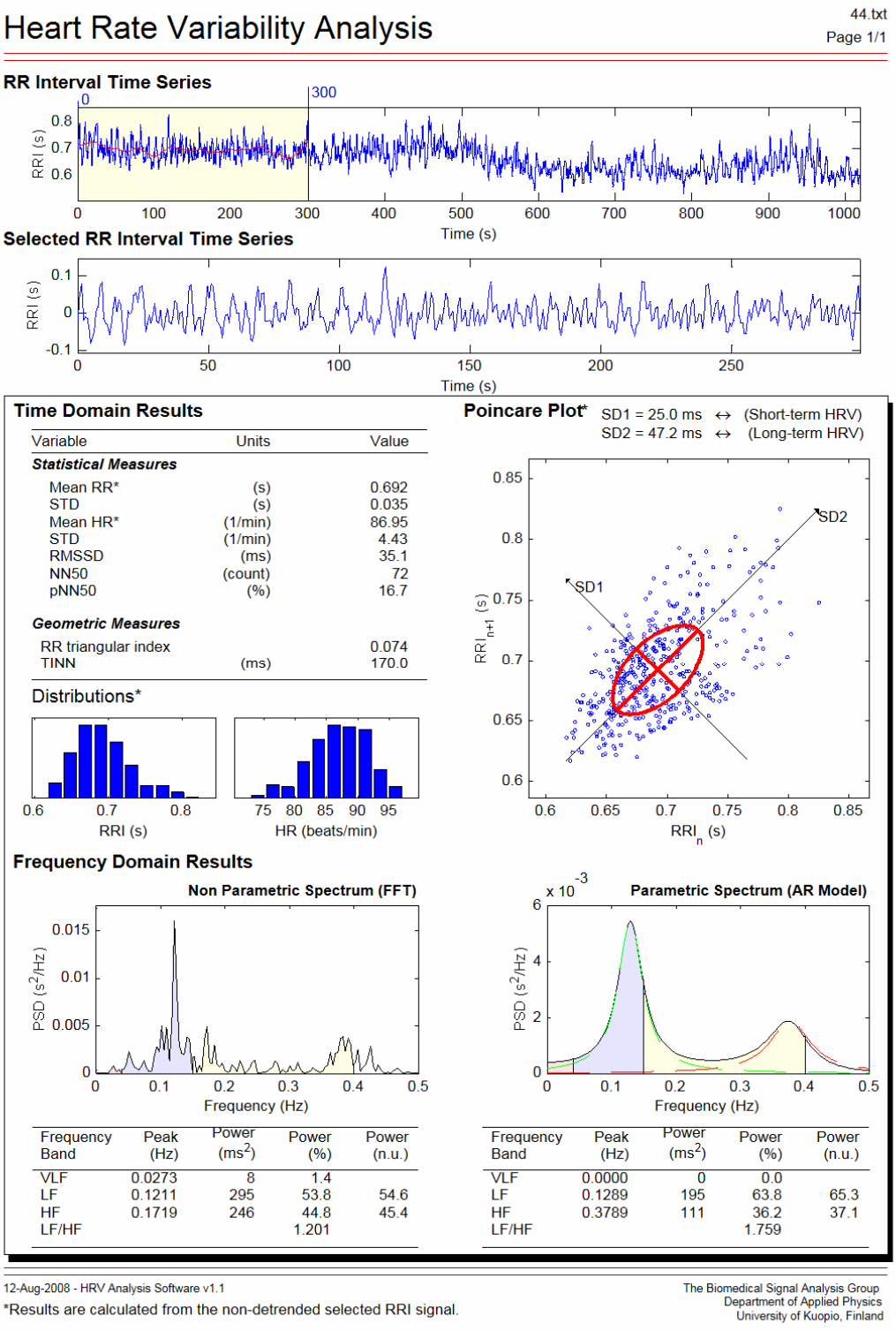

Figure A-31: Baseline HRV data for control subject 36

Subject 36 Focussed attention

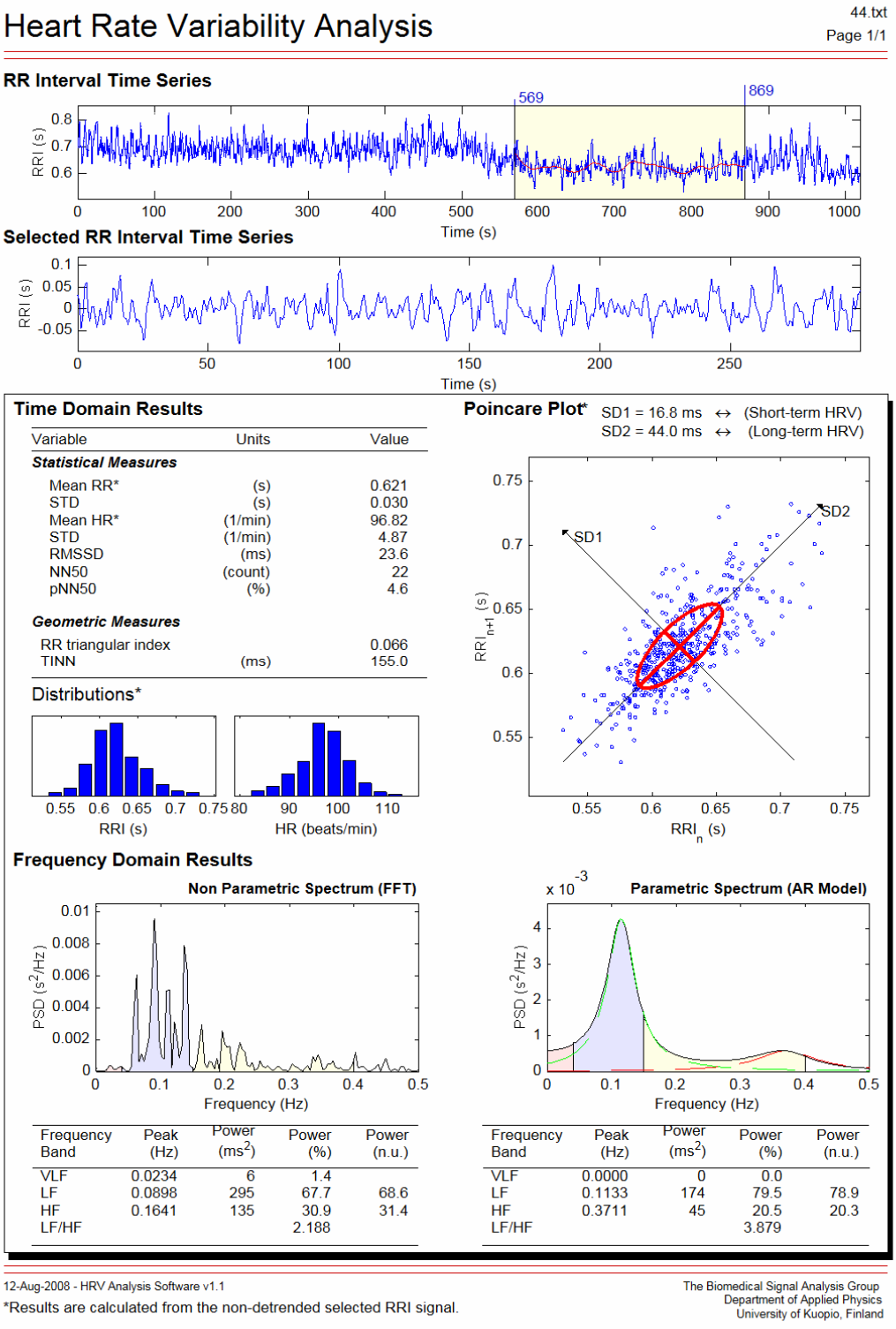

Figure A-32: HRV data during focussed attention for control subject 36

Subject 37 Baseline

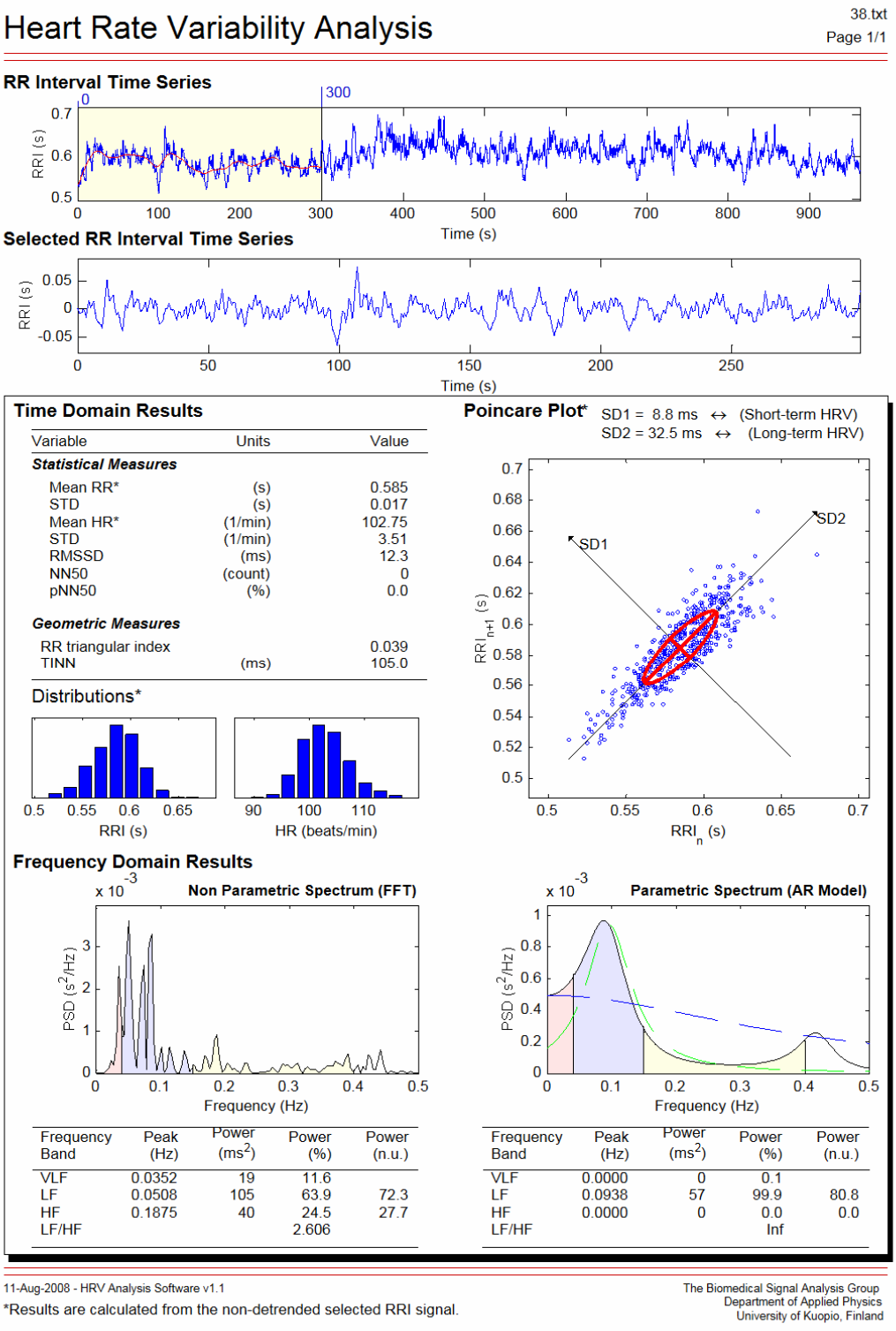

Figure A-33: Baseline HRV data for control subject 37

Subject 37 Focussed attention

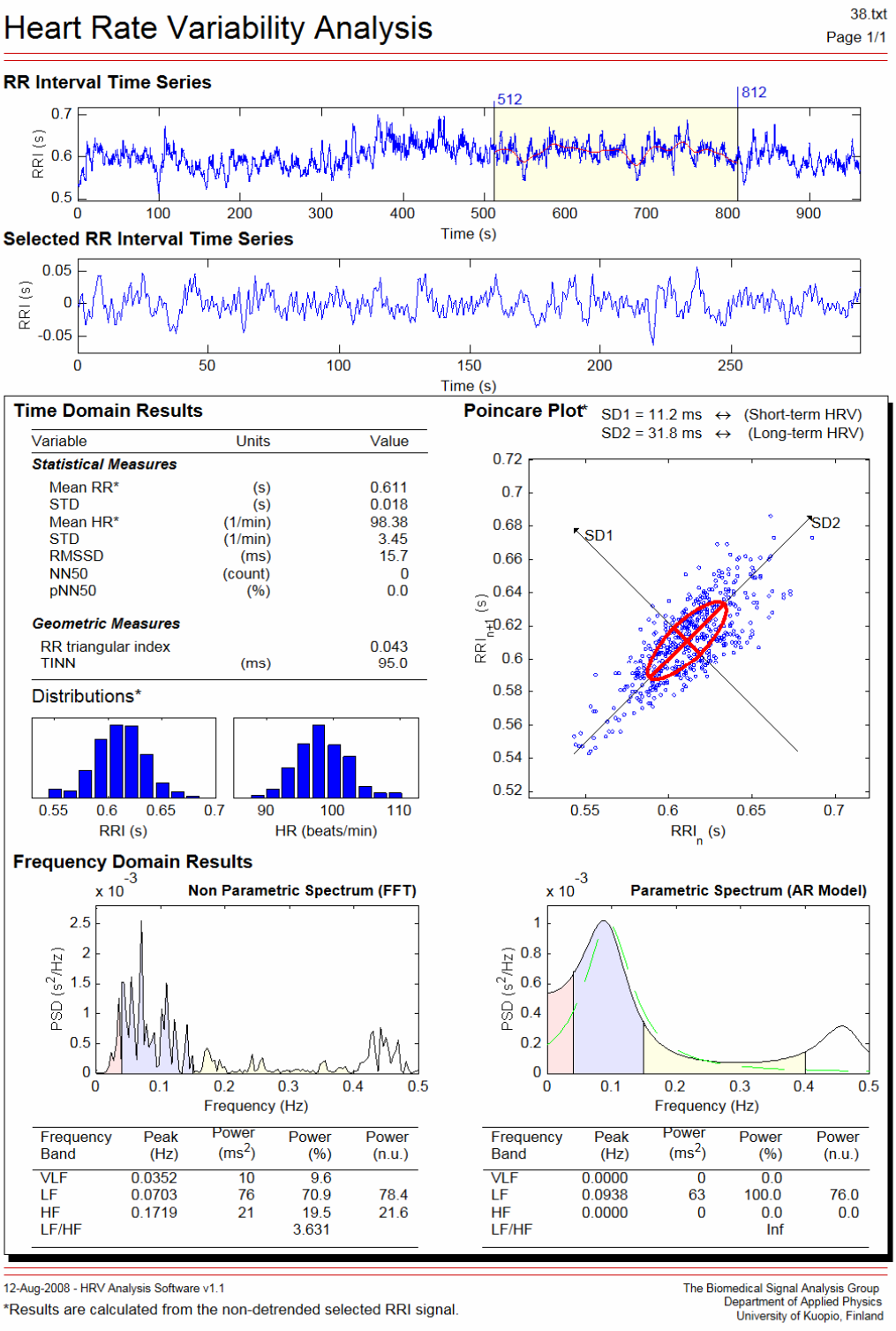

Figure A-34: HRV data during focussed attention for control subject 37

Subject 38 Baseline

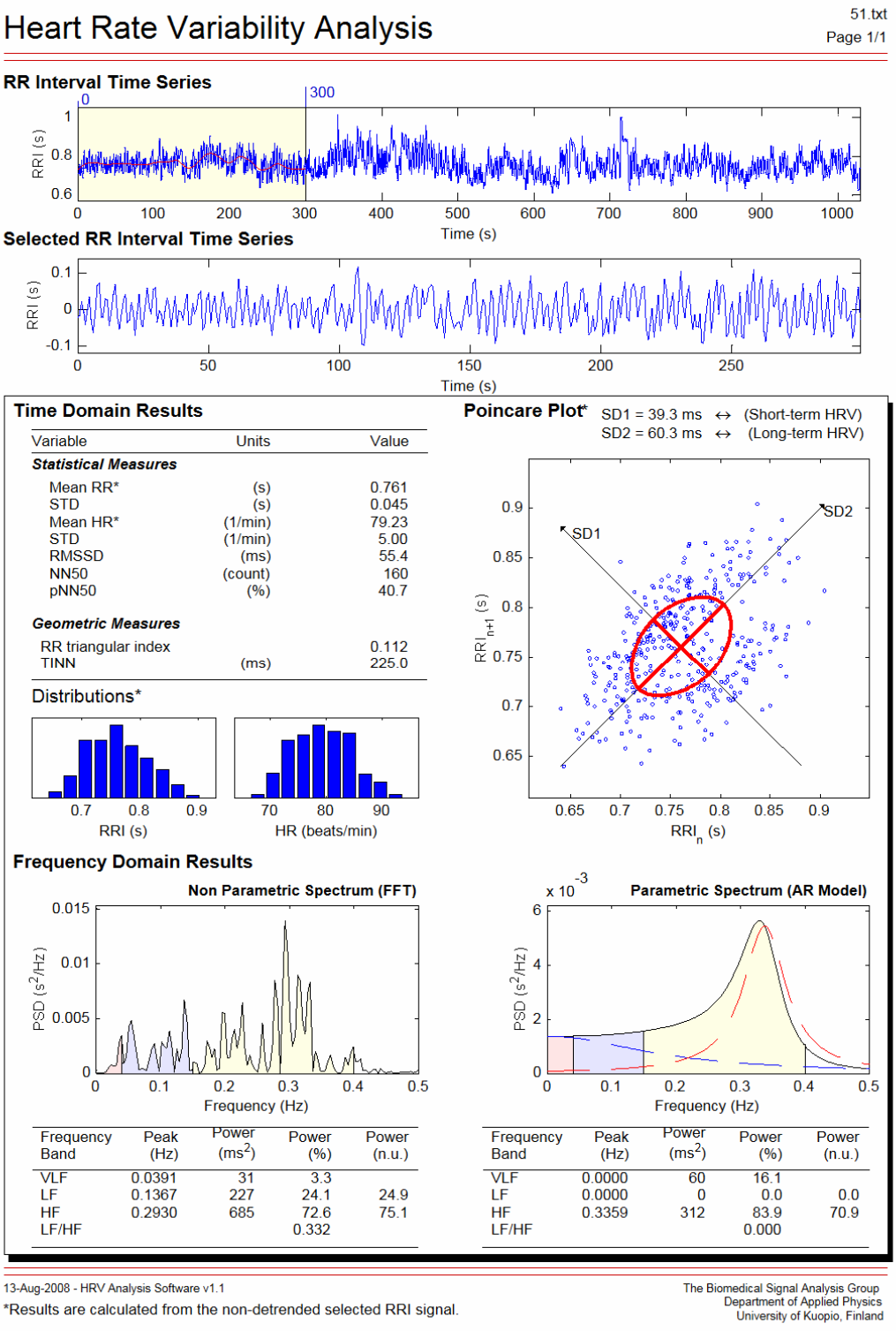

Figure A-35: Baseline HRV data for control subject 38

Subject 38 Focussed attention

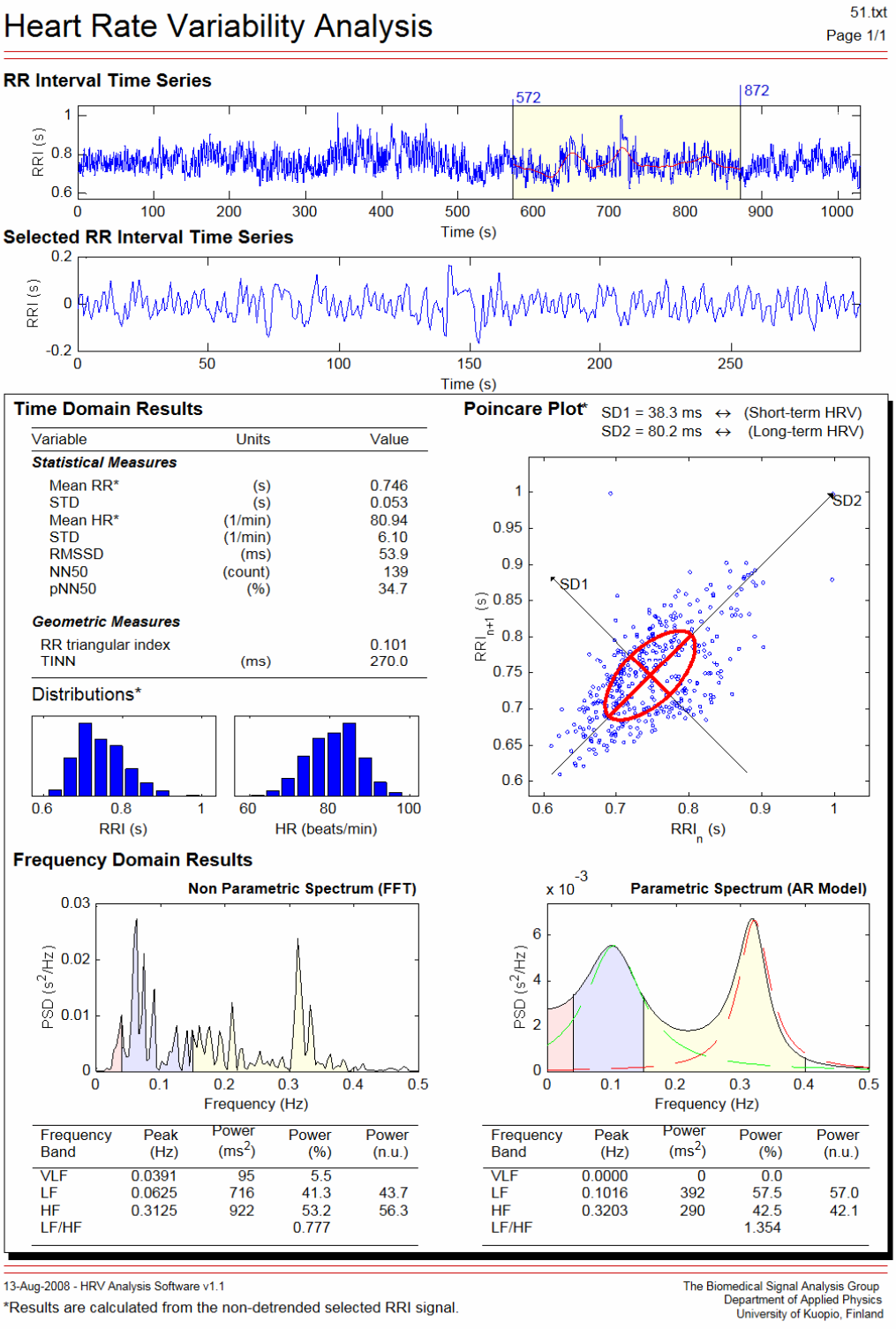

Figure A-36: HRV data during focussed attention for control subject 38

Stimulant-free ADHD children

Subject 01 Baseline

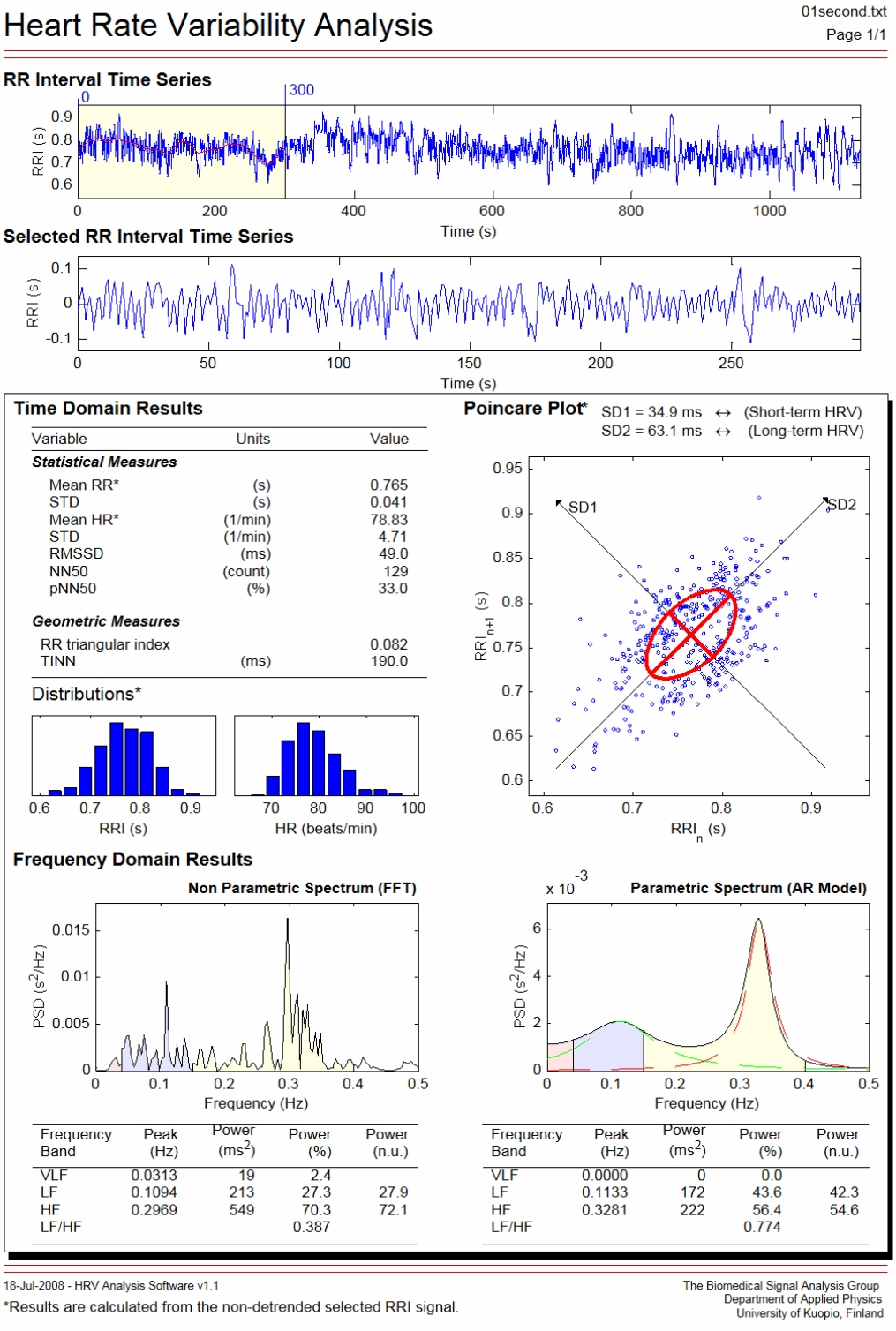

Figure A-37: Baseline HRV data for subject 01, tested while stimulant-free

Subject 01 Focussed attention

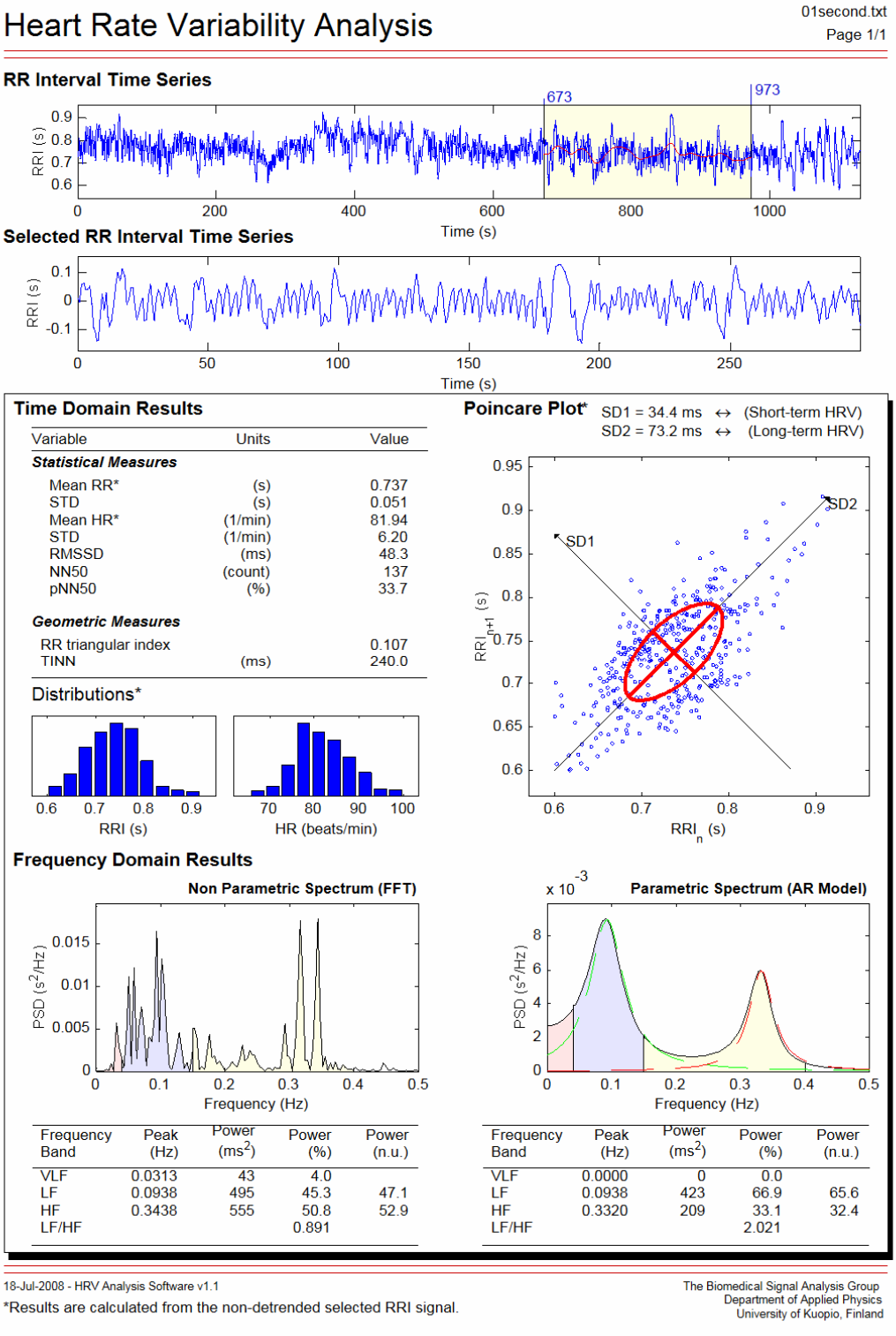

Figure A-38: HRV data during focussed attention for subject 01, tested while stimulant-free

Subject 03 Baseline

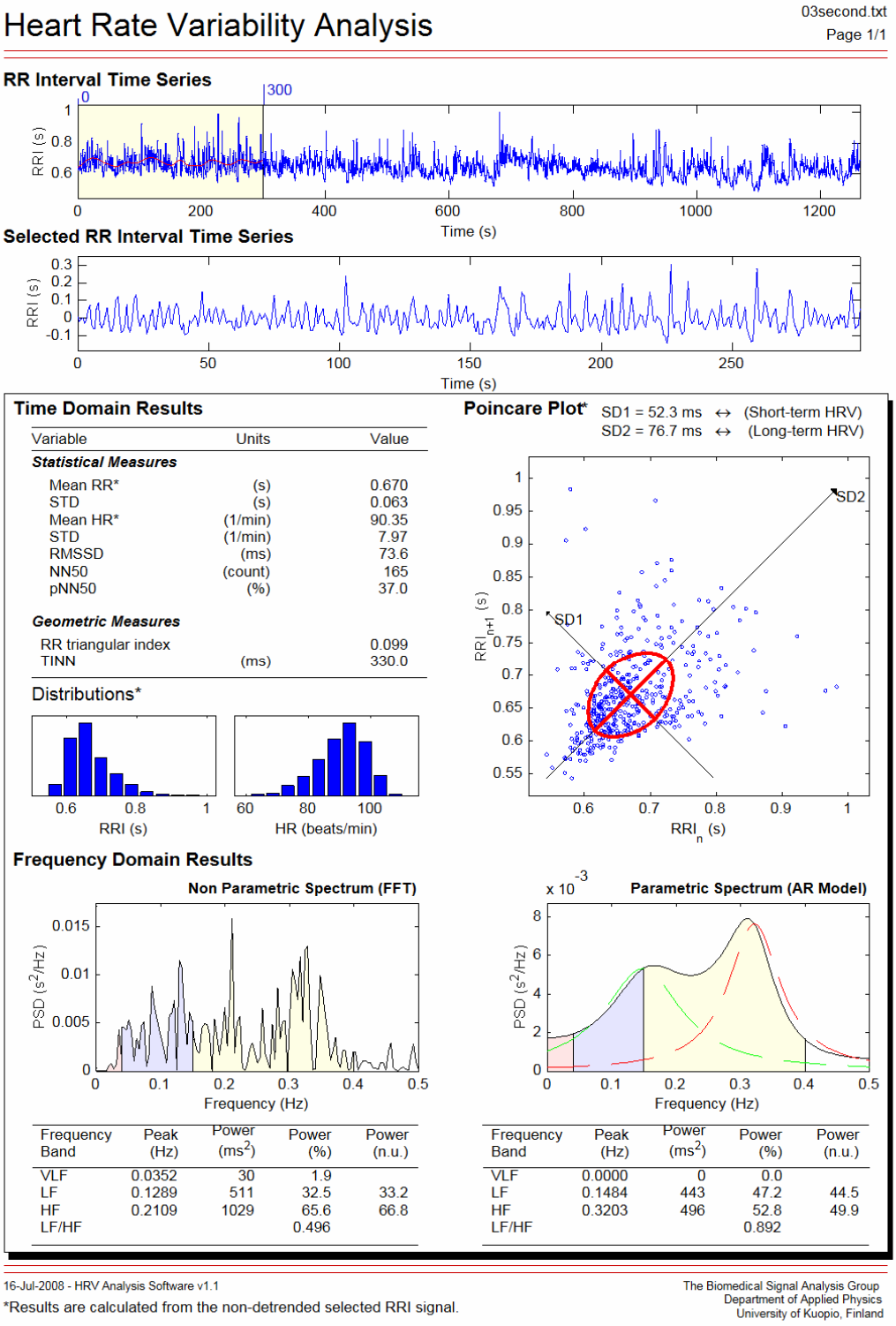

Figure A-39: Baseline HRV data for subject 03, tested while stimulant-free

Subject 03 Focussed attention

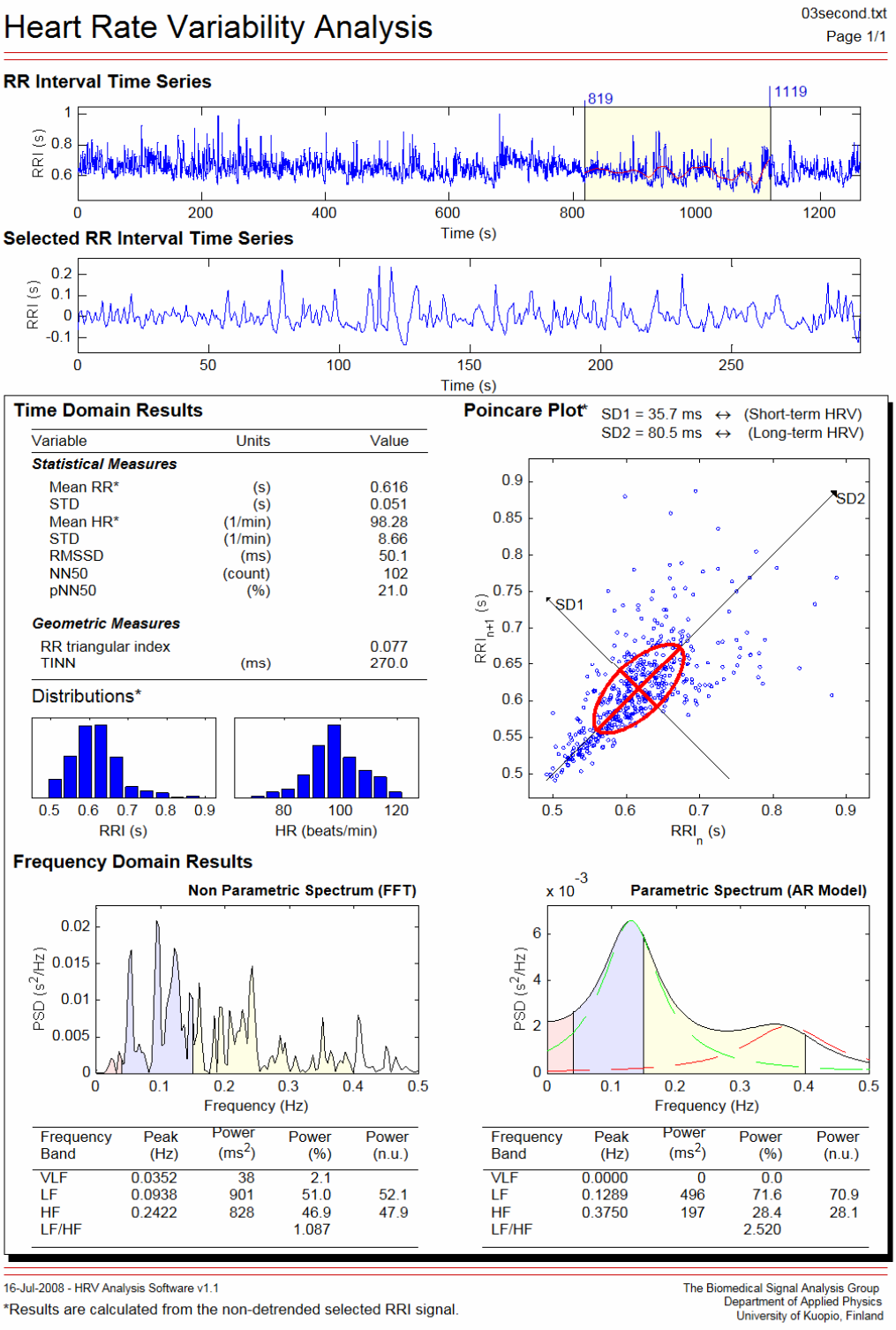

Figure A-40: HRV data during focussed attention for subject 03, tested while stimulant-free

Subject 04 Baseline

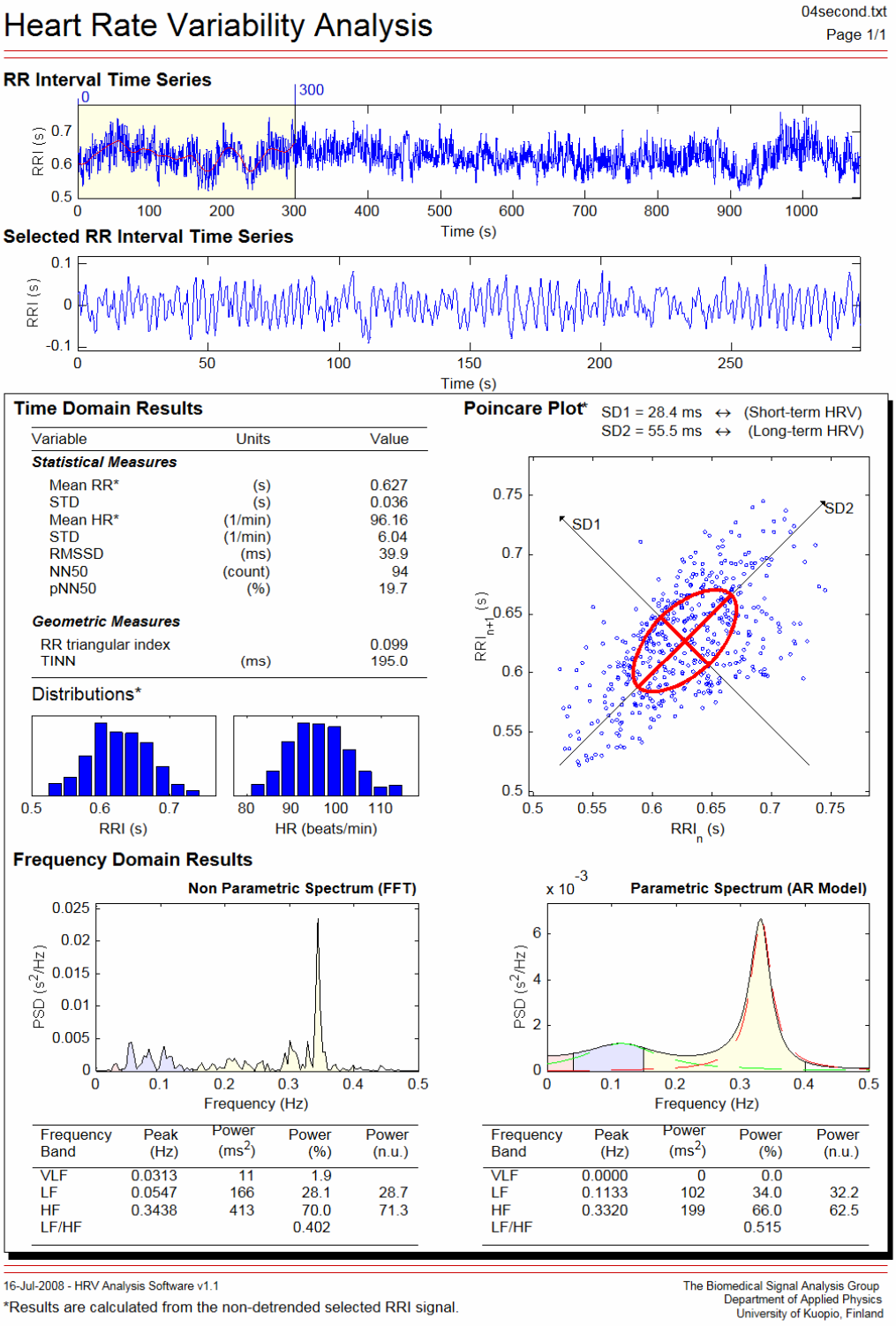

Figure A-41: Baseline HRV data for subject 04, tested while stimulant-free

Subject 04 Focussed attention

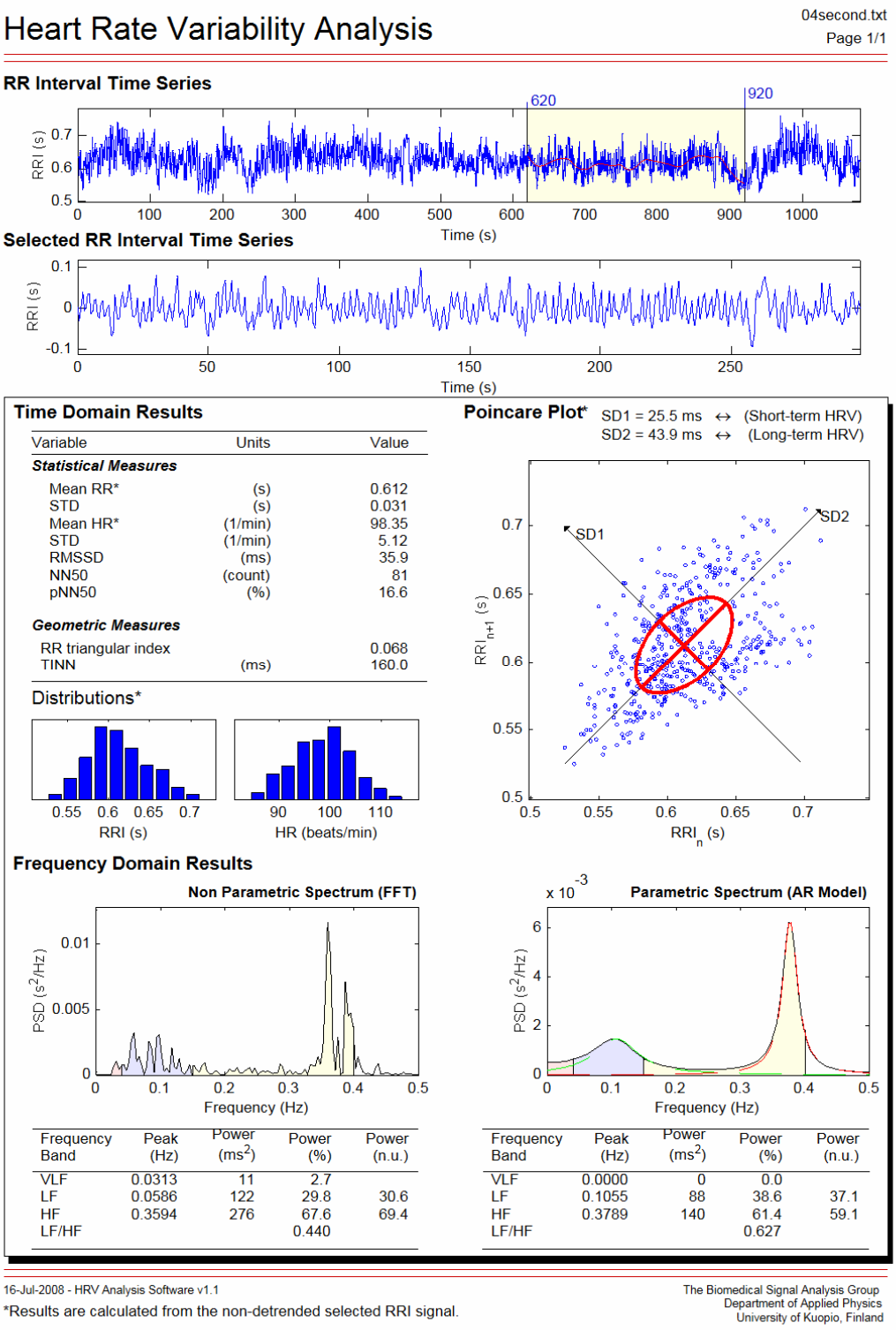

Figure A-42: HRV data during focussed attention for subject 04, tested while stimulant-free

Subject 05 Baseline

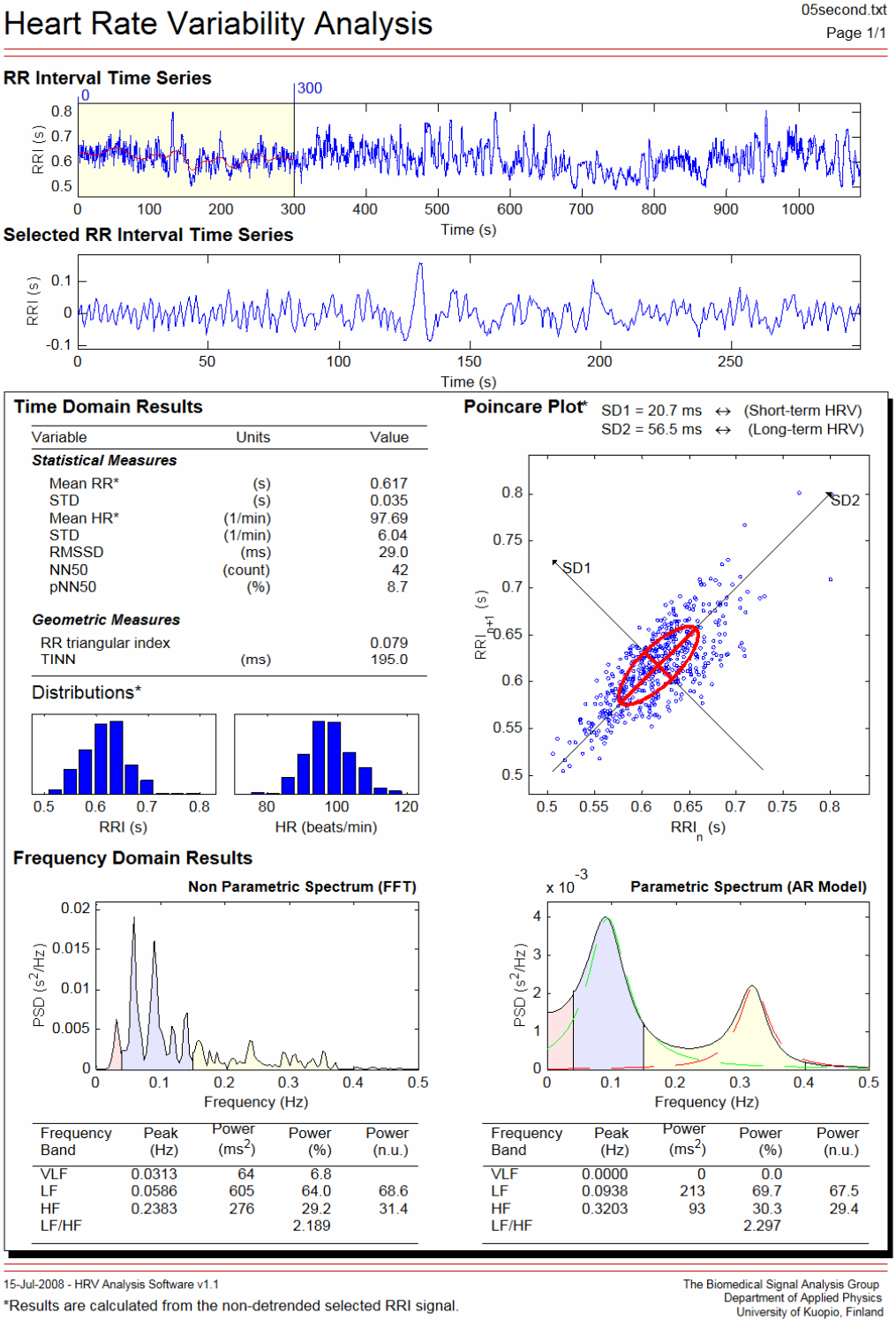

Figure A-43: Baseline HRV data for subject 05, tested while stimulant-free

Subject 05 Focussed attention

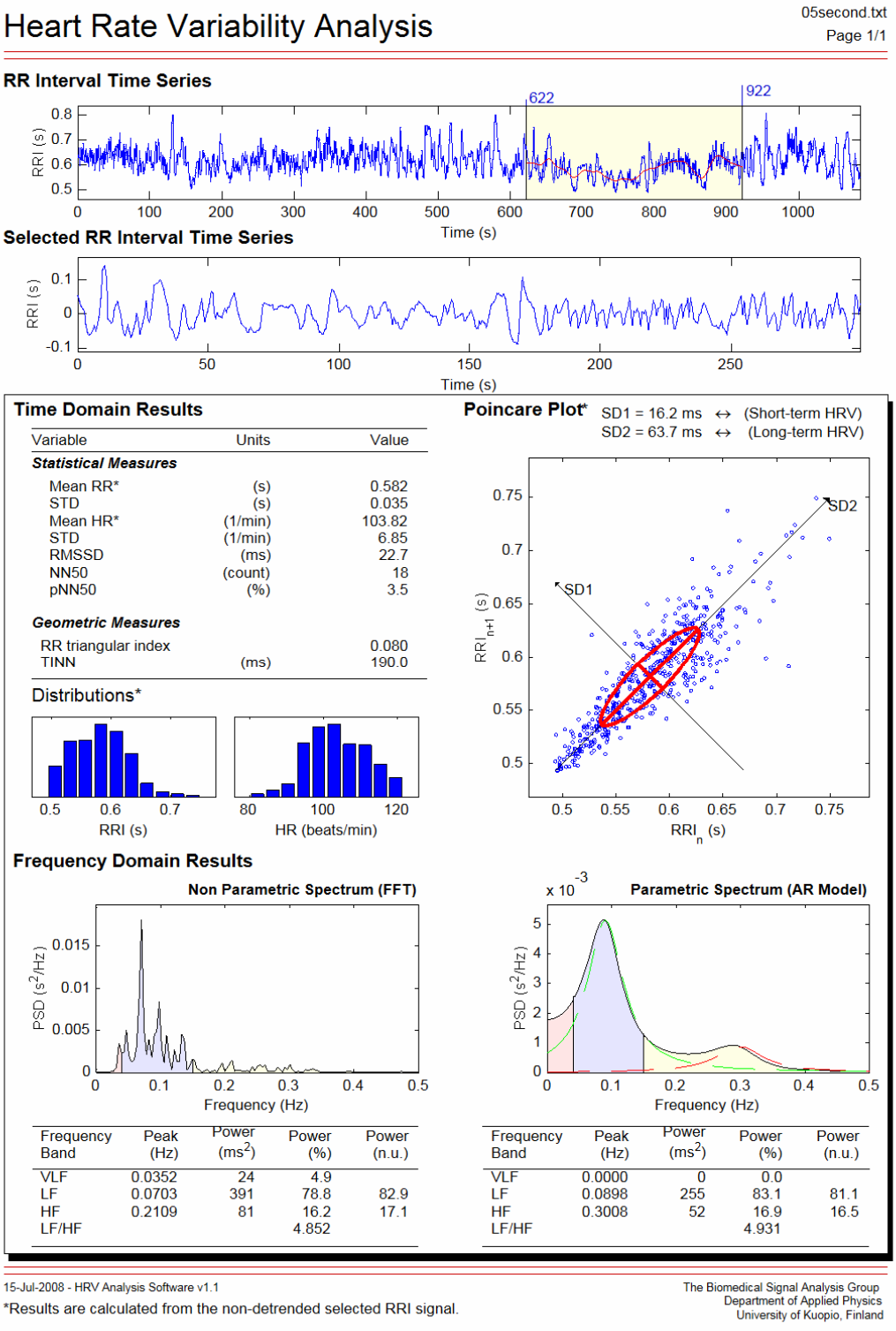

Figure A-44: HRV data during focussed attention for subject 05, tested while stimulant-free

Subject 06 Baseline

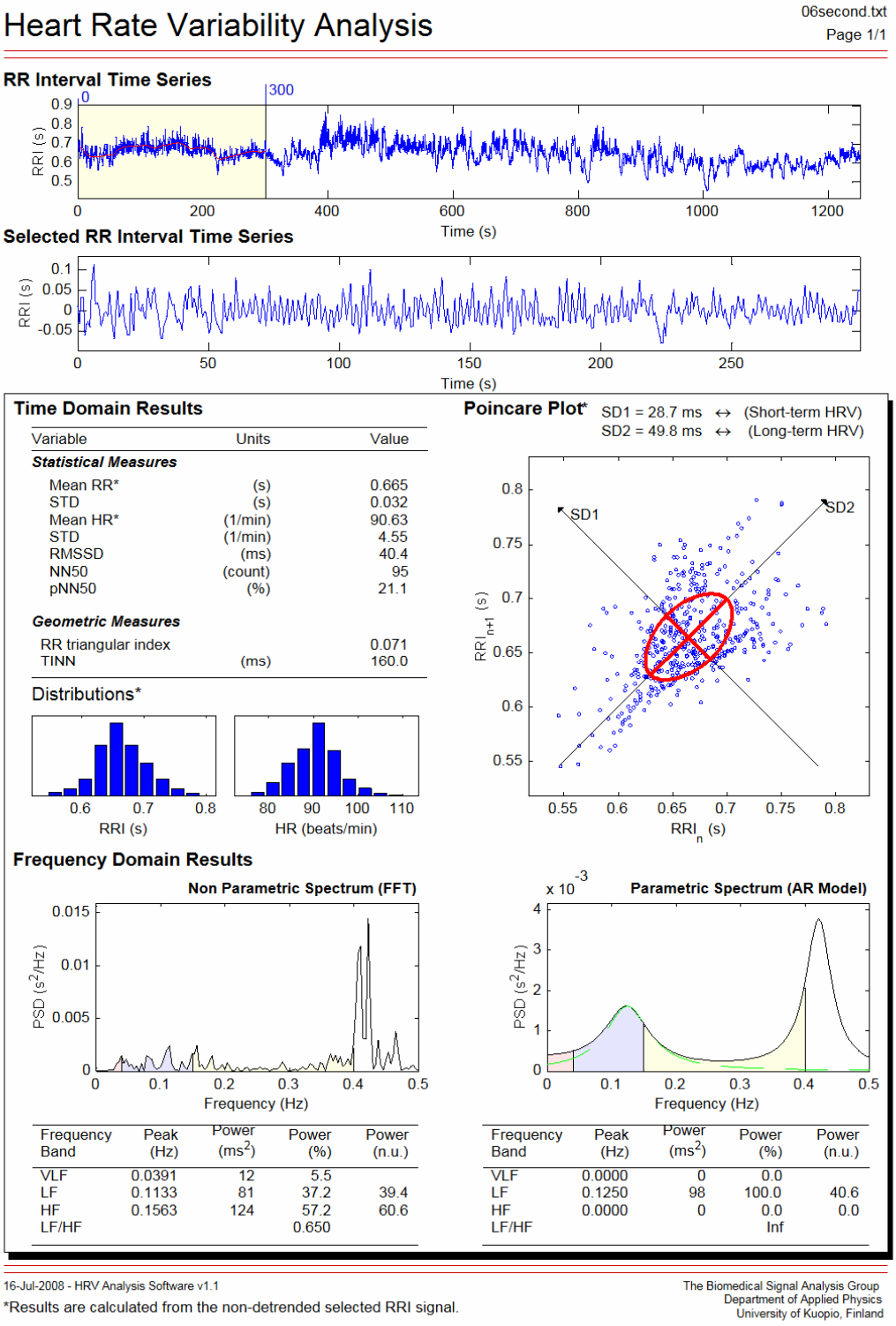

Figure A-45: Baseline HRV data for subject 06, tested while stimulant-free

Subject 06 Focussed attention

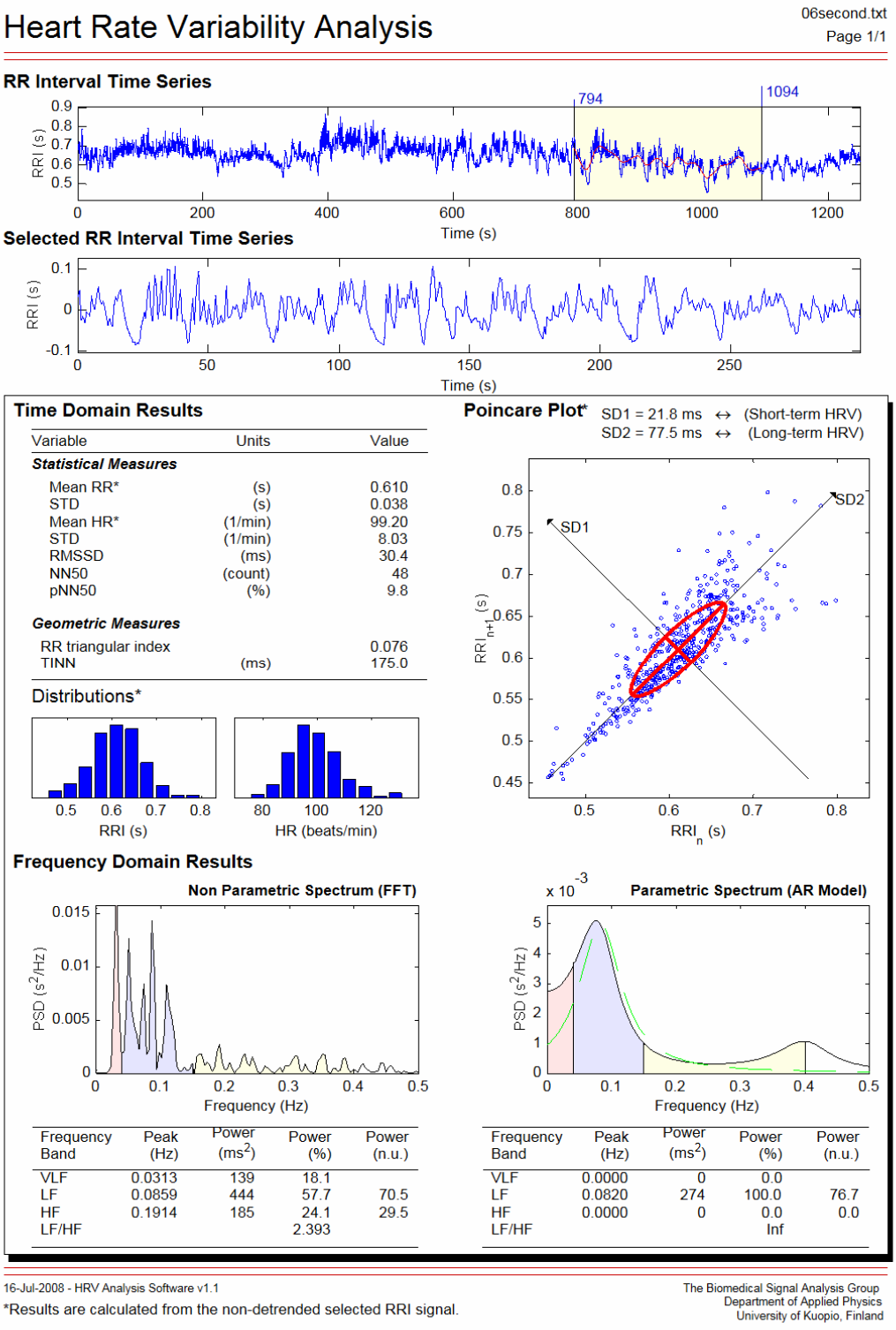

Figure A-46: HRV data during focussed attention for subject 06, tested while stimulant-free

Subject 07 Baseline

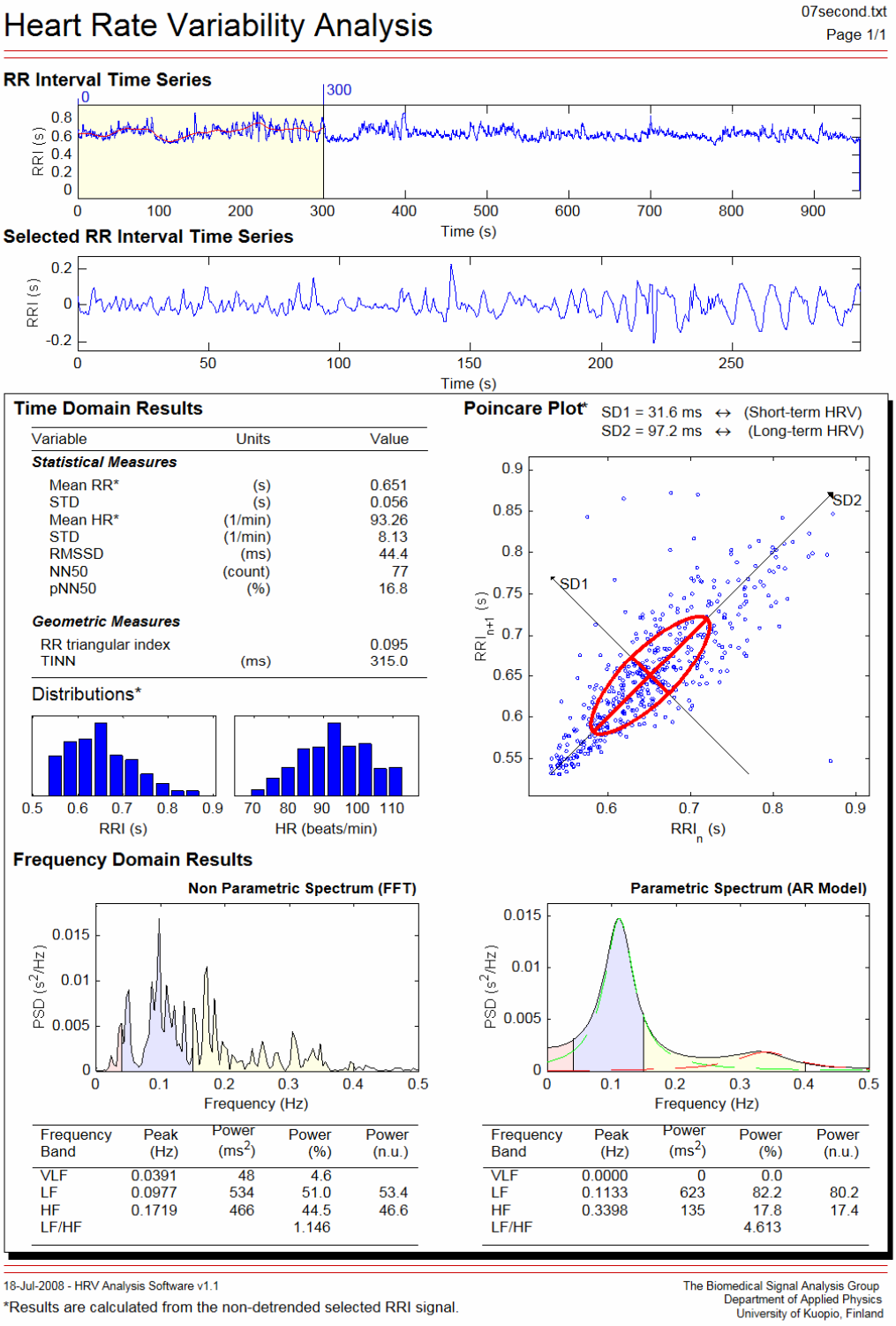

Figure A-47: Baseline HRV data for subject 07, tested while stimulant-free

Subject 07 Focussed attention

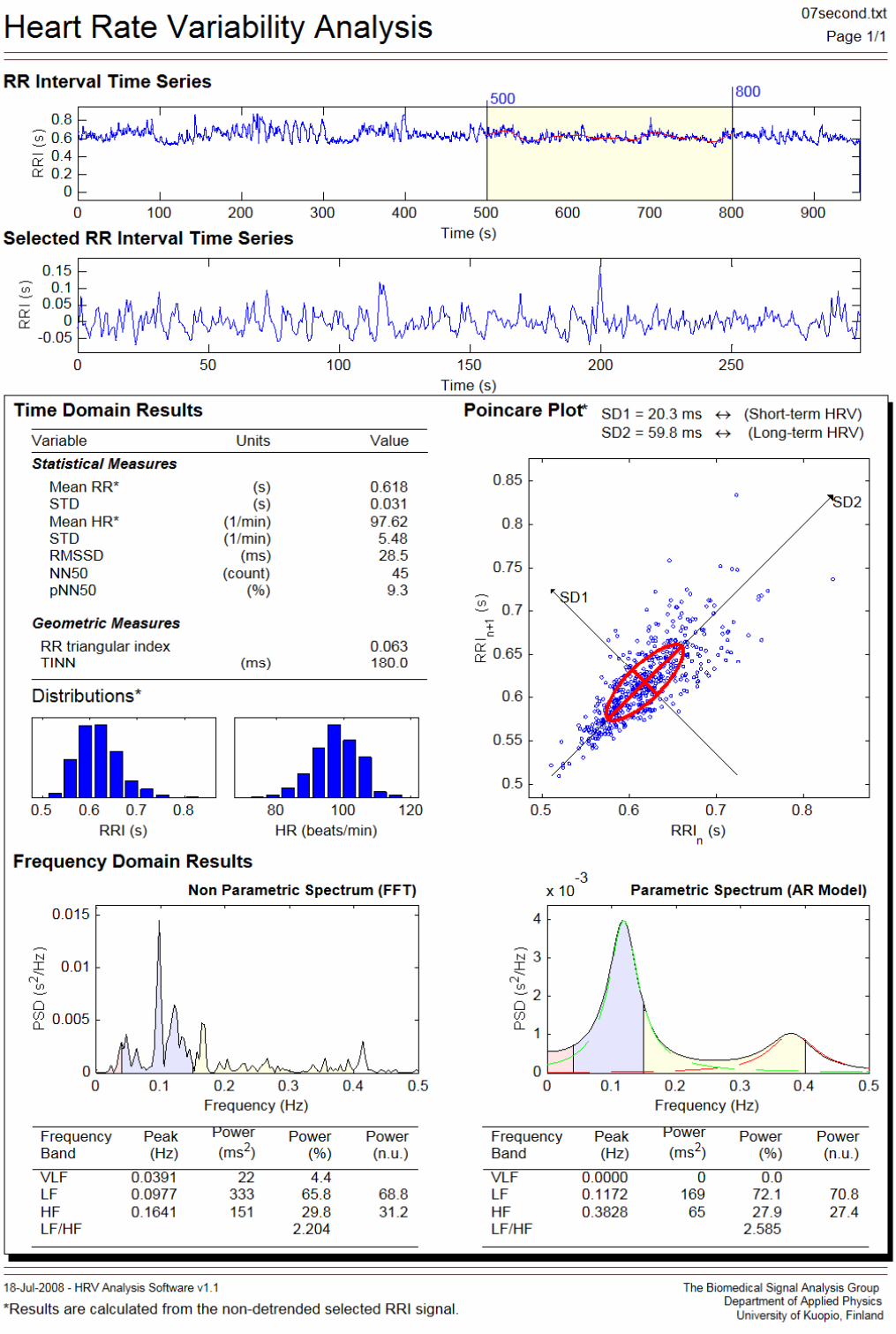

Figure A-48: HRV data during focussed attention for subject 07, tested while stimulant-free

Subject 08 Baseline

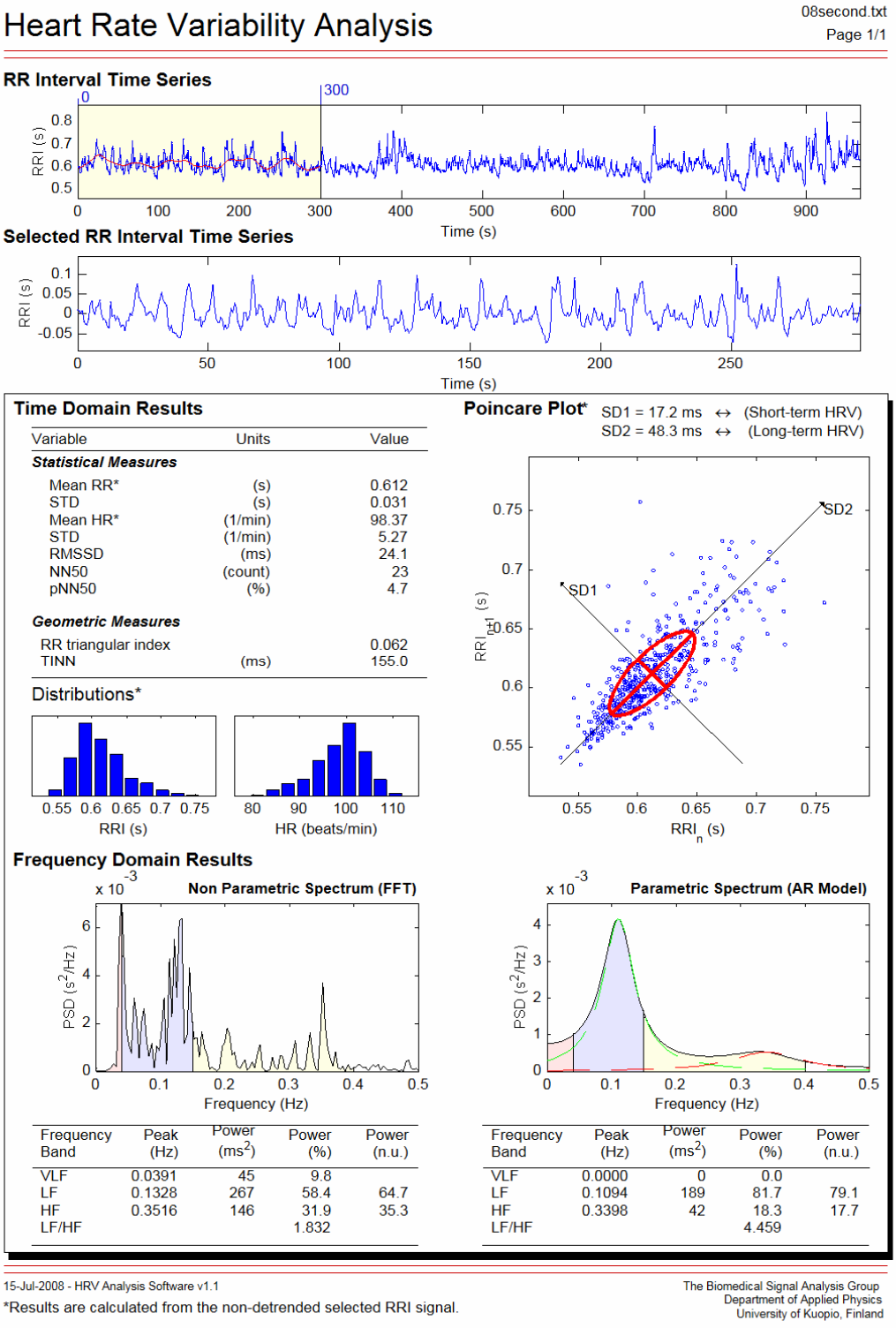

Figure A-49: Baseline HRV data for subject 08, tested while stimulant-free

Subject 08 Focussed attention

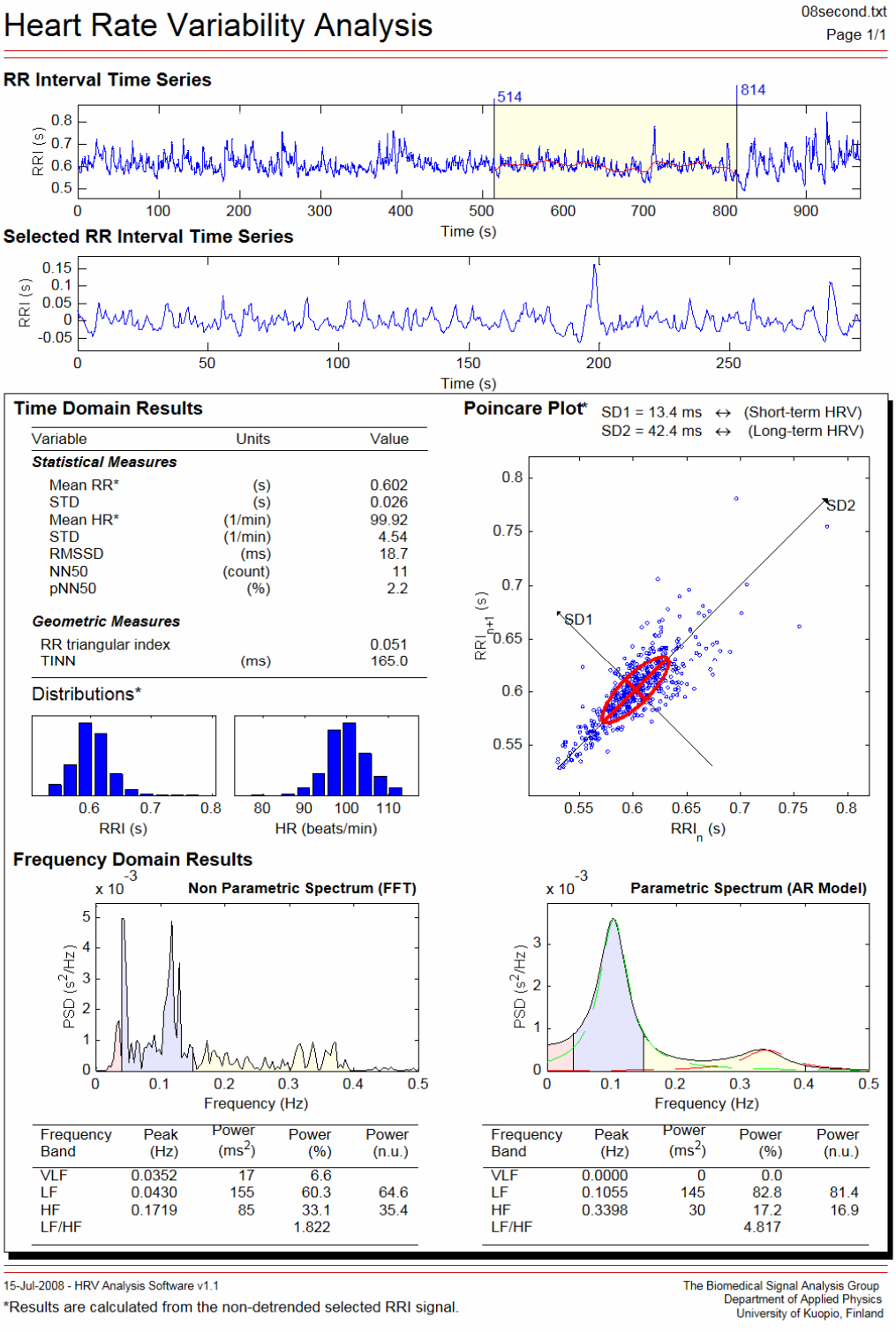

Figure A-50: HRV data during focussed attention for subject 08, tested while stimulant-free

Subject 09 Baseline

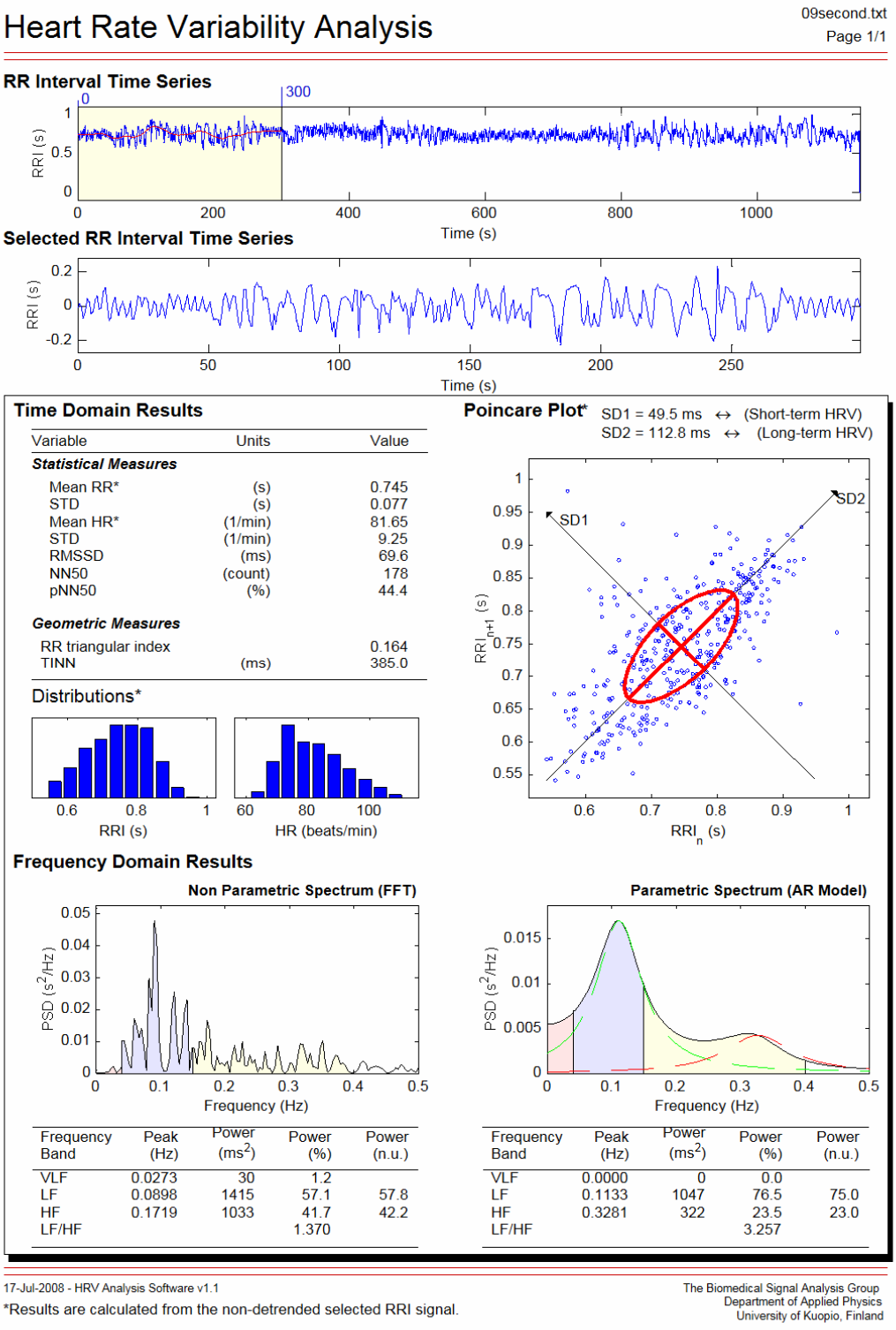

Figure A-51: Baseline HRV data for subject 09, tested while stimulant-free

Subject 09 Focussed attention

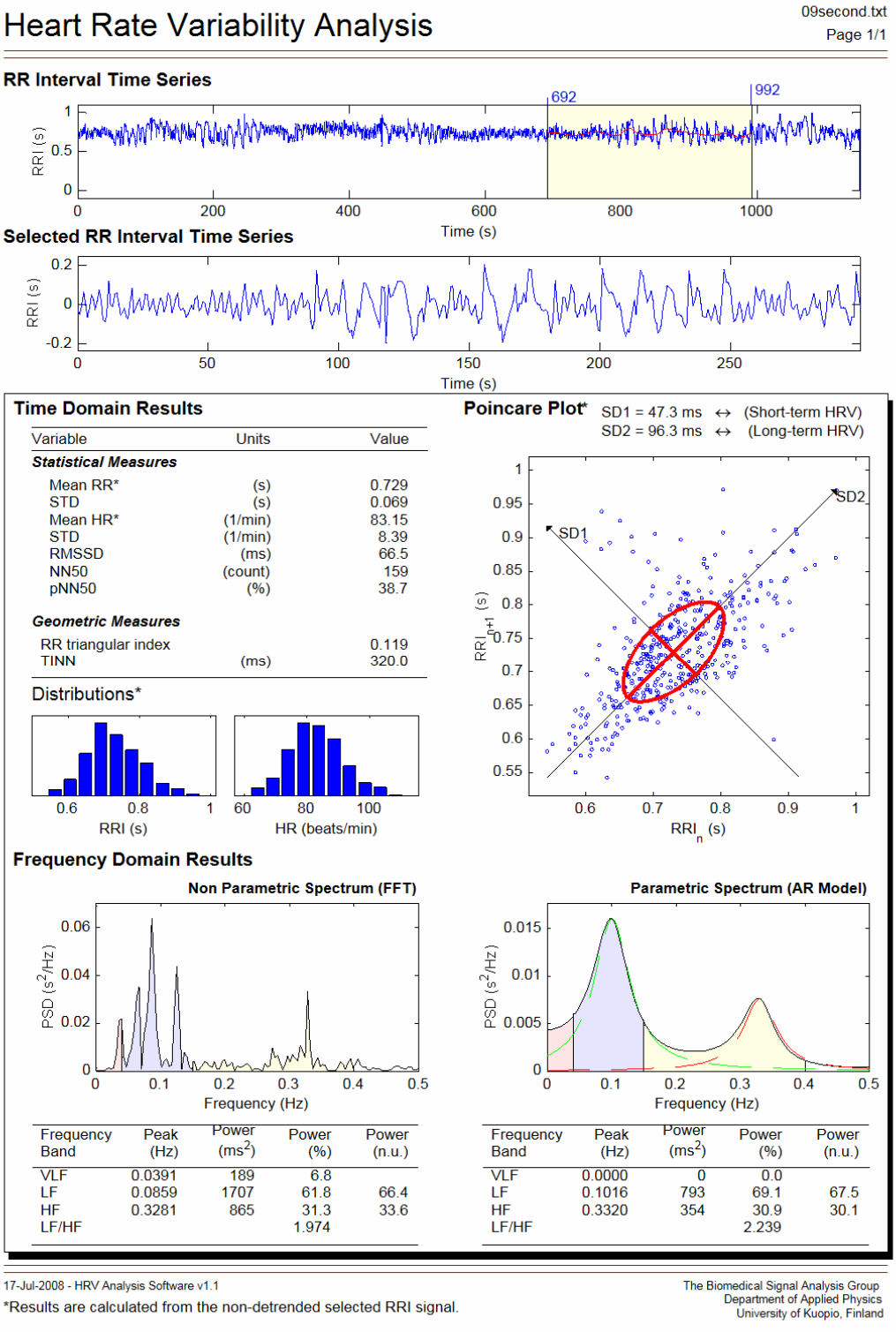

Figure A-52: HRV data during focussed attention for subject 09, tested while stimulant-free

Subject 10 Baseline

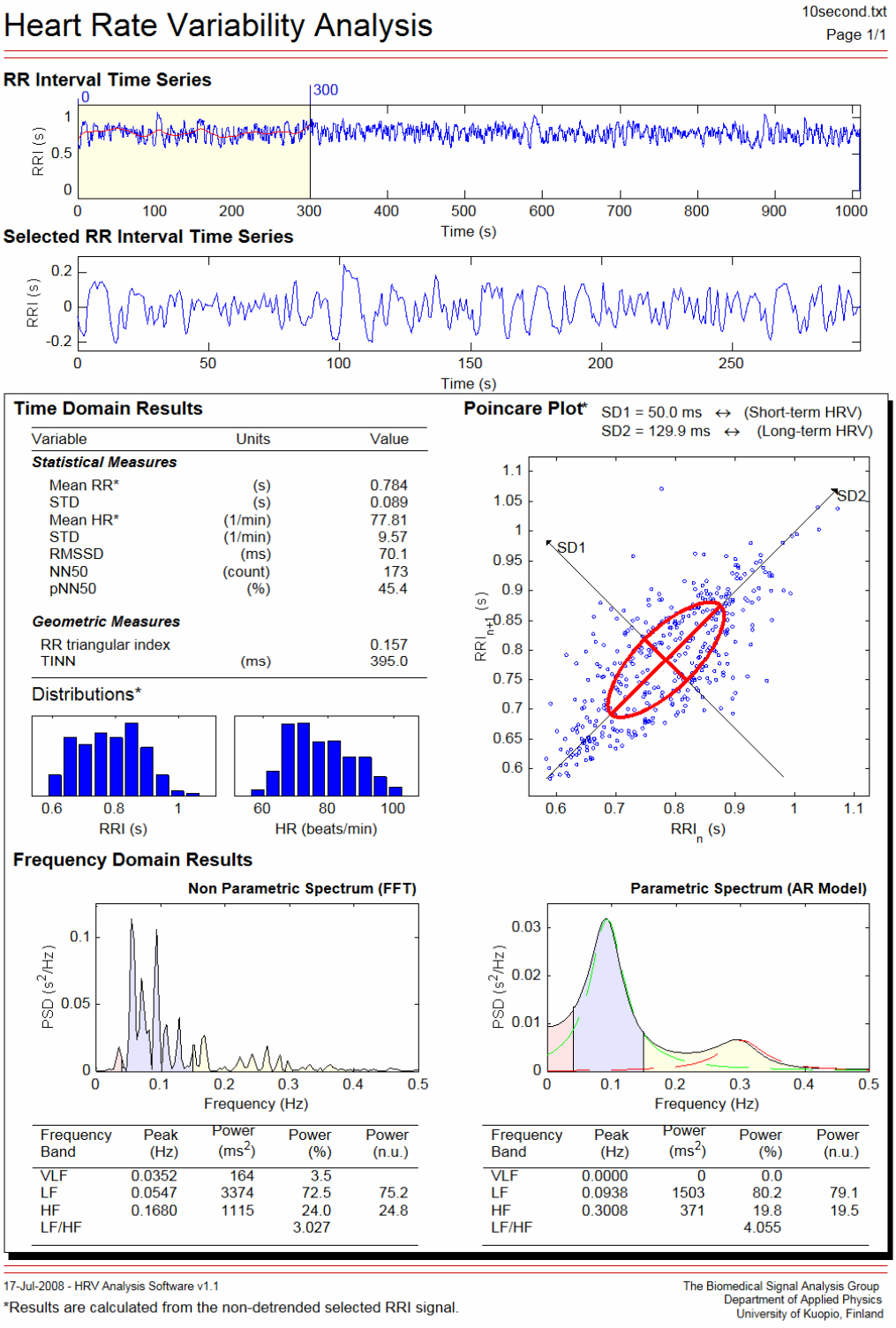

Figure A-53: Baseline HRV data for subject 10, tested while stimulant-free

Subject 10 Focussed attention

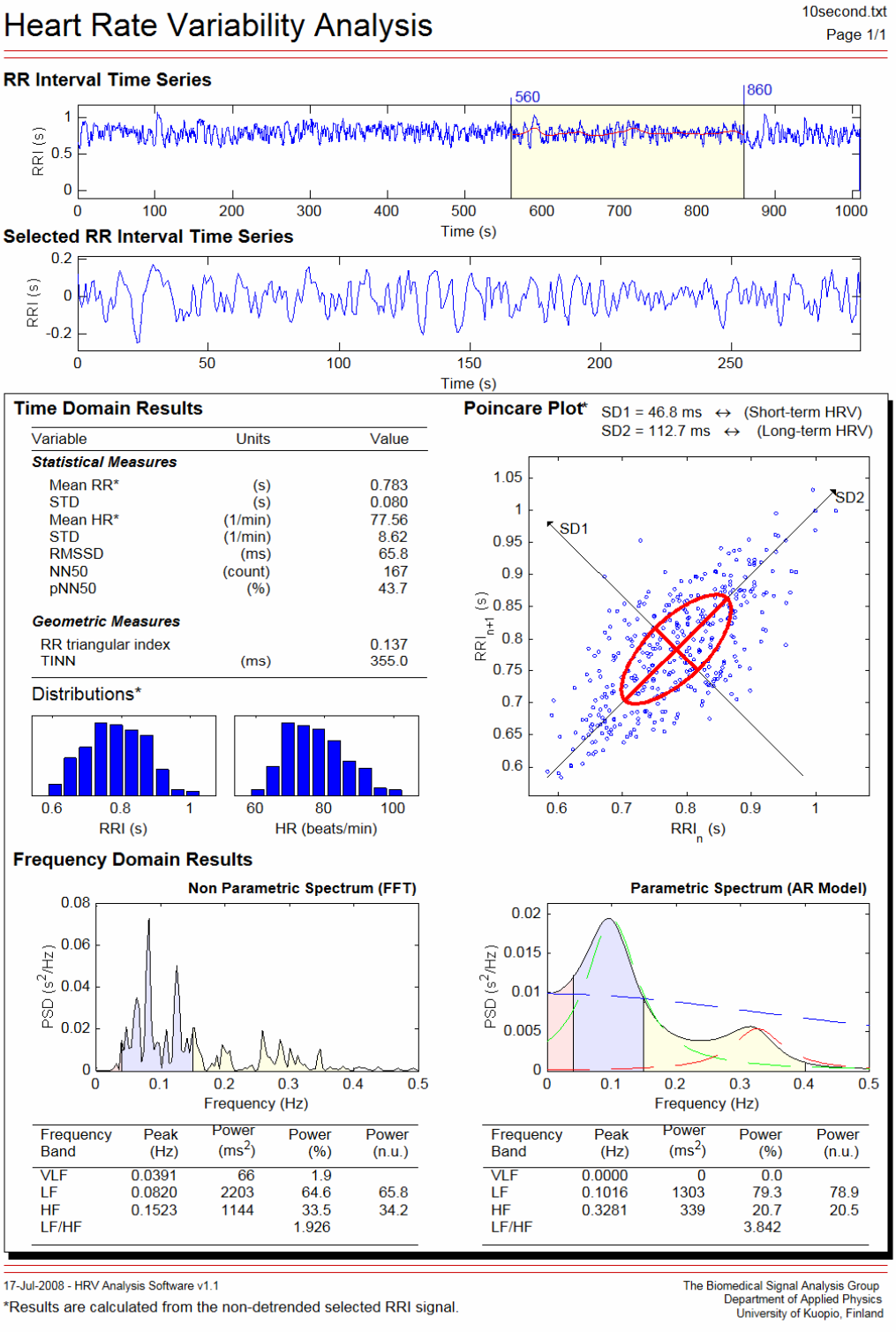

Figure A-54: HRV data during focussed attention for subject 10, tested while stimulant-free

Subject 11 Baseline

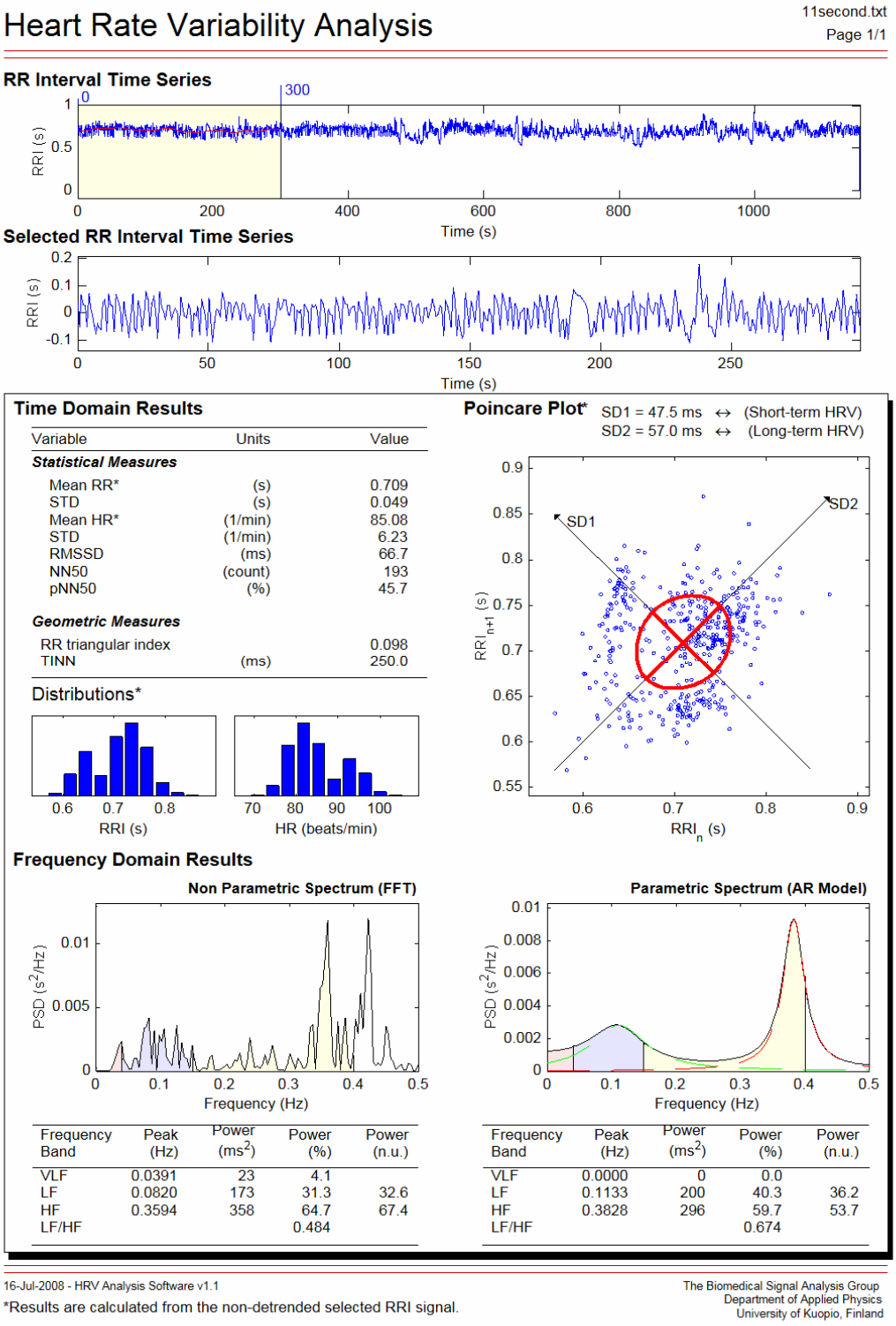

Figure A-55: Baseline HRV data for subject 11, tested while stimulant-free

Subject 11 Focussed attention

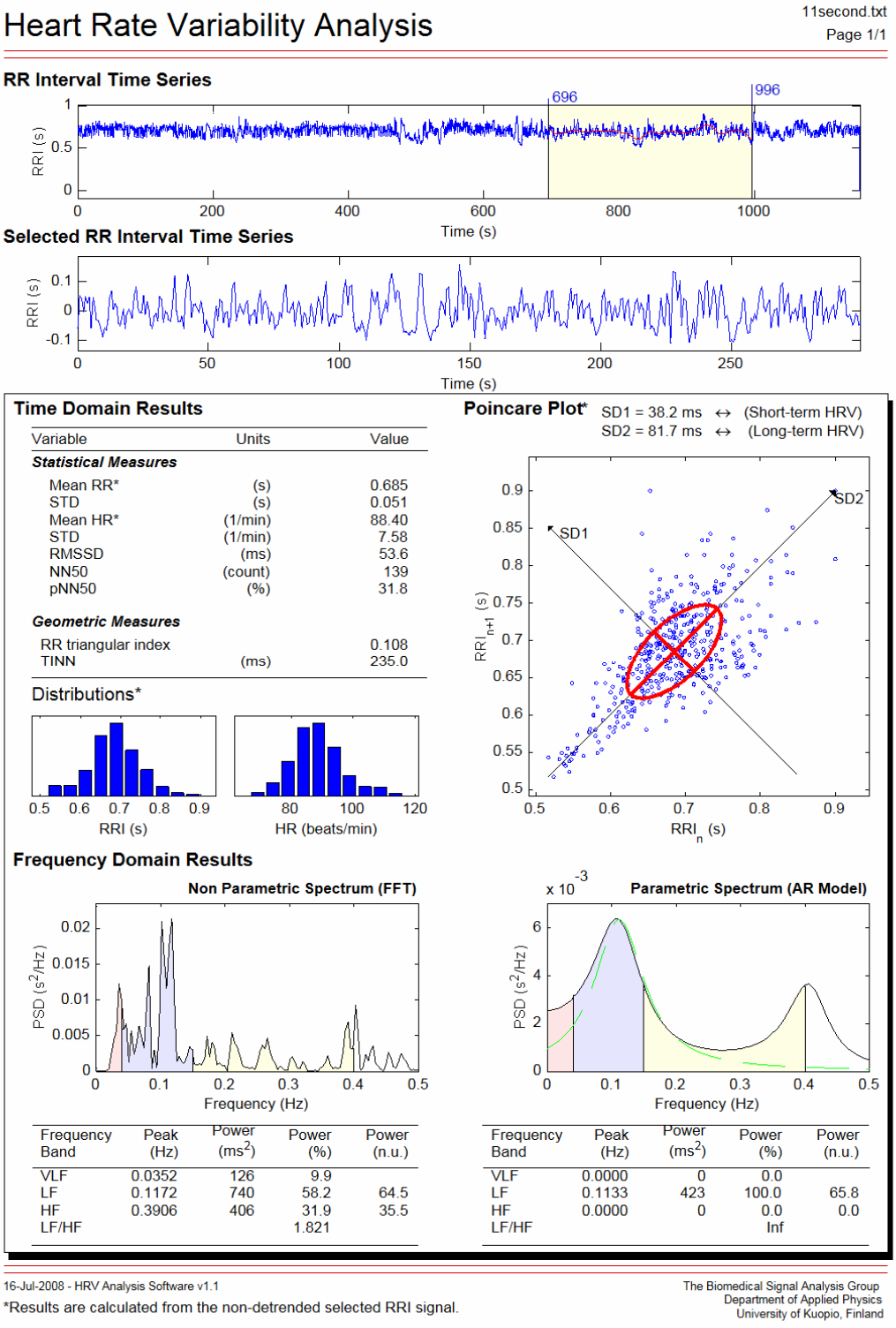

Figure A-56: HRV data during focussed attention for subject 11, tested while stimulant-free

Subject 12 Baseline

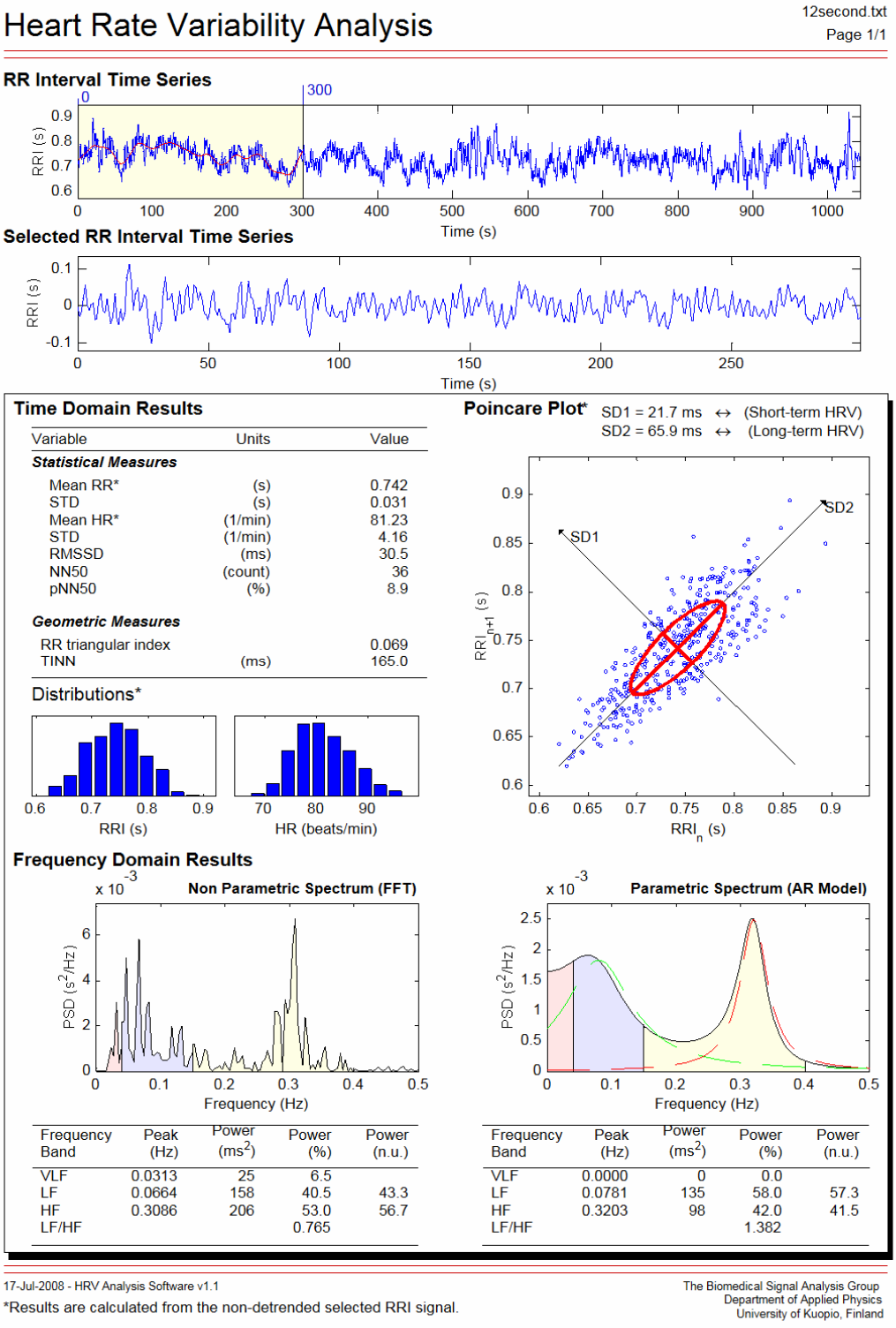

Figure A-57: Baseline HRV data for subject 12, tested while stimulant-free

Subject 12 Focussed attention

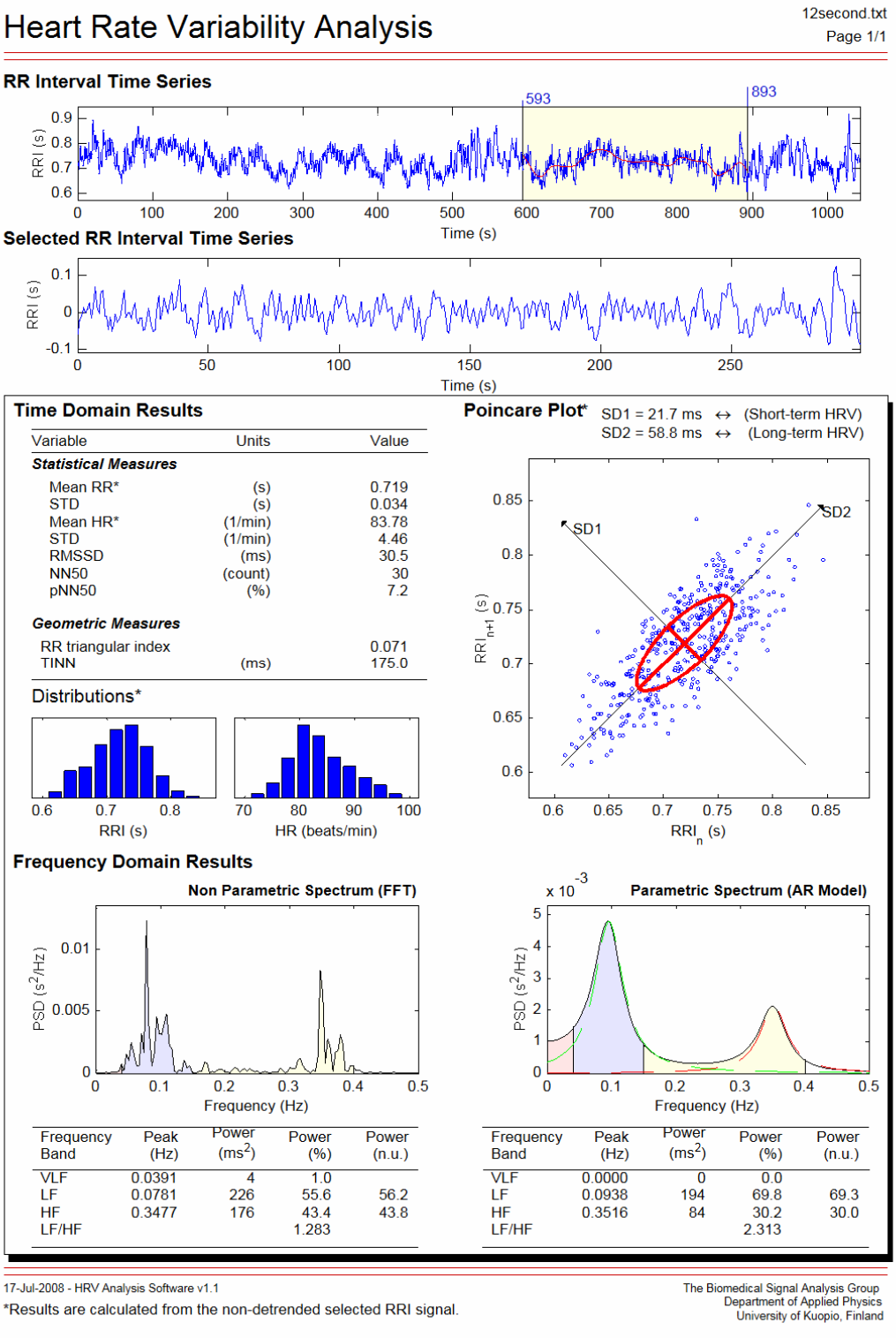

Figure A-58: HRV data during focussed attention for subject 12, tested while stimulant-free

Subject 13 Baseline

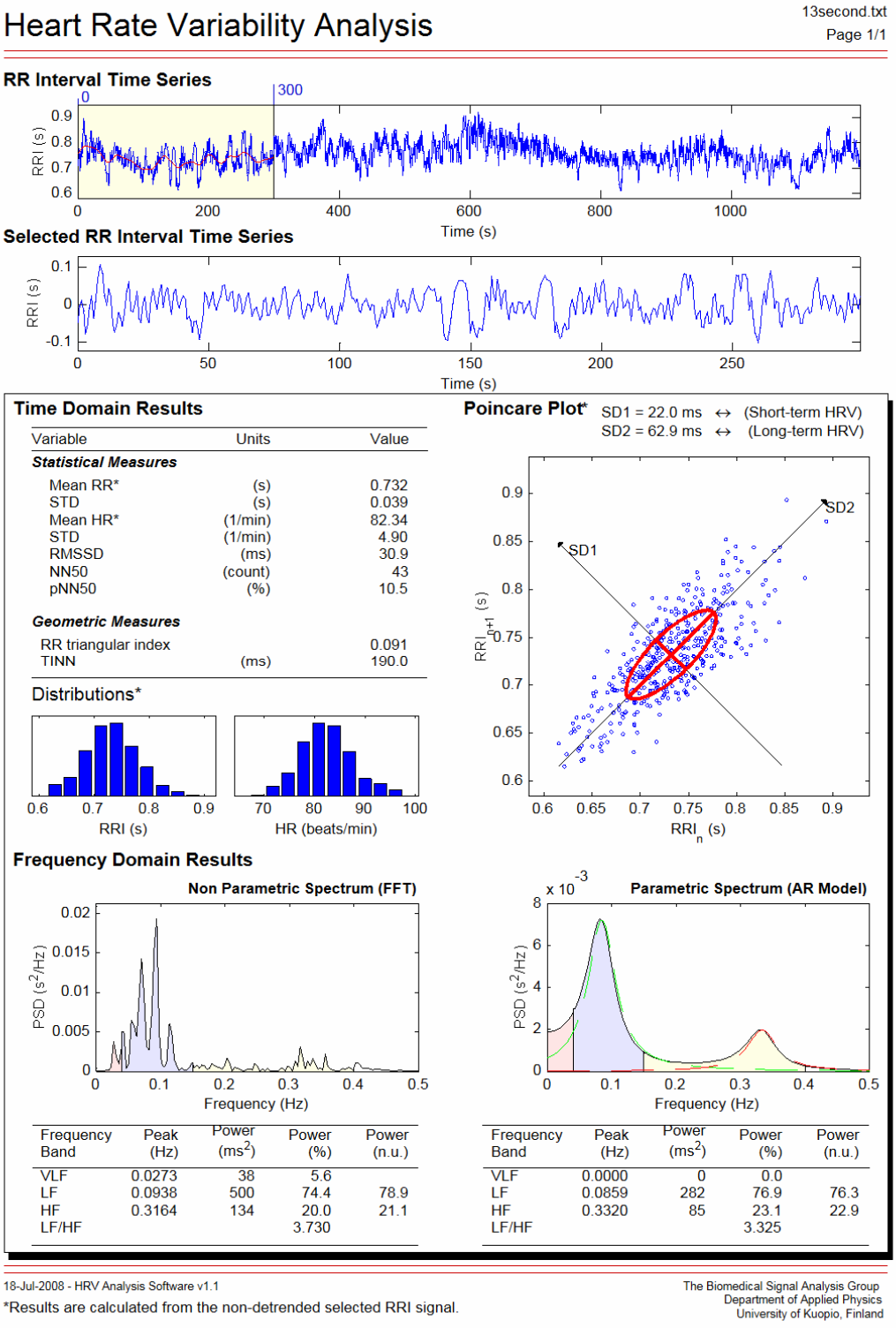

Figure A-59: Baseline HRV data for subject 13, tested while stimulant-free

Subject 13 Focussed attention

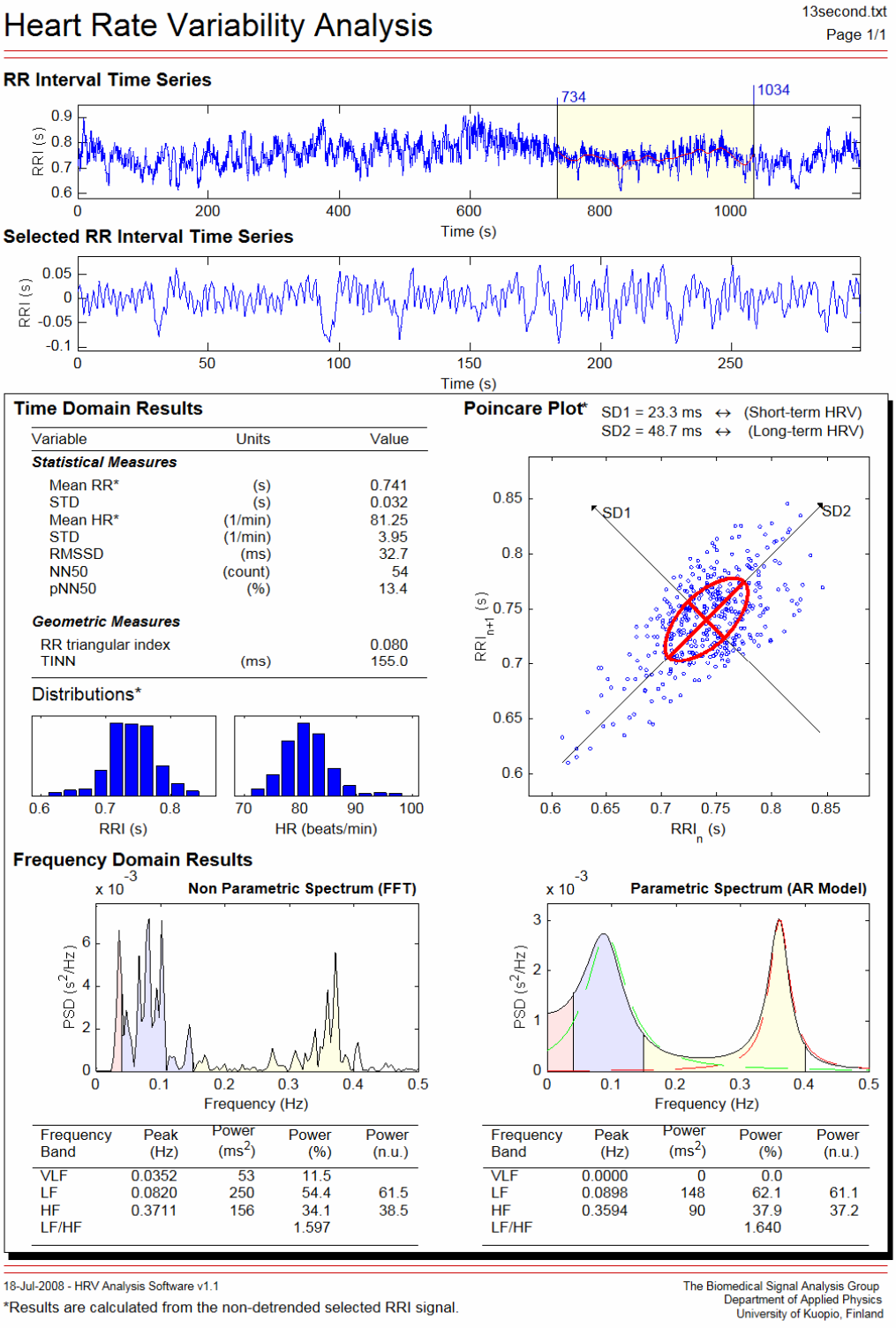

Figure A-60: HRV data during focussed attention for subject 13, tested while stimulant-free

Subject 14 Baseline

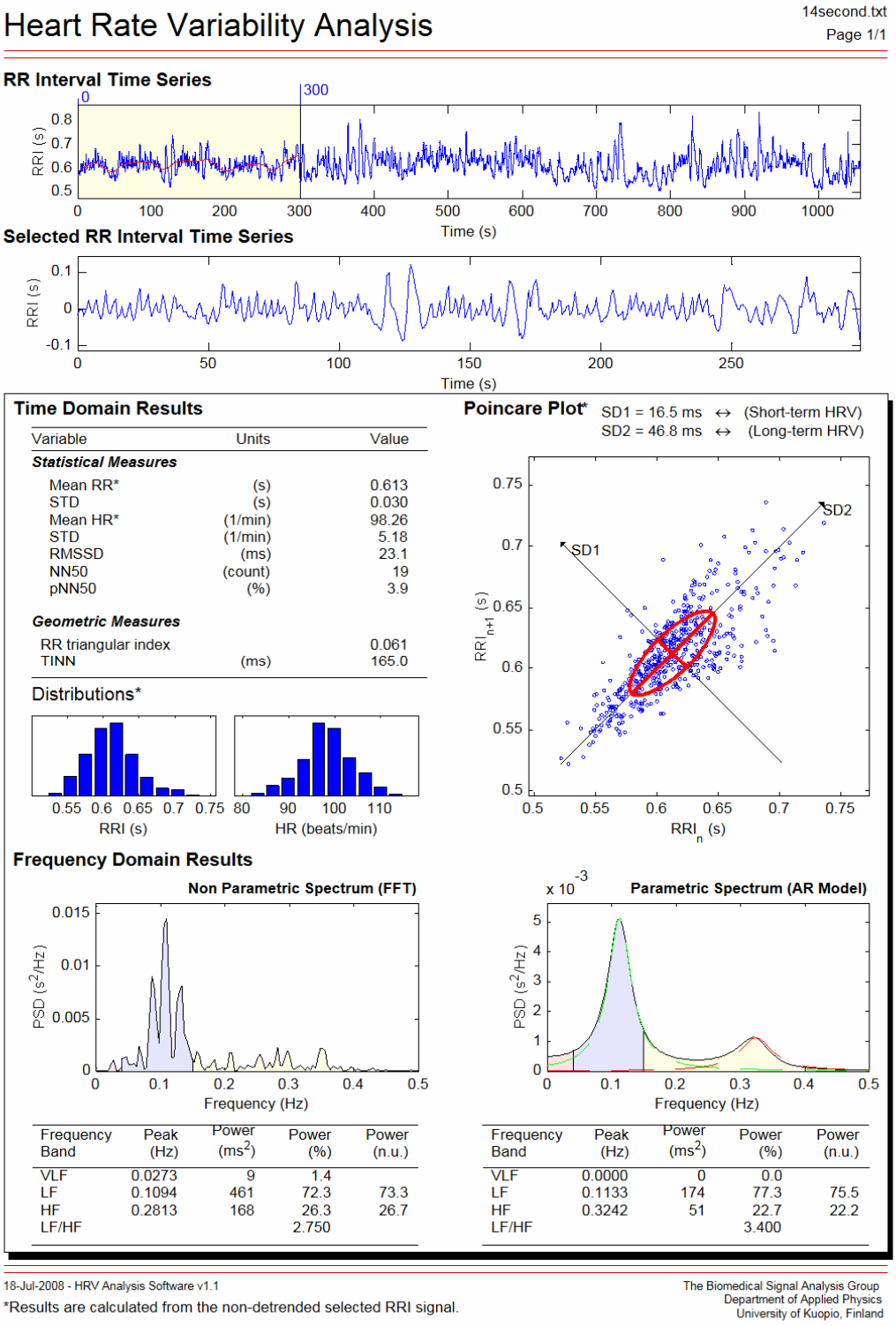

Figure A-61: Baseline HRV data for subject 14, tested while stimulant-free

Subject 14 Focussed attention

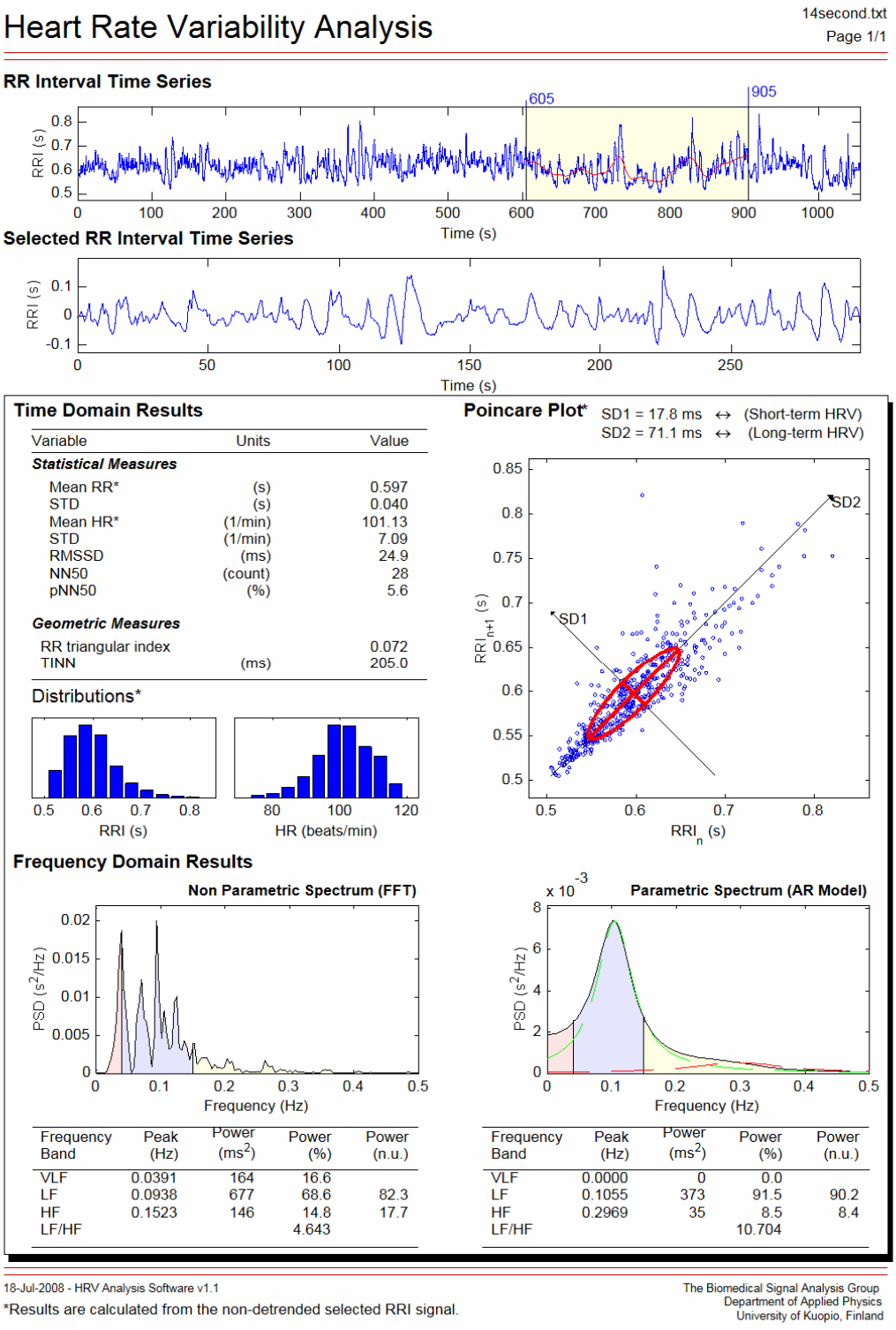

Figure A-62: HRV data during focussed attention for subject 14, tested while stimulant-free

Subject 15 Baseline

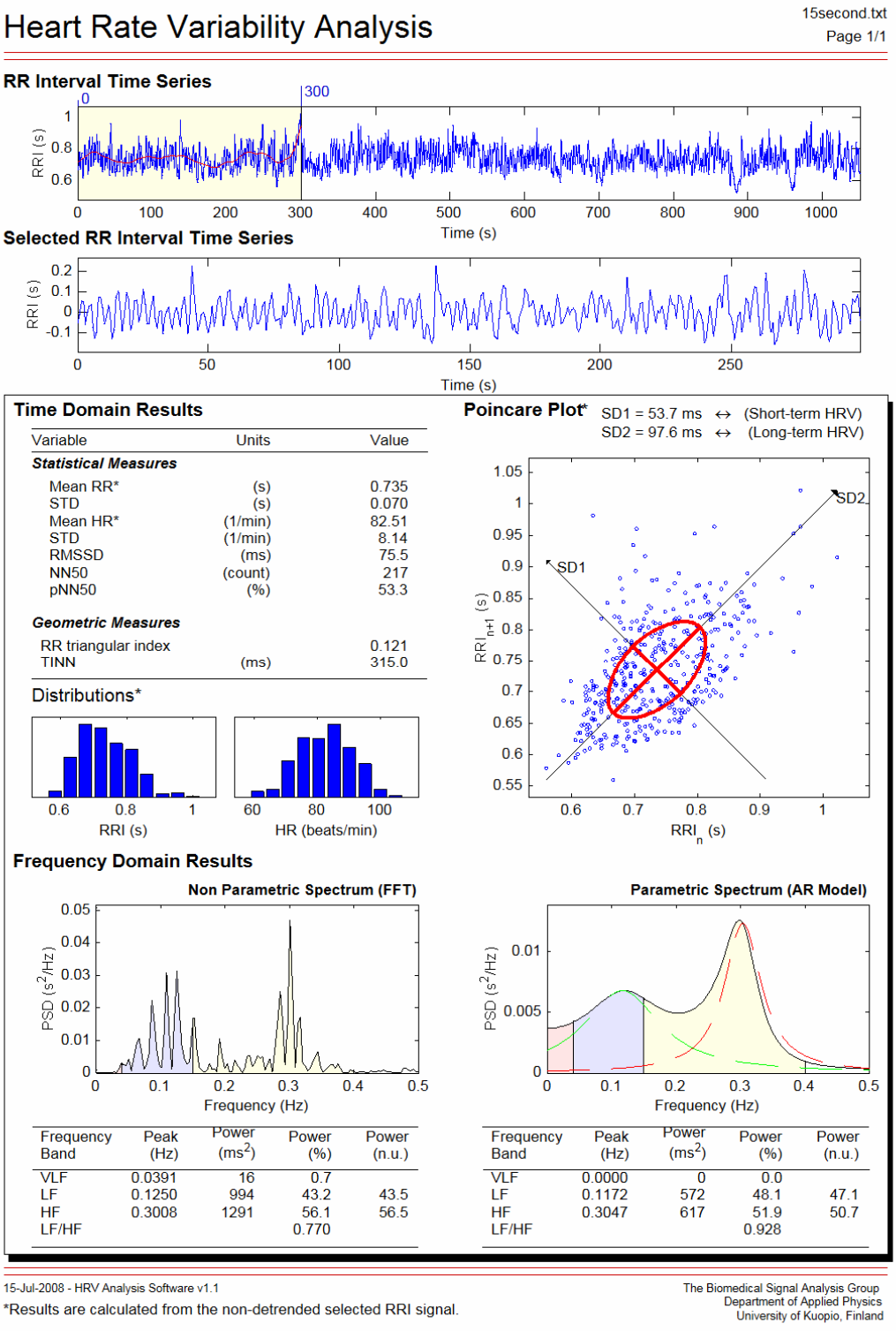

Figure A-63: Baseline HRV data for subject 15, tested while stimulant-free

Subject 15 Focussed attention

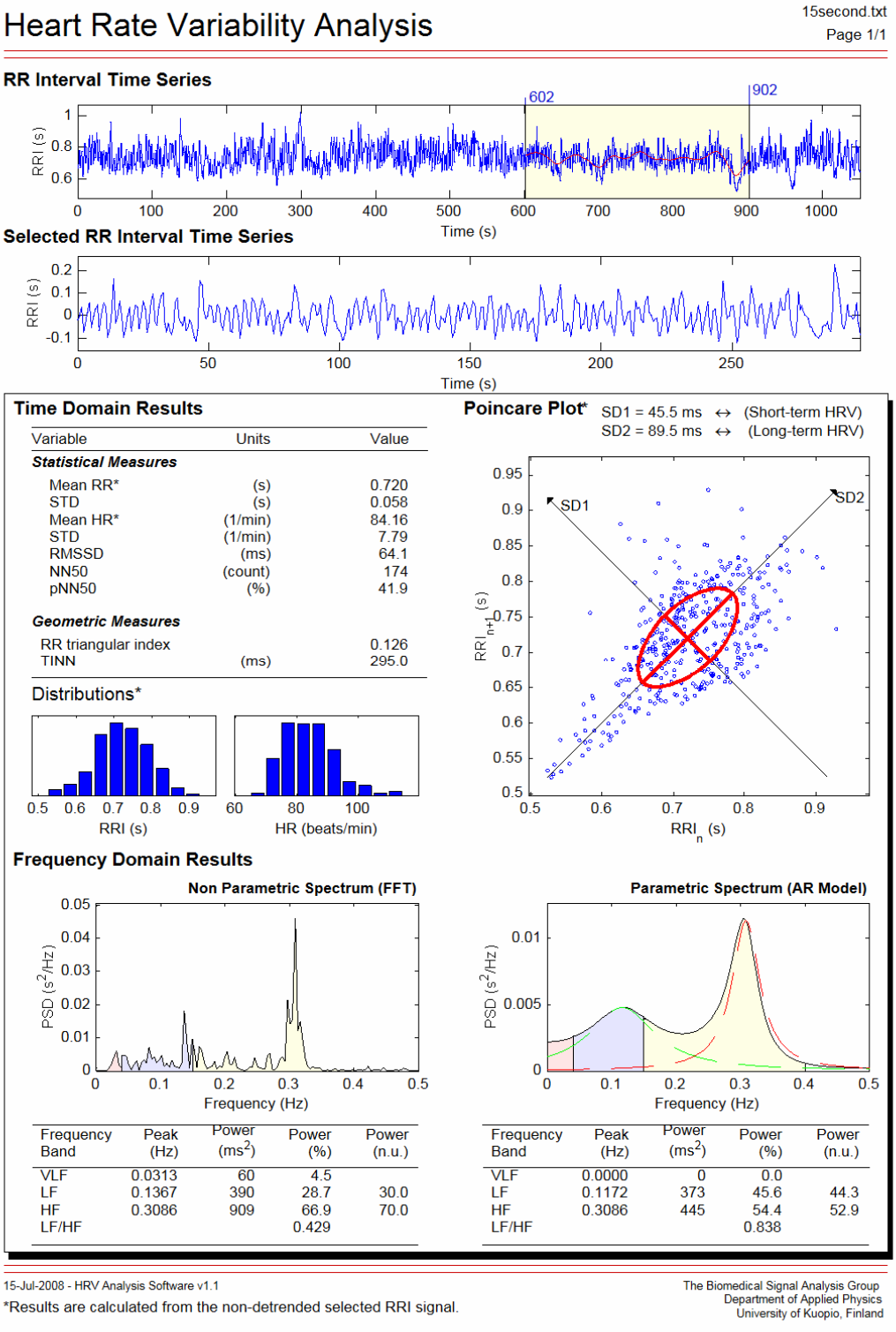

Figure A-64: HRV data during focussed attention for subject 15, tested while stimulant-free

Subject 16 Baseline

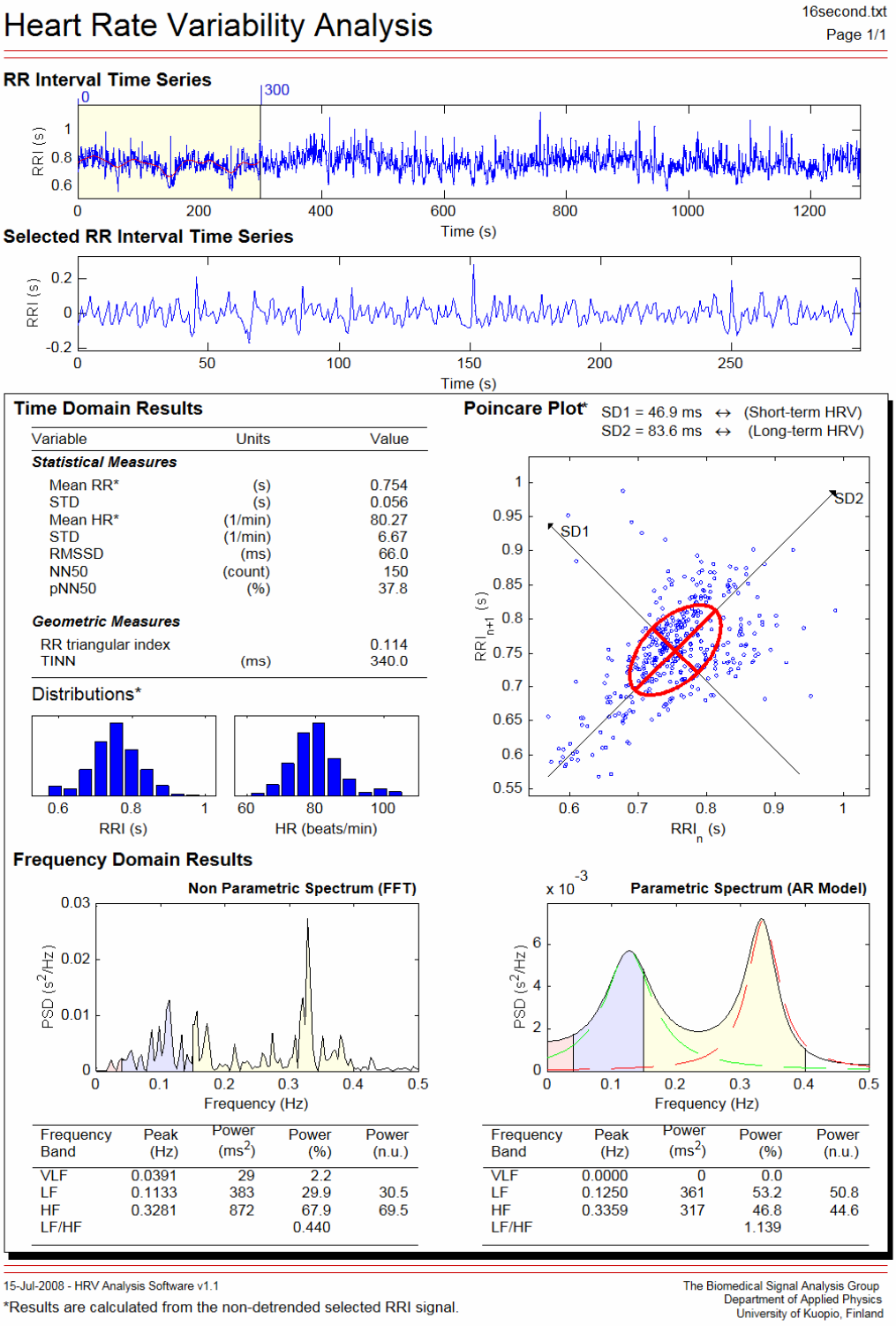

Figure A-65: Baseline HRV data for subject 16, tested while stimulant-free

Subject 16 Focussed attention

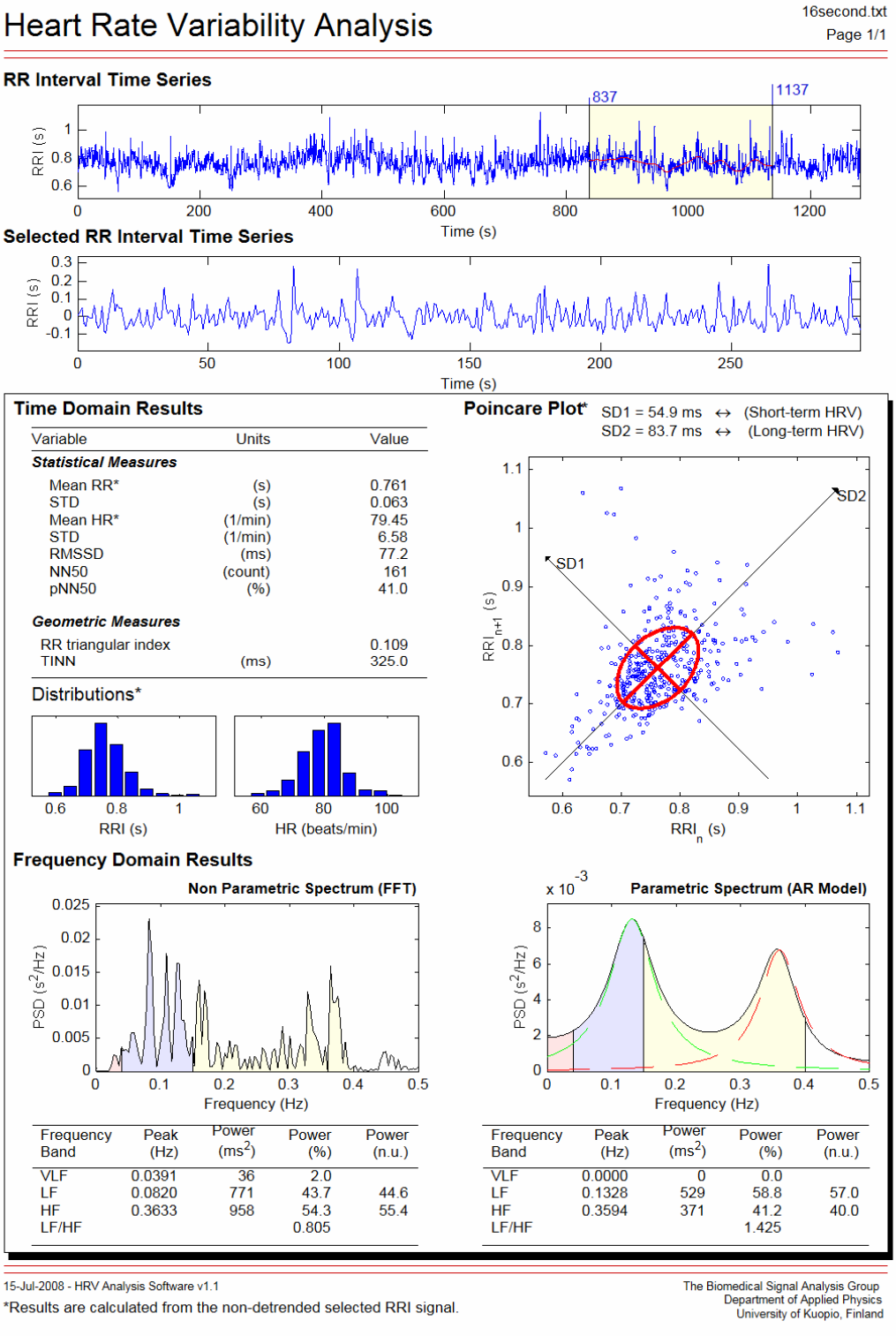

Figure A-66: HRV data during focussed attention for subject 16, tested while stimulant-free

Subject 17 Baseline

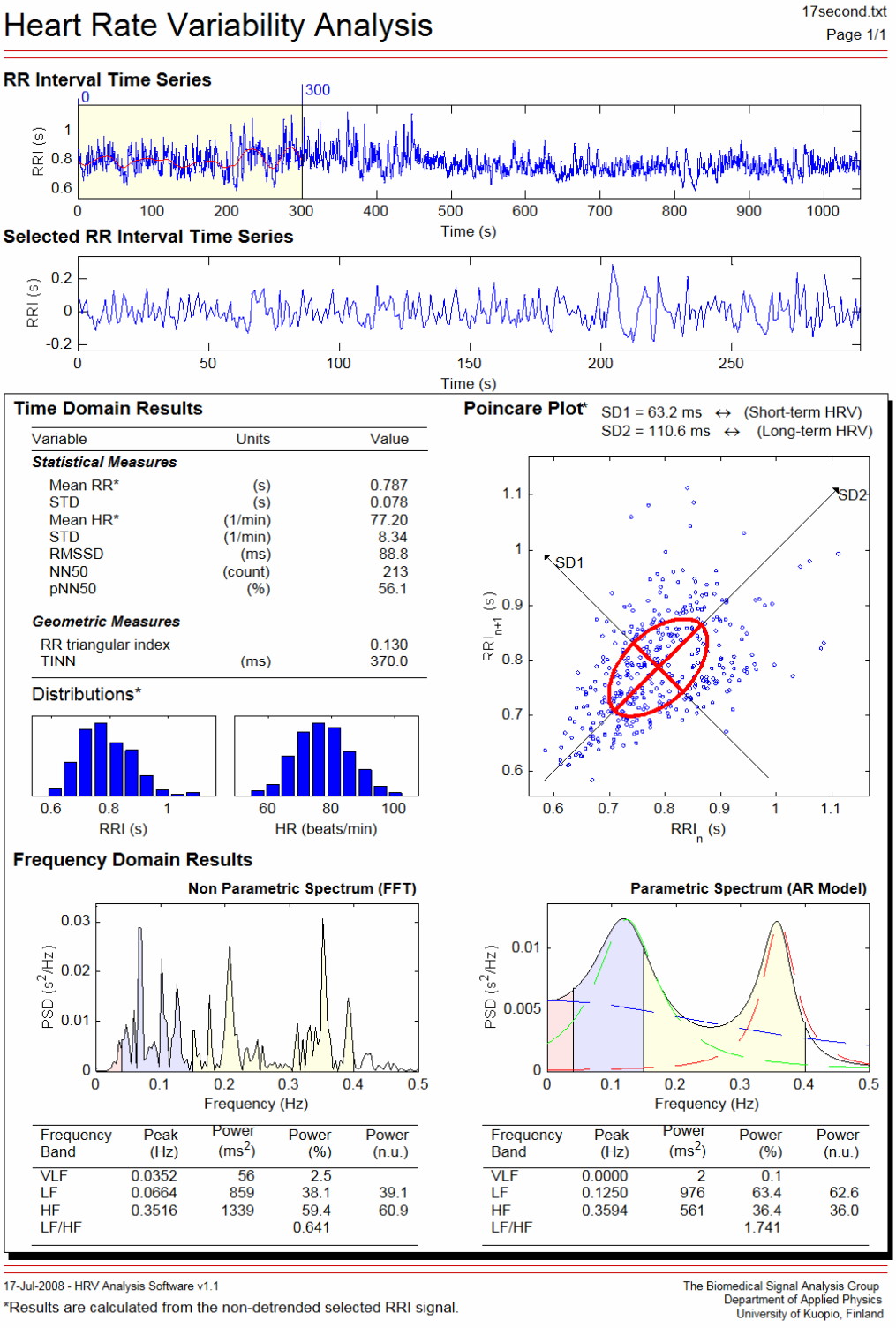

Figure A-67: Baseline HRV data for subject 17, tested while stimulant-free

Subject 17 Focussed attention

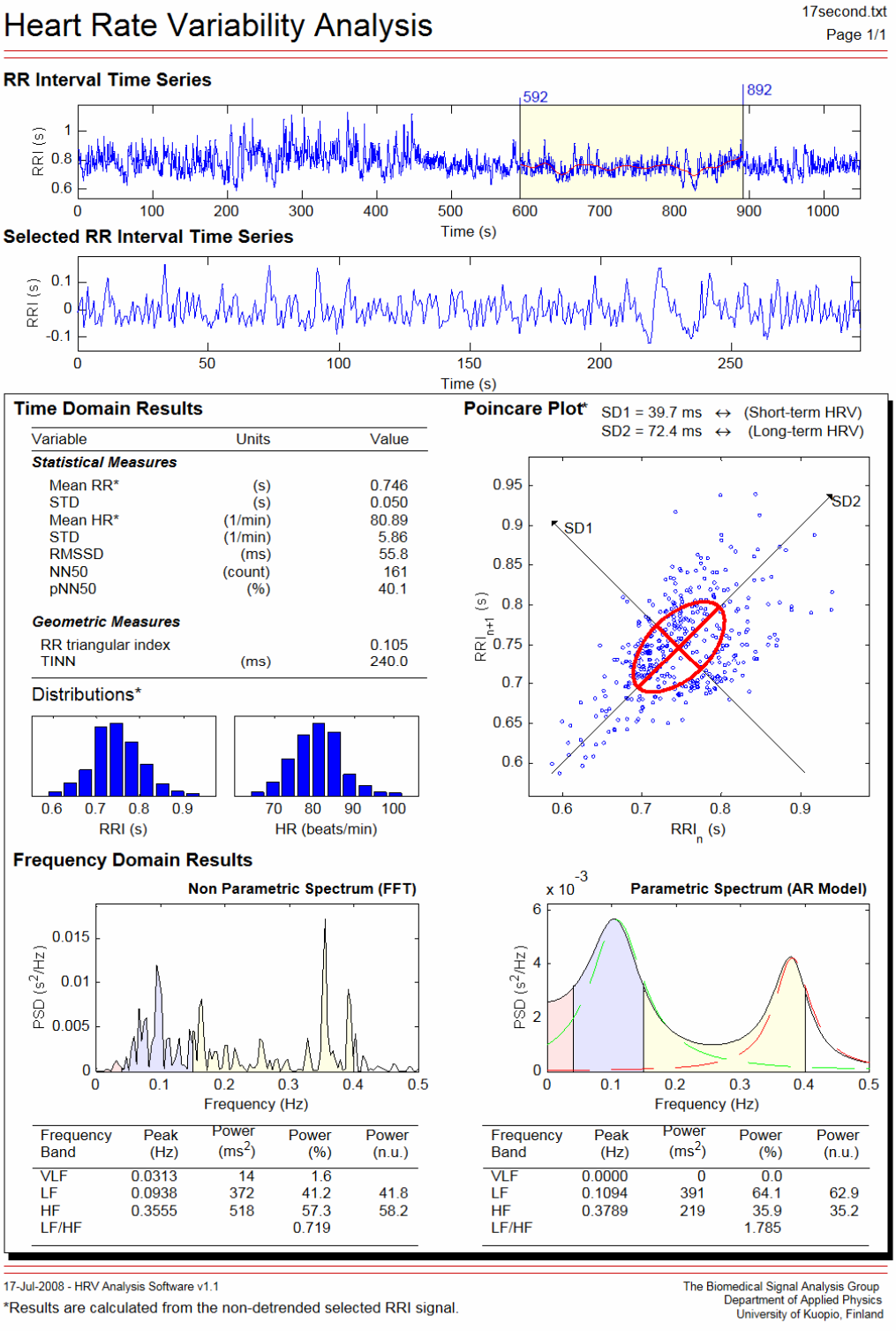

Figure A-68: HRV data during focussed attention for subject 17, tested while stimulant-free

Subject 18 Baseline

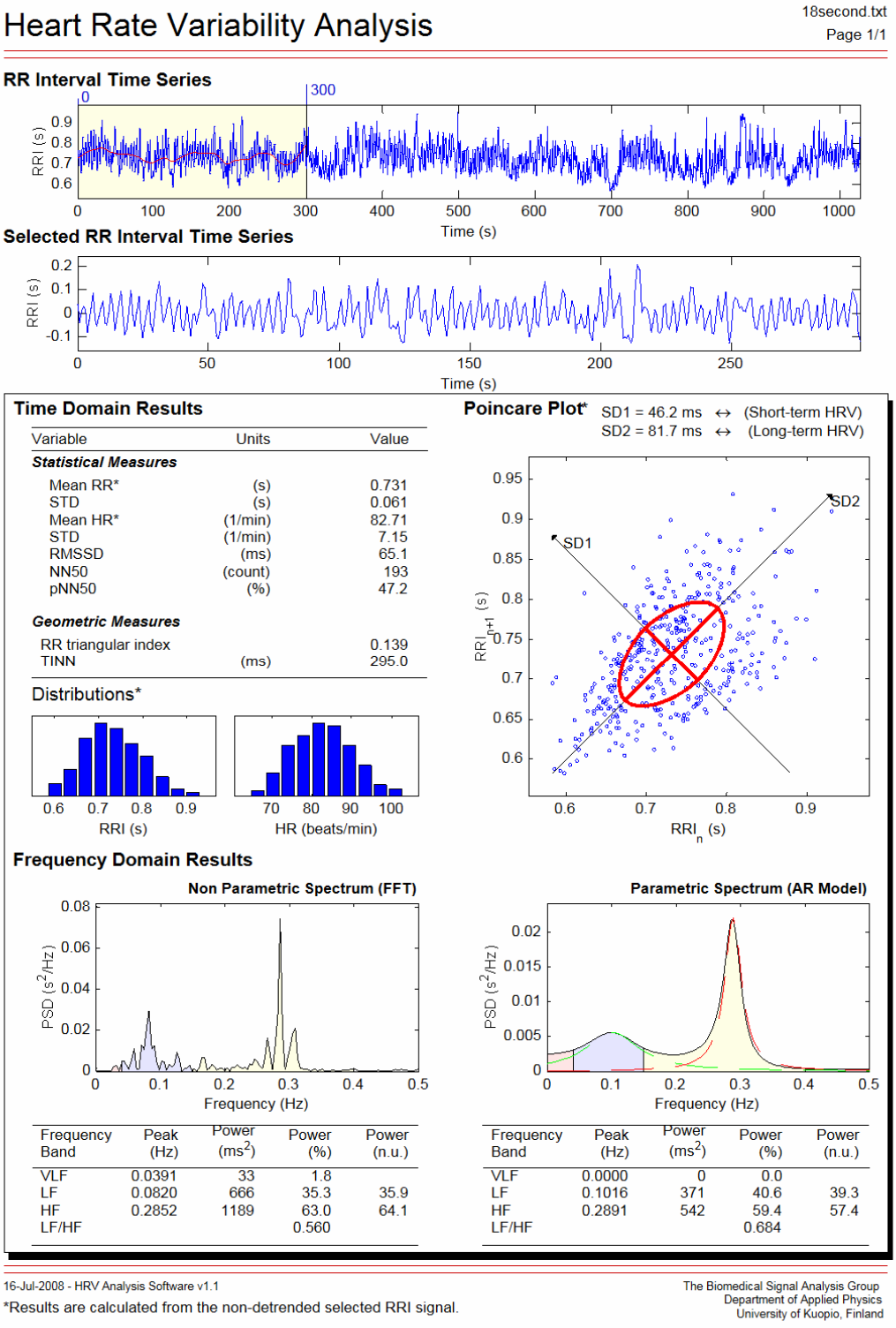

Figure A-69: Baseline HRV data for subject 18, tested while stimulant-free

Subject 18 Focussed attention

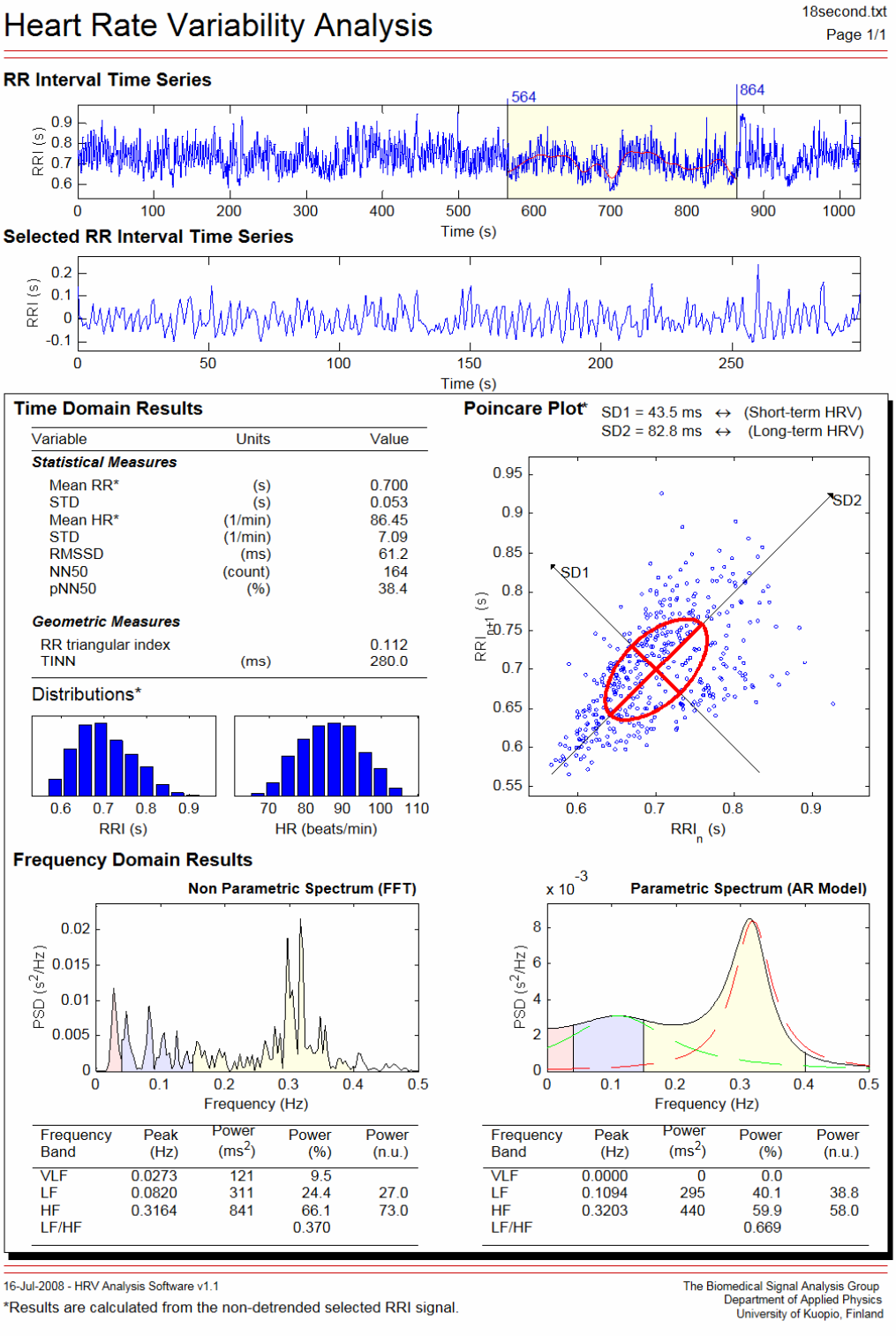

Figure A-70: HRV data during focussed attention for subject 18, tested while stimulant-free

Subject 19 Baseline

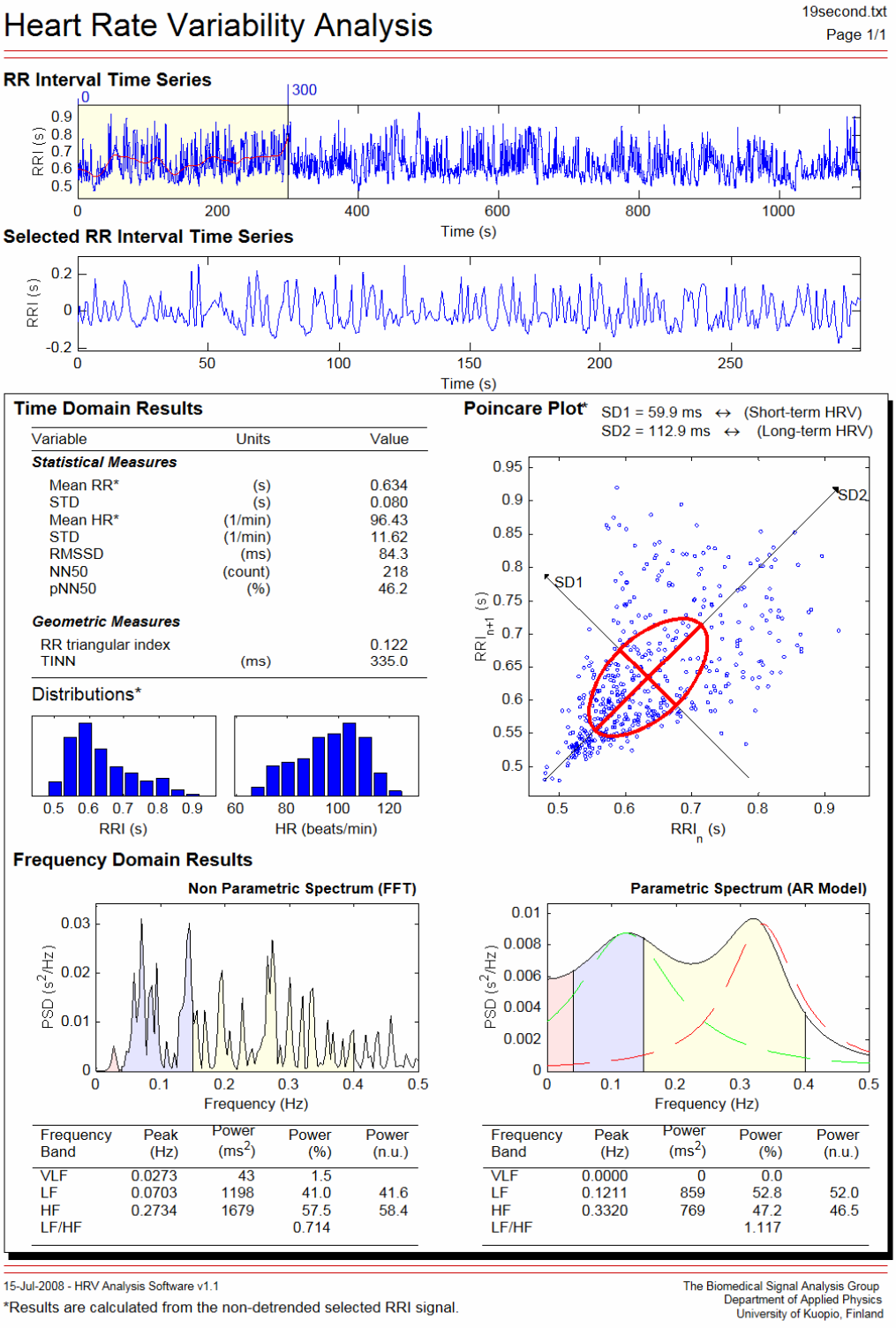

Figure A-71: Baseline HRV data for subject 19, tested while stimulant-free

Subject 19 Focussed attention

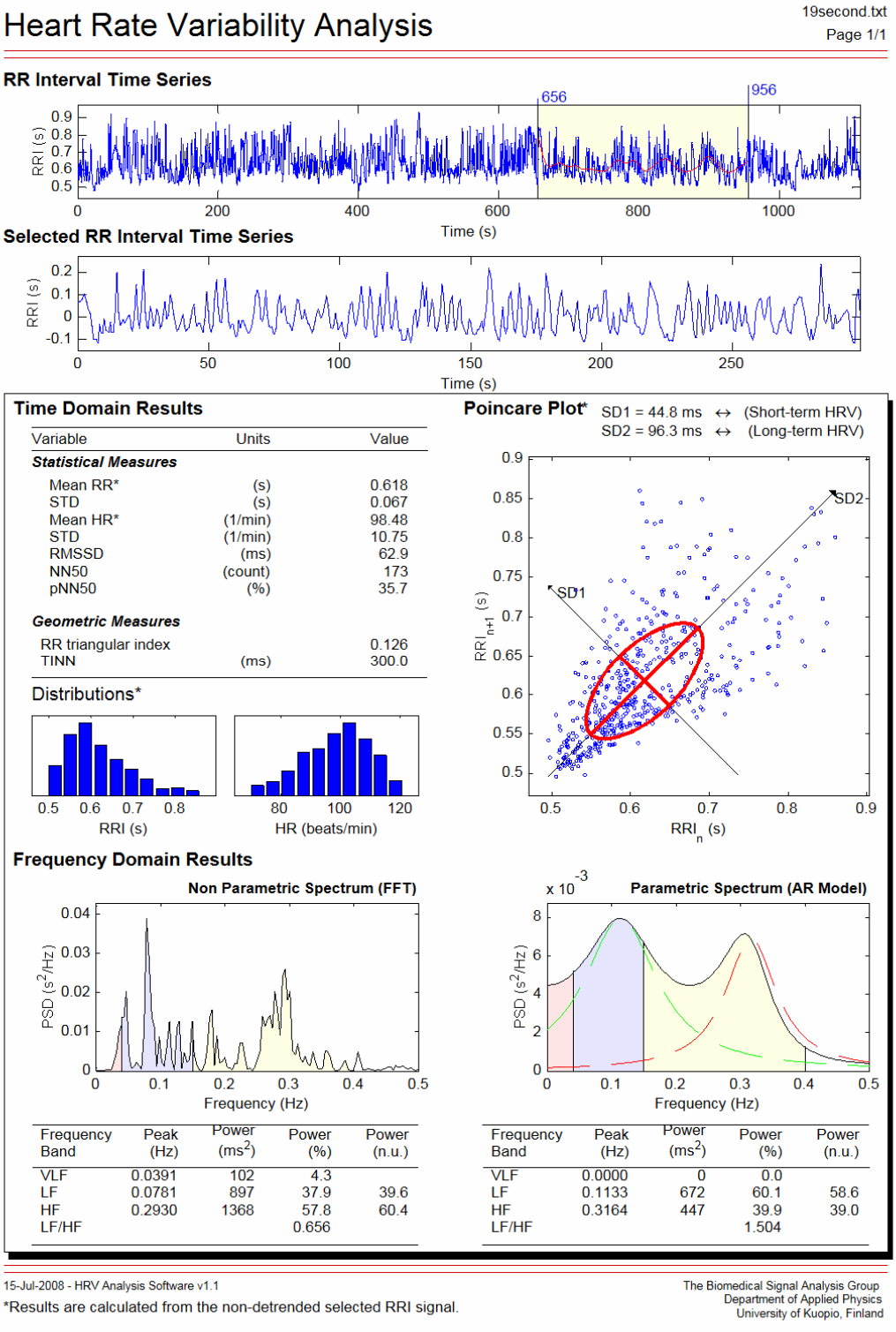

Figure A-72: HRV data during focussed attention for subject 19, tested while stimulant-free

Subject 20 Baseline

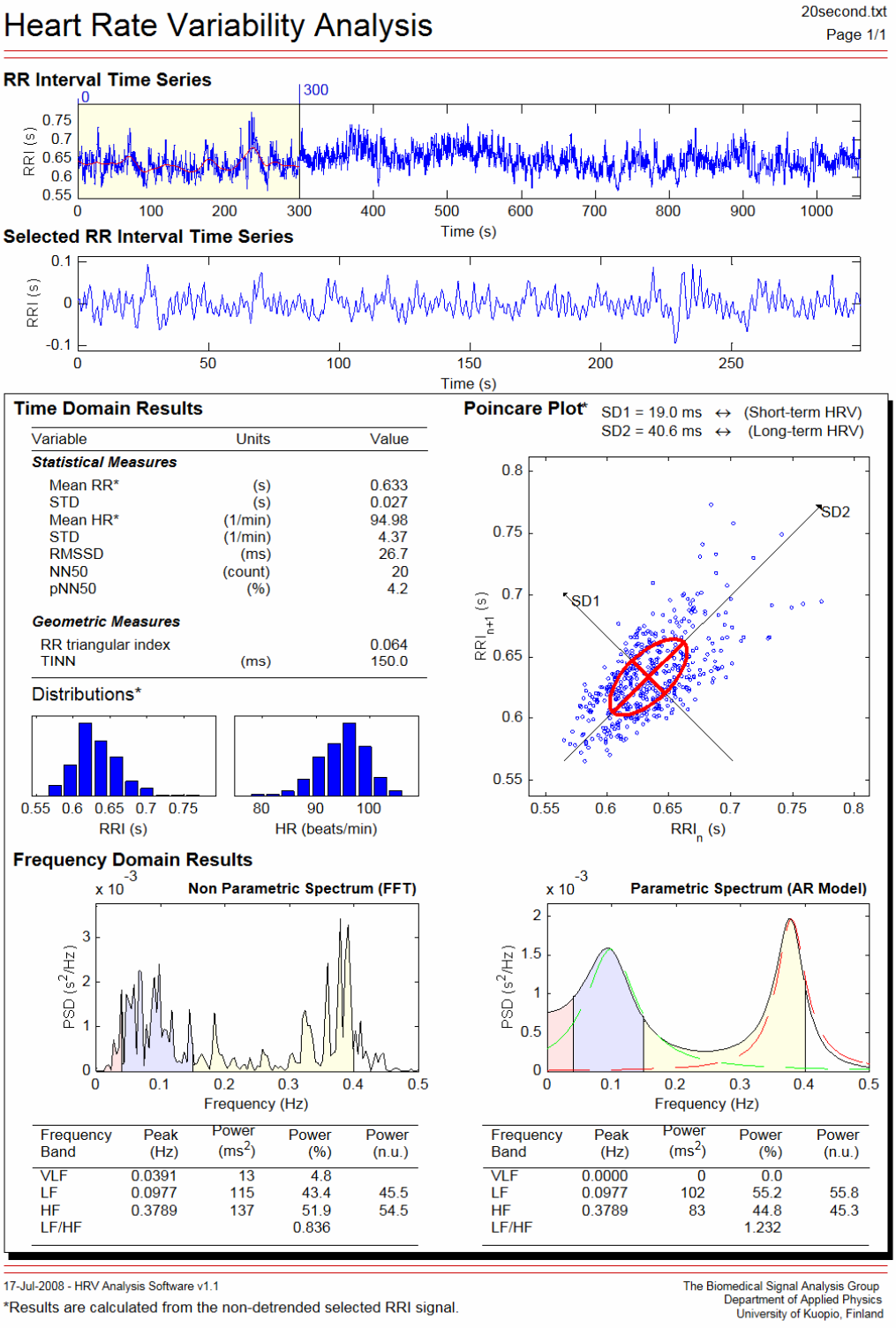

Figure A-73: Baseline HRV data for subject 20, tested while stimulant-free

Subject 20 Focussed attention

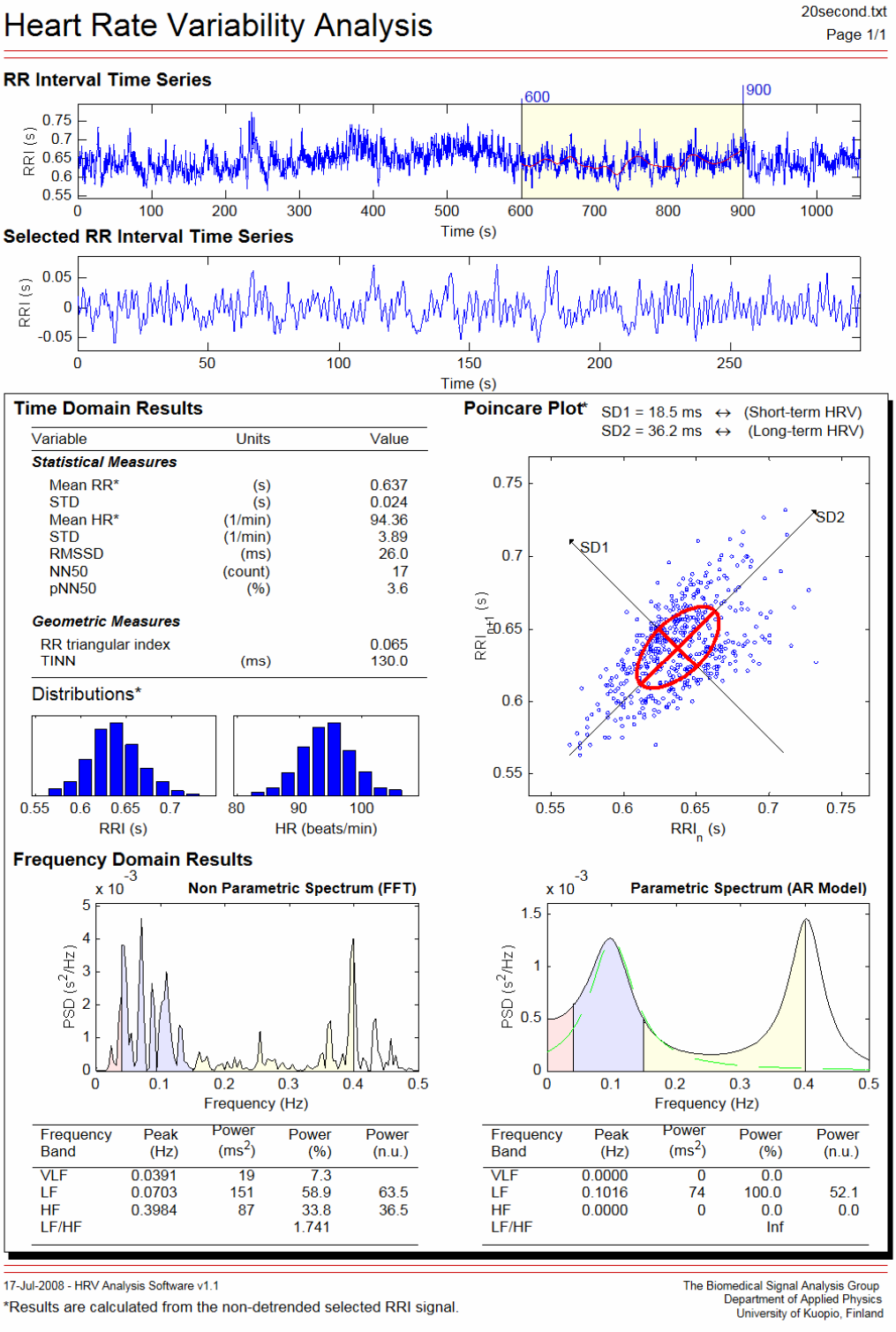

Figure A-74: HRV data during focussed attention for subject 20, tested while stimulant-free

ADHD children on stimulant medication

Subject 01 Baseline

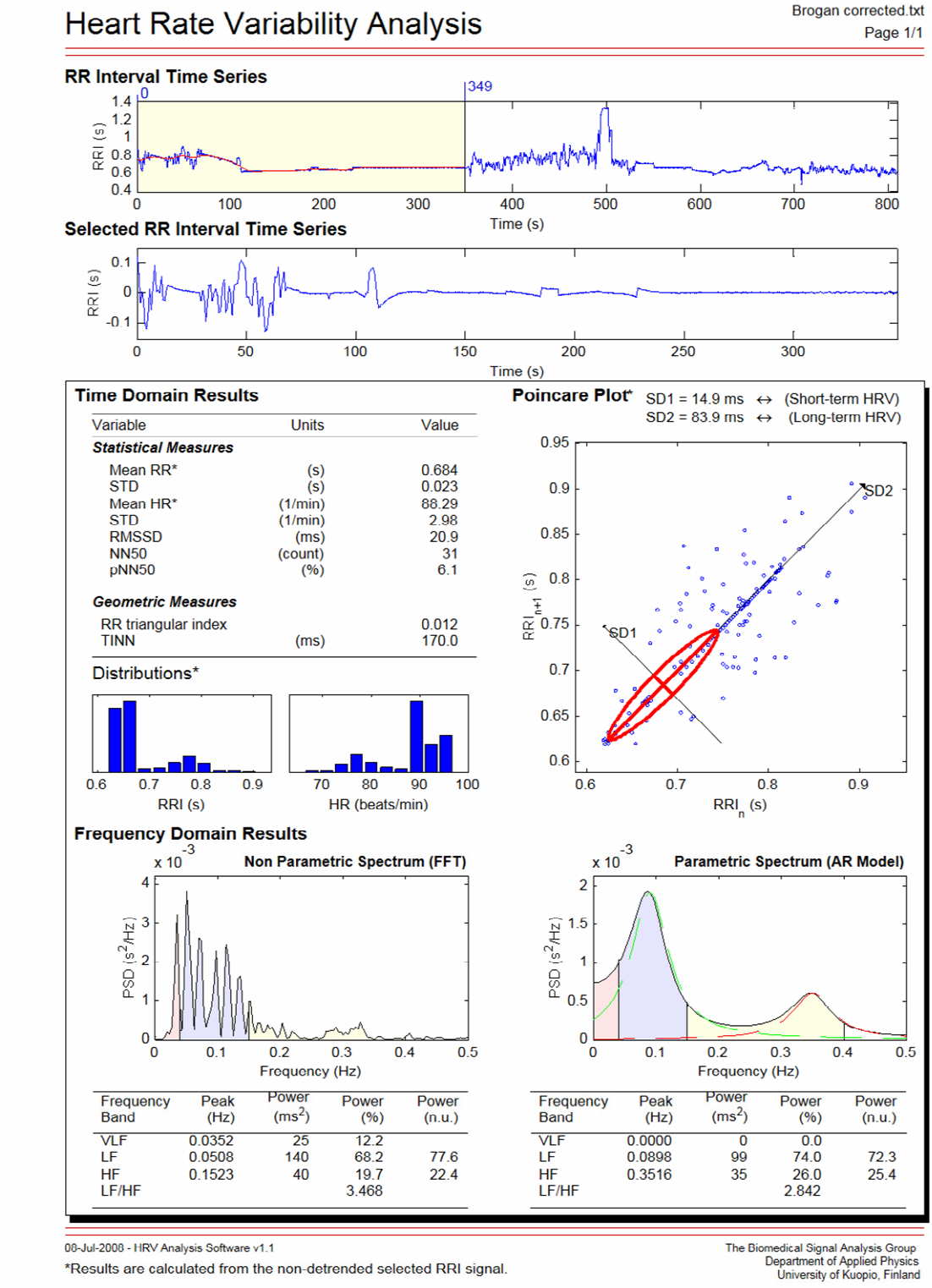

Figure A-75: Baseline HRV data for subject 01, tested while on stimulant medication

Subject 01 Focussed attention

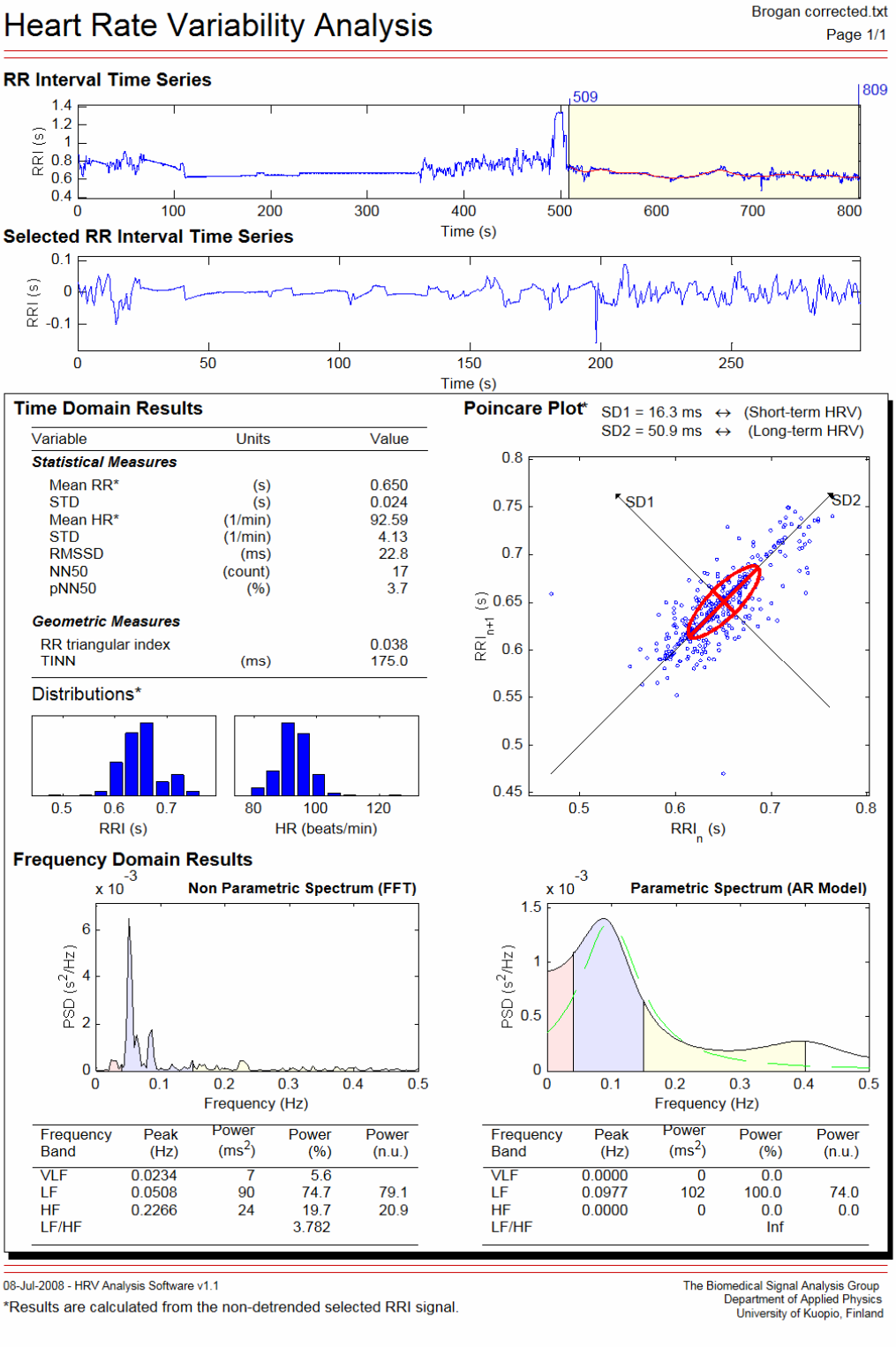

Figure A-76: HRV data during focussed attention for subject 01, tested while on stimulant medication

Subject 03 Baseline

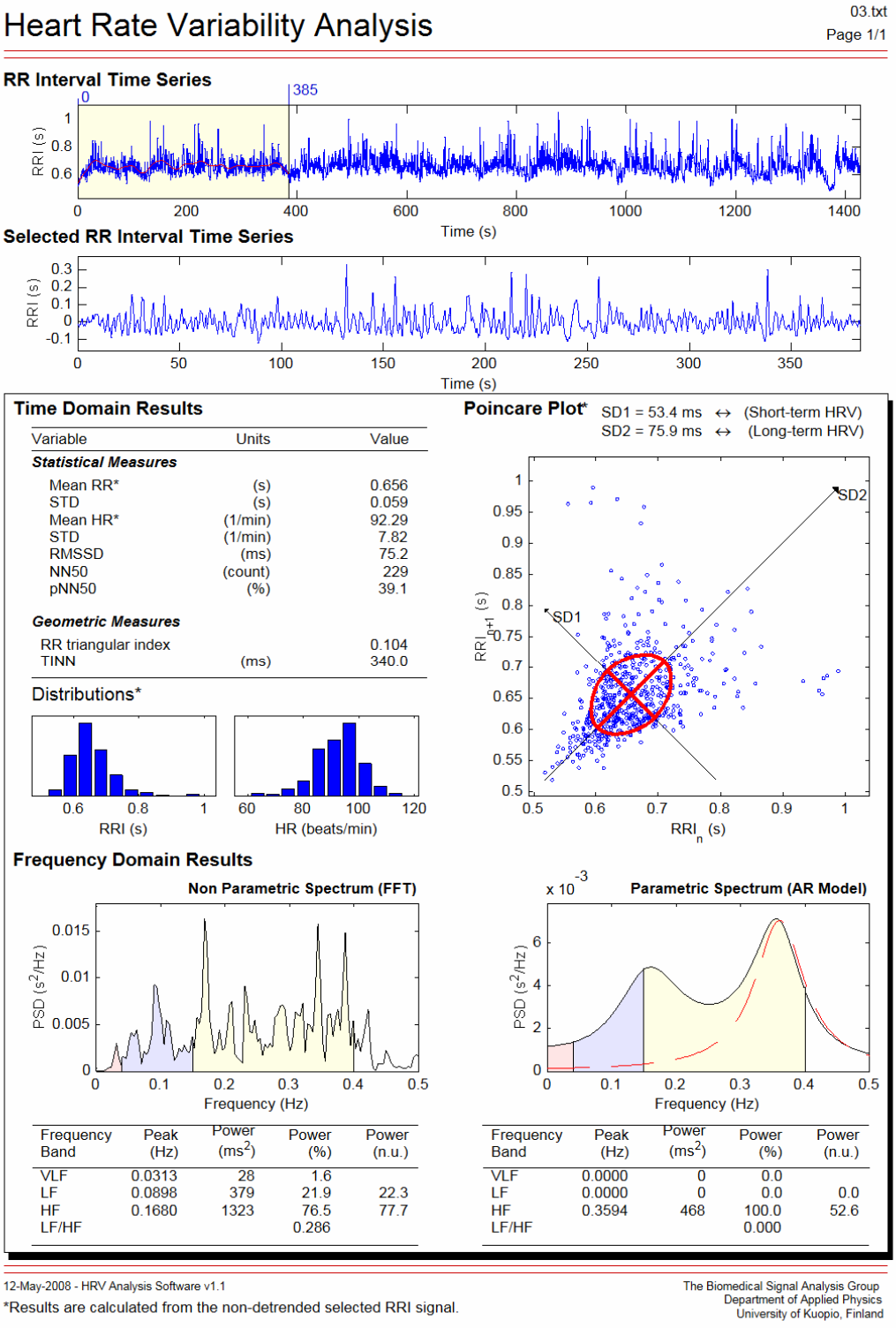

Figure A-77: Baseline HRV data for subject 03, tested while on stimulant medication

Subject 03 Focussed attention

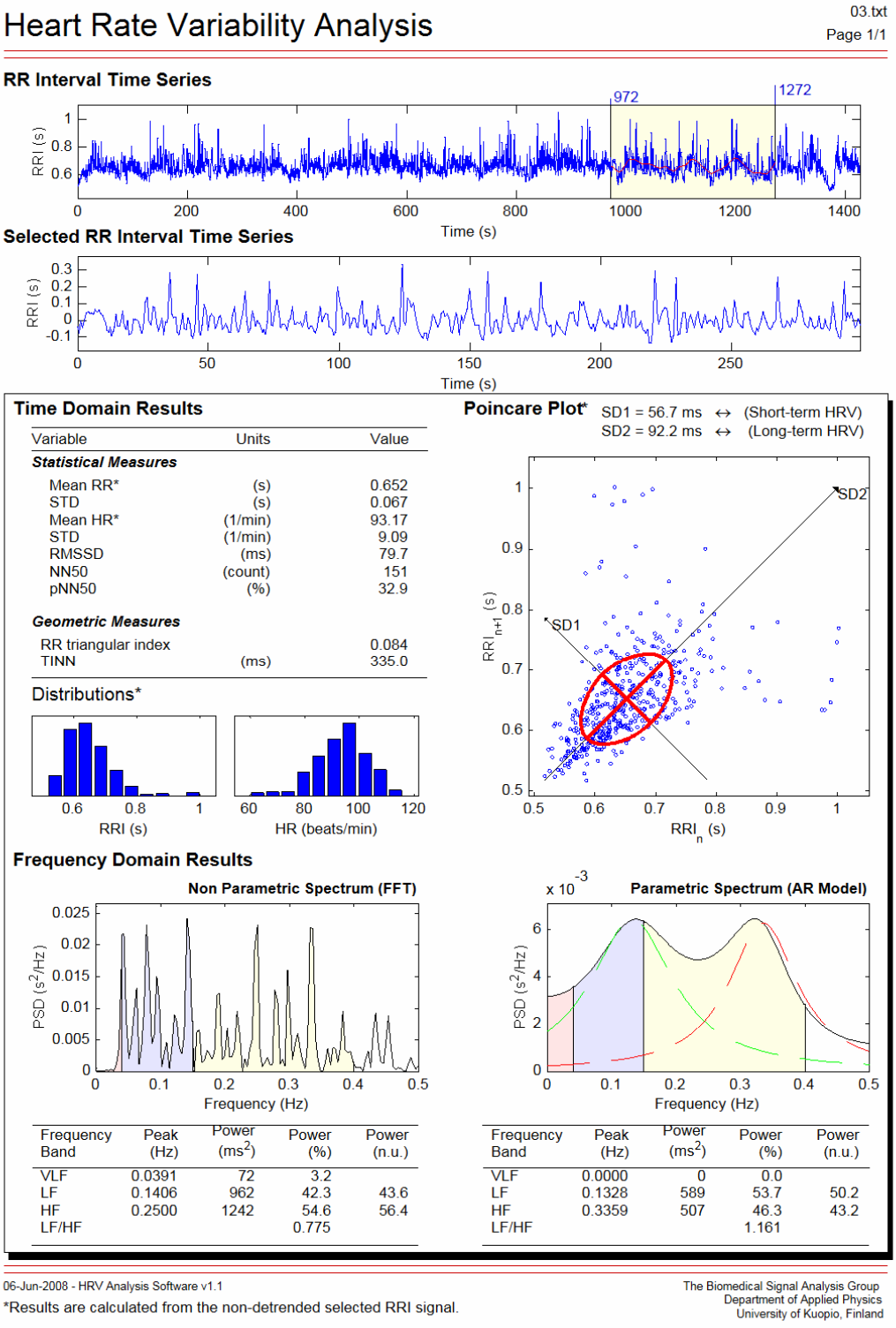

Figure A-78: HRV data during focussed attention for subject 03, tested while on stimulant medication

Subject 04 Baseline

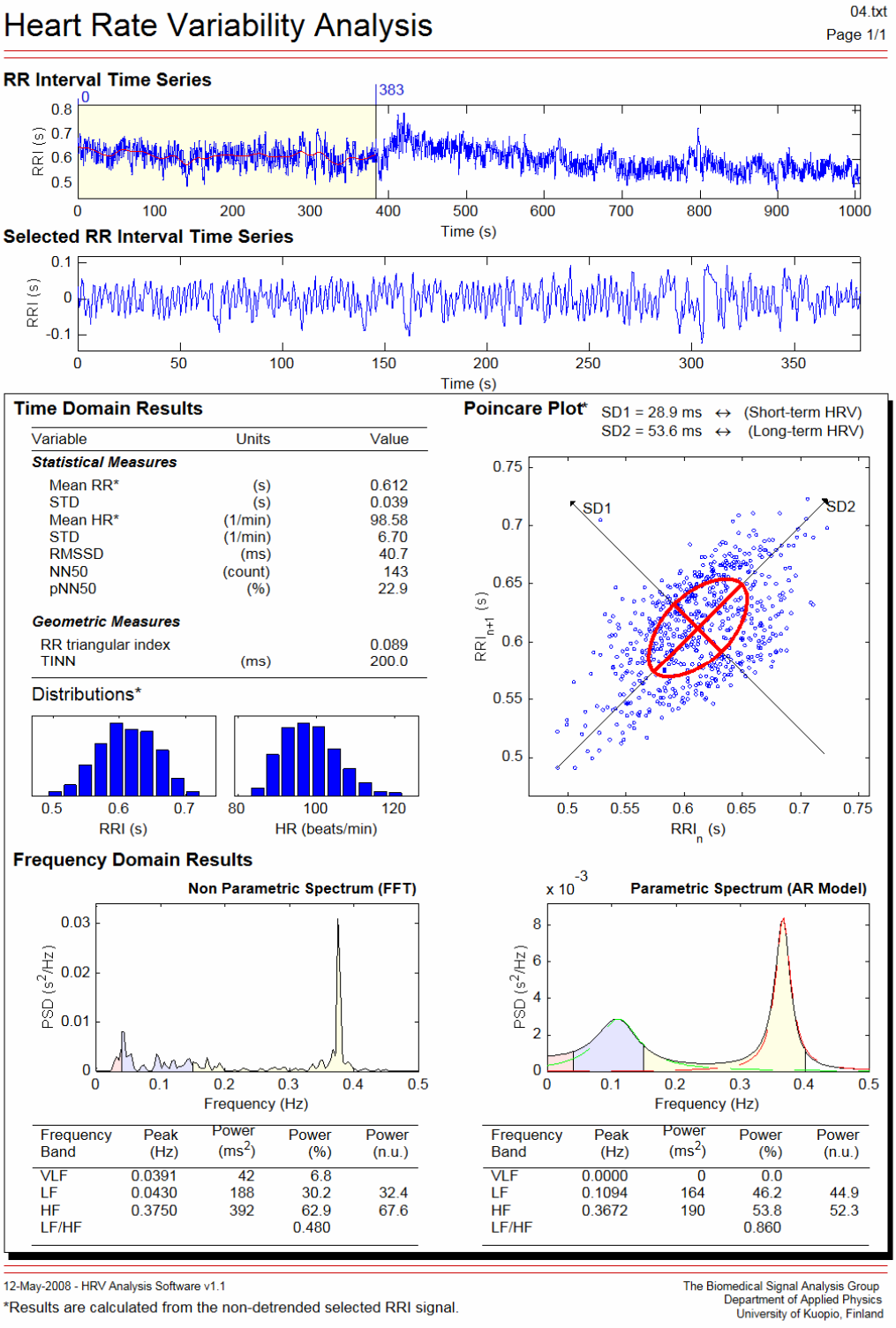

Figure A-79: Baseline HRV data for subject 04, tested while on stimulant medication

Subject 04 Focussed attention

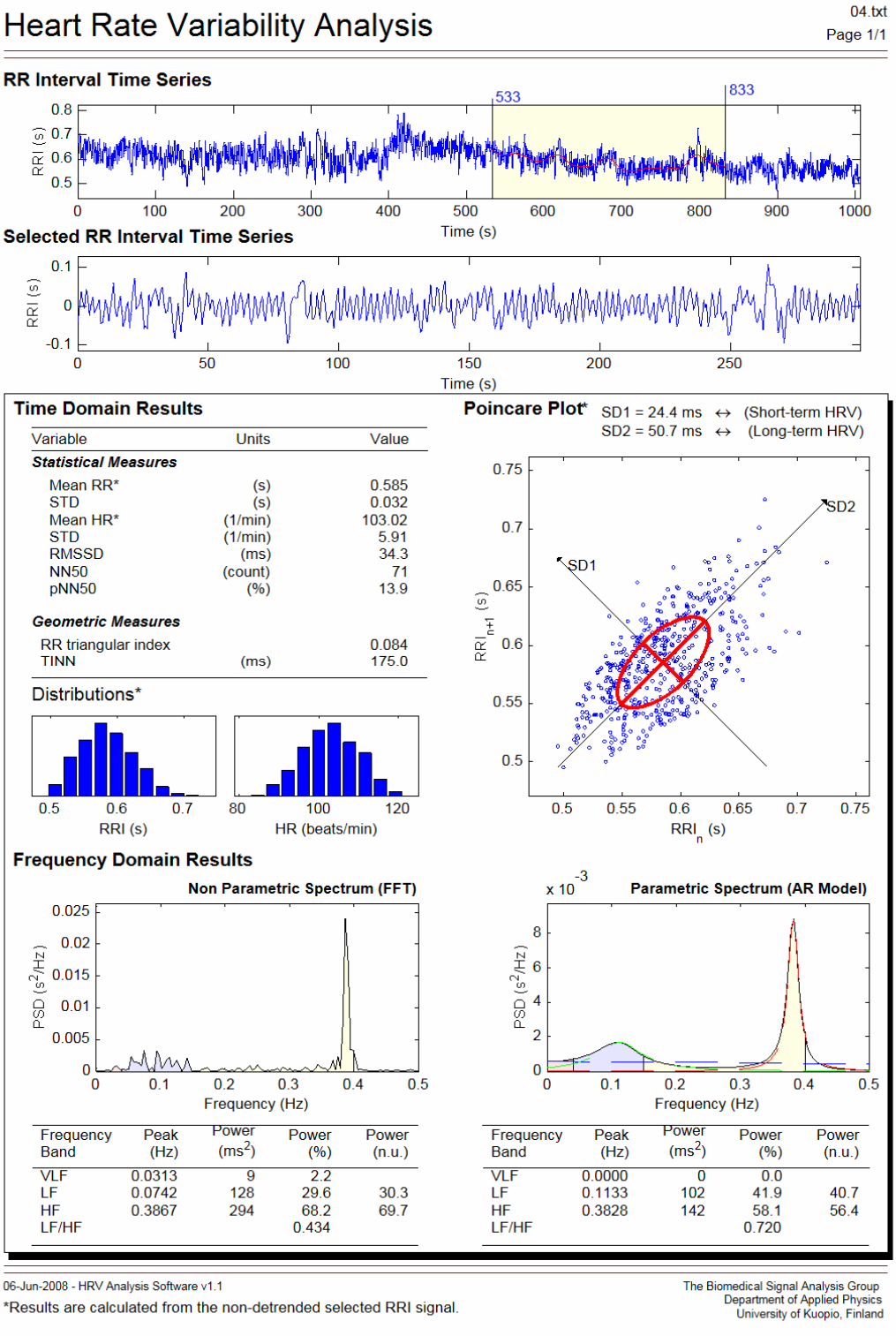

Figure A-80: HRV data during focussed attention for subject 04, tested while on stimulant medication

Subject 05 Baseline

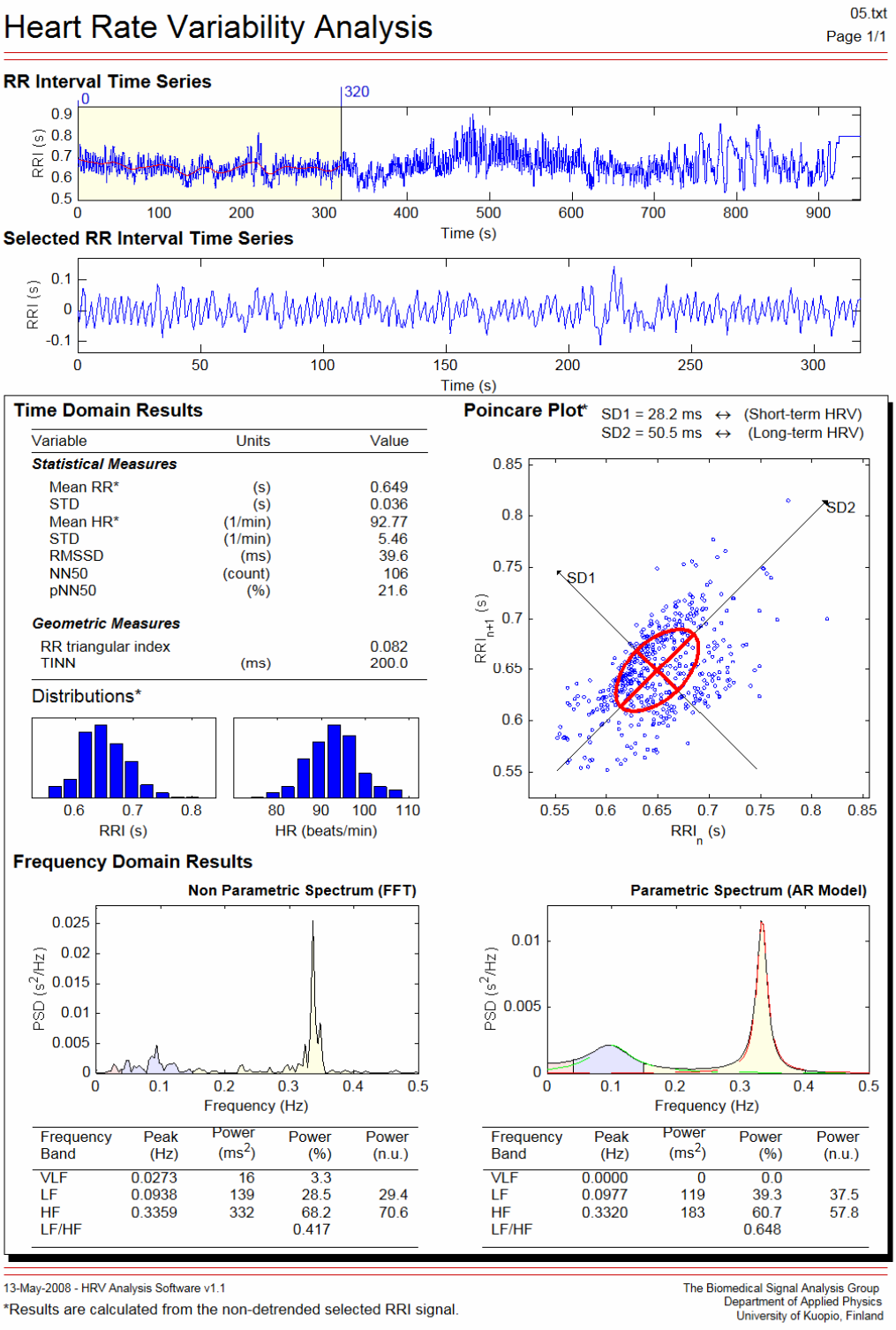

Figure A-81: Baseline HRV data for subject 05, tested while on stimulant medication

Subject 05 Focussed attention

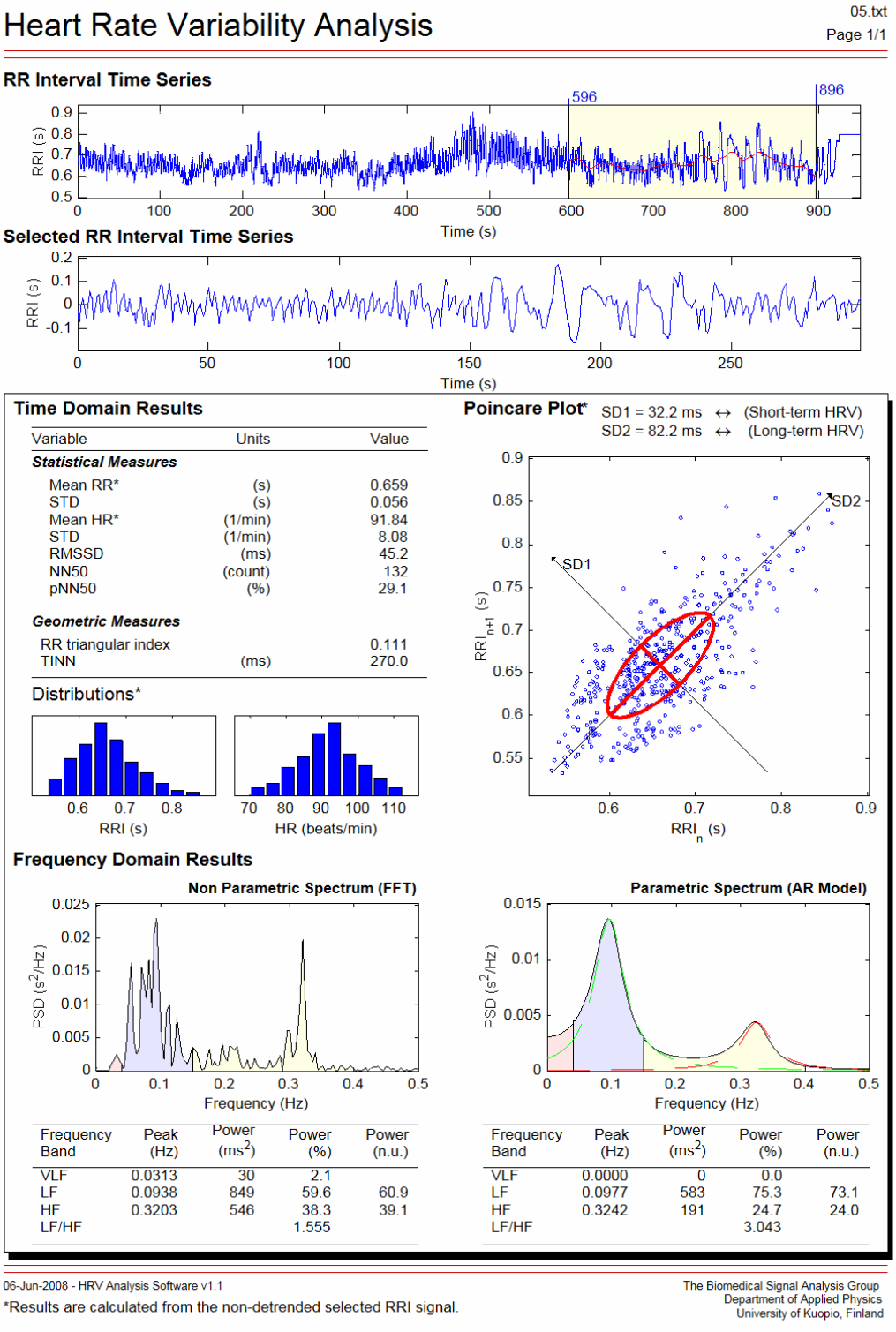

Figure A-82: HRV data during focussed attention for subject 05, tested while on stimulant medication

Subject 06 Baseline

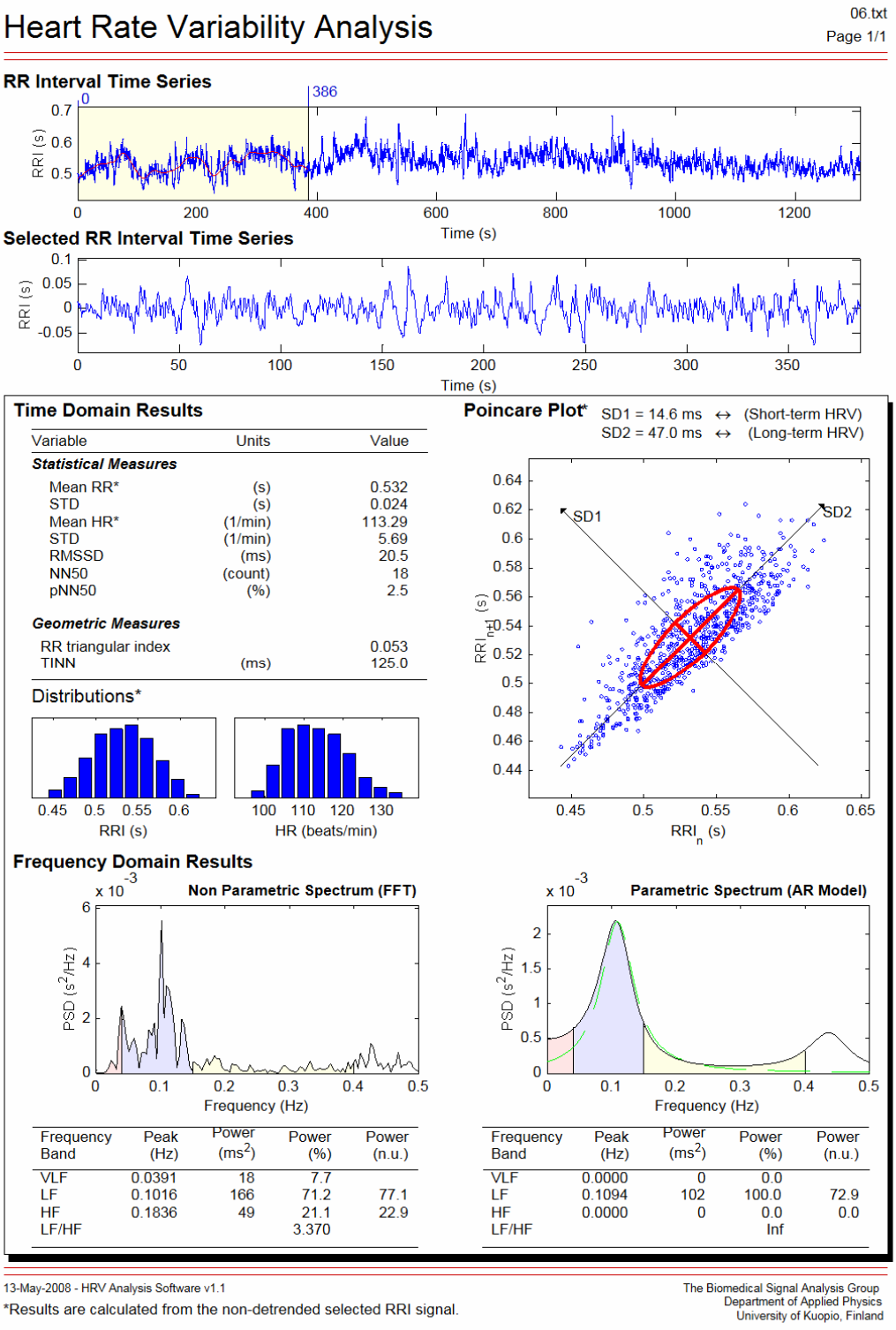

Figure A-83: Baseline HRV data for subject 06, tested while on stimulant medication

Subject 06 Focussed attention

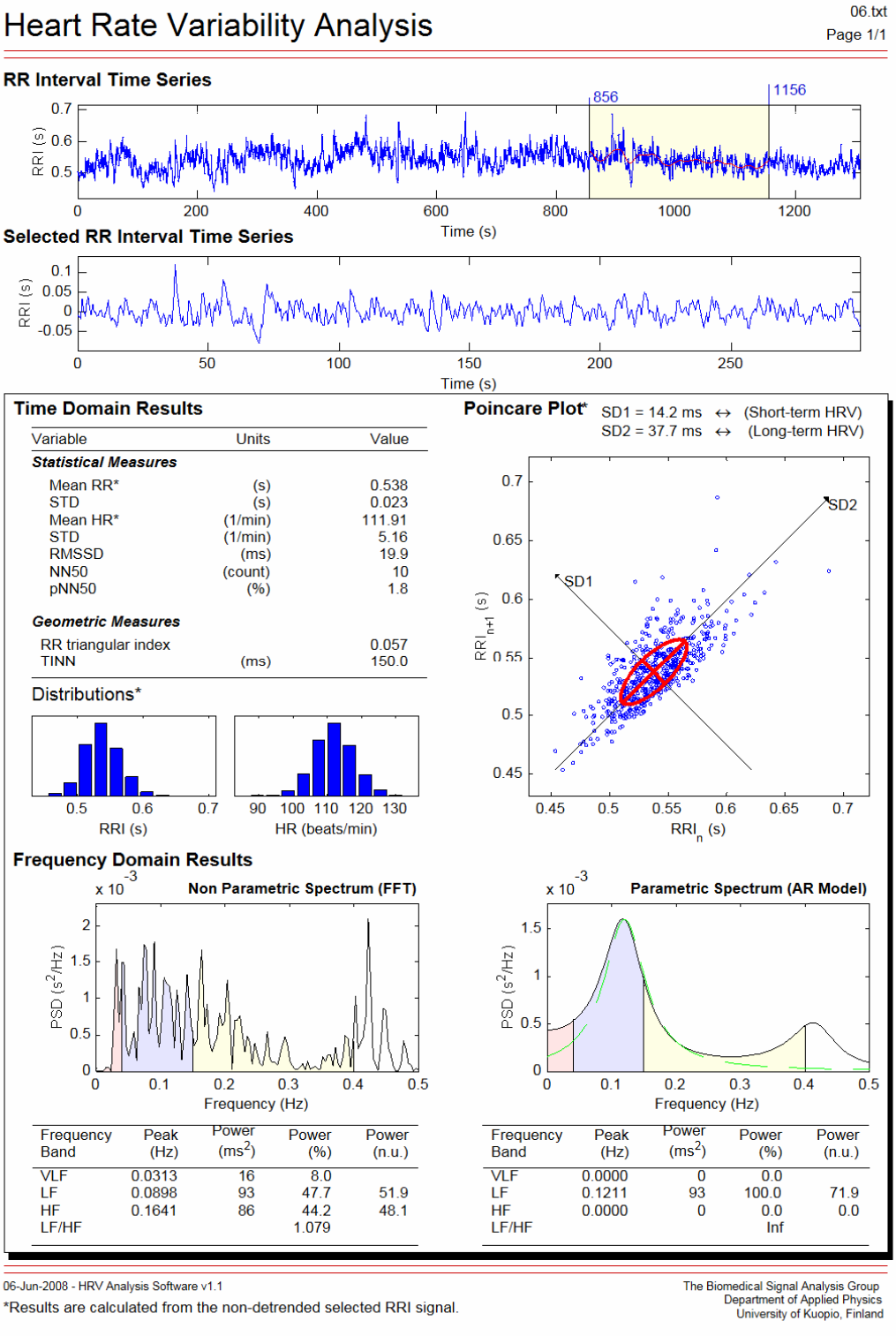

Figure A-84: HRV data during focussed attention for subject 06, tested while on stimulant medication

Subject 07 Baseline

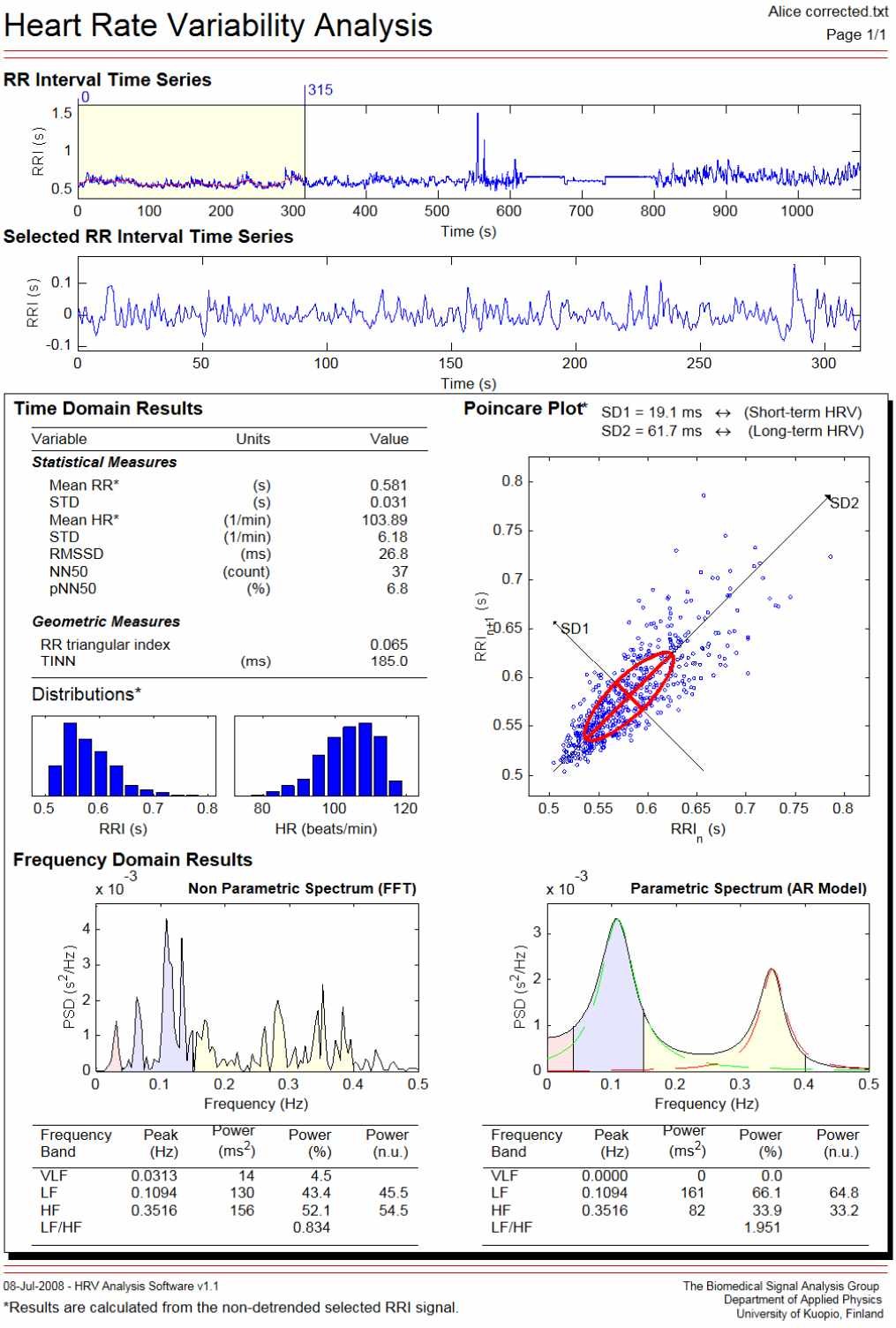

Figure A-85: Baseline HRV data for subject 07, tested while on stimulant medication

Subject 07 Focussed attention

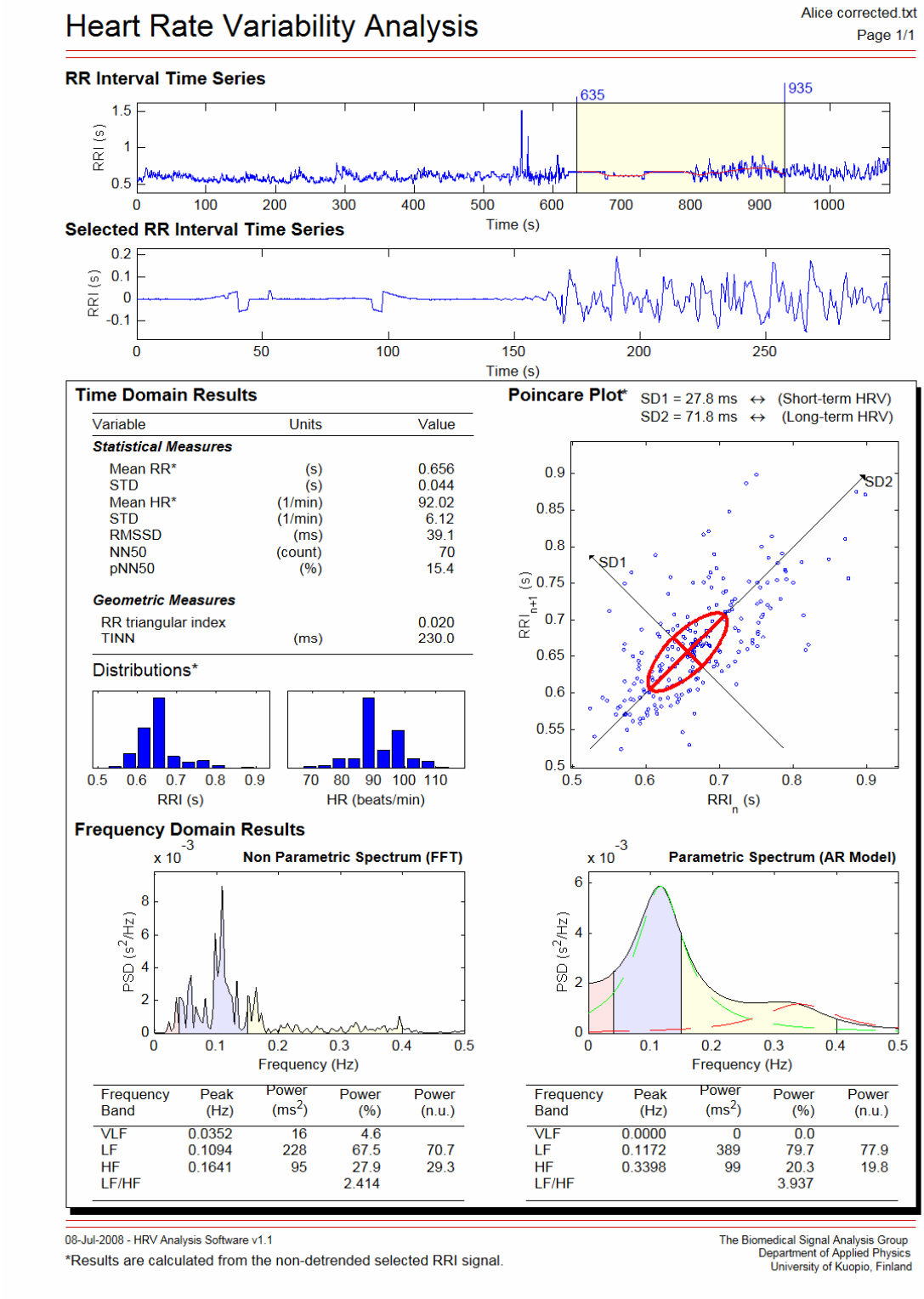

Figure A-86: HRV data during focussed attention for subject 07, tested while on stimulant medication

Subject 08 Baseline

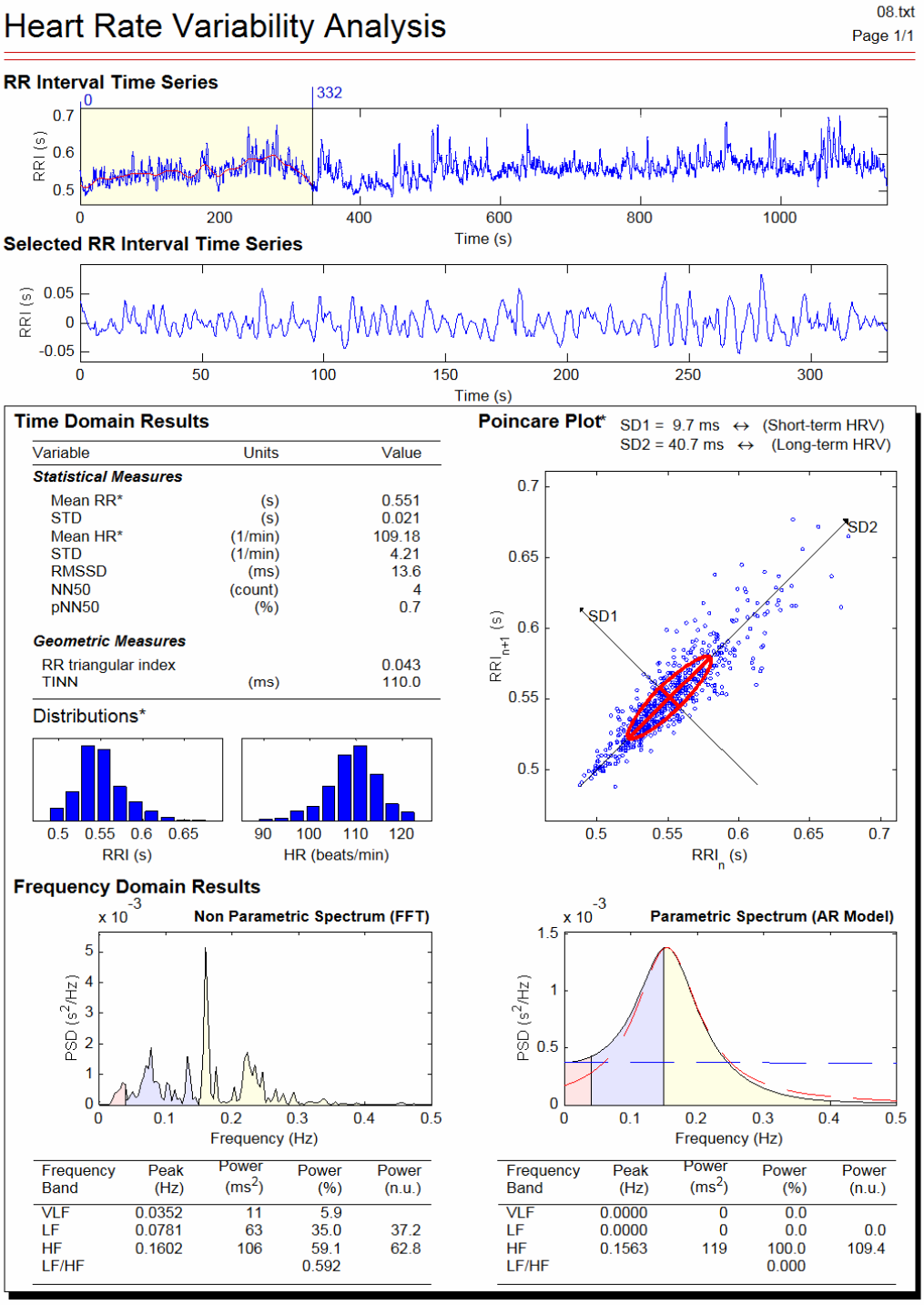

Figure A-87: Baseline HRV data for subject 08, tested while on stimulant medication

Subject 08 Focussed attention

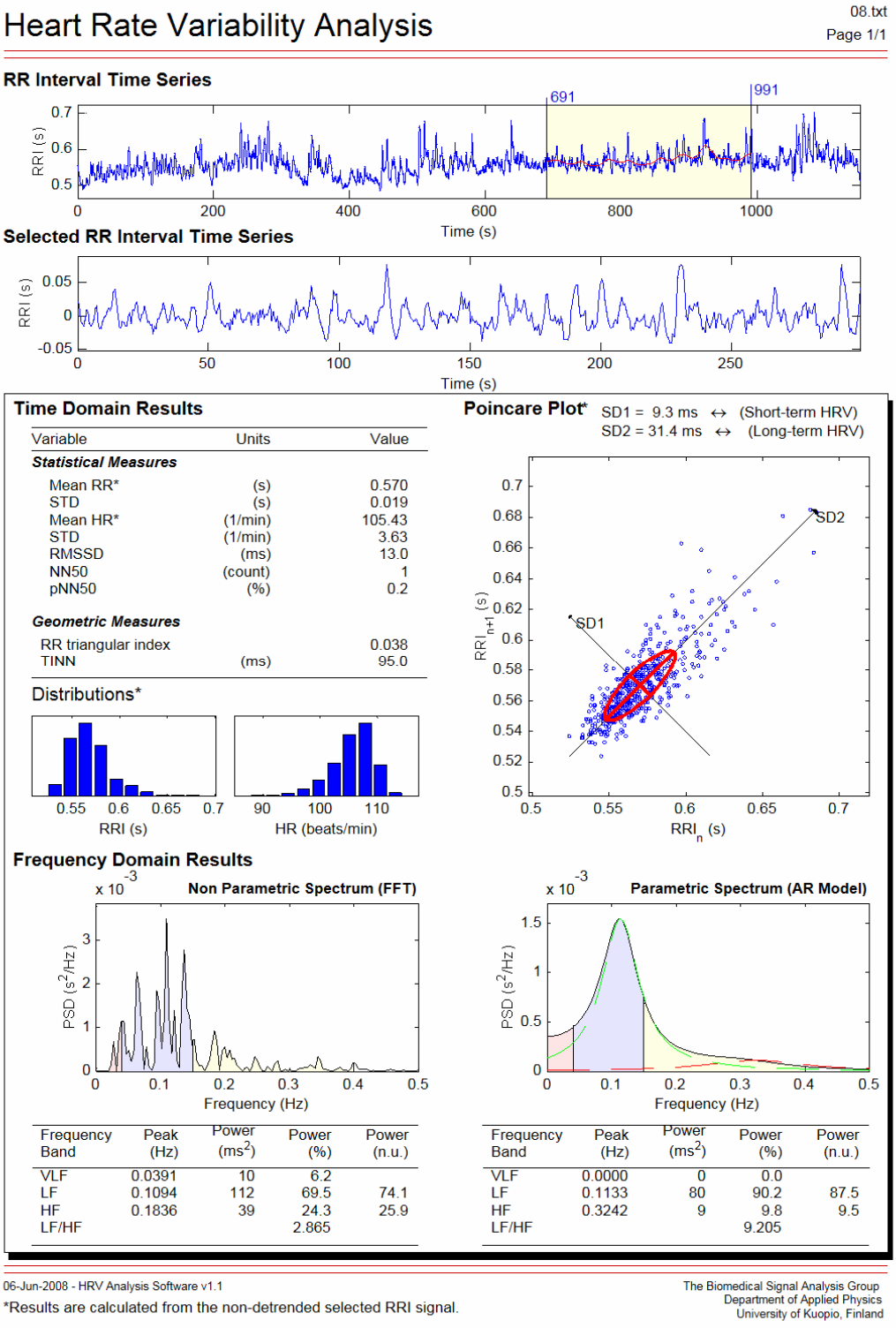

Figure A-88: HRV data during focussed attention for subject 08, tested while on stimulant medication

Subject 09 Baseline

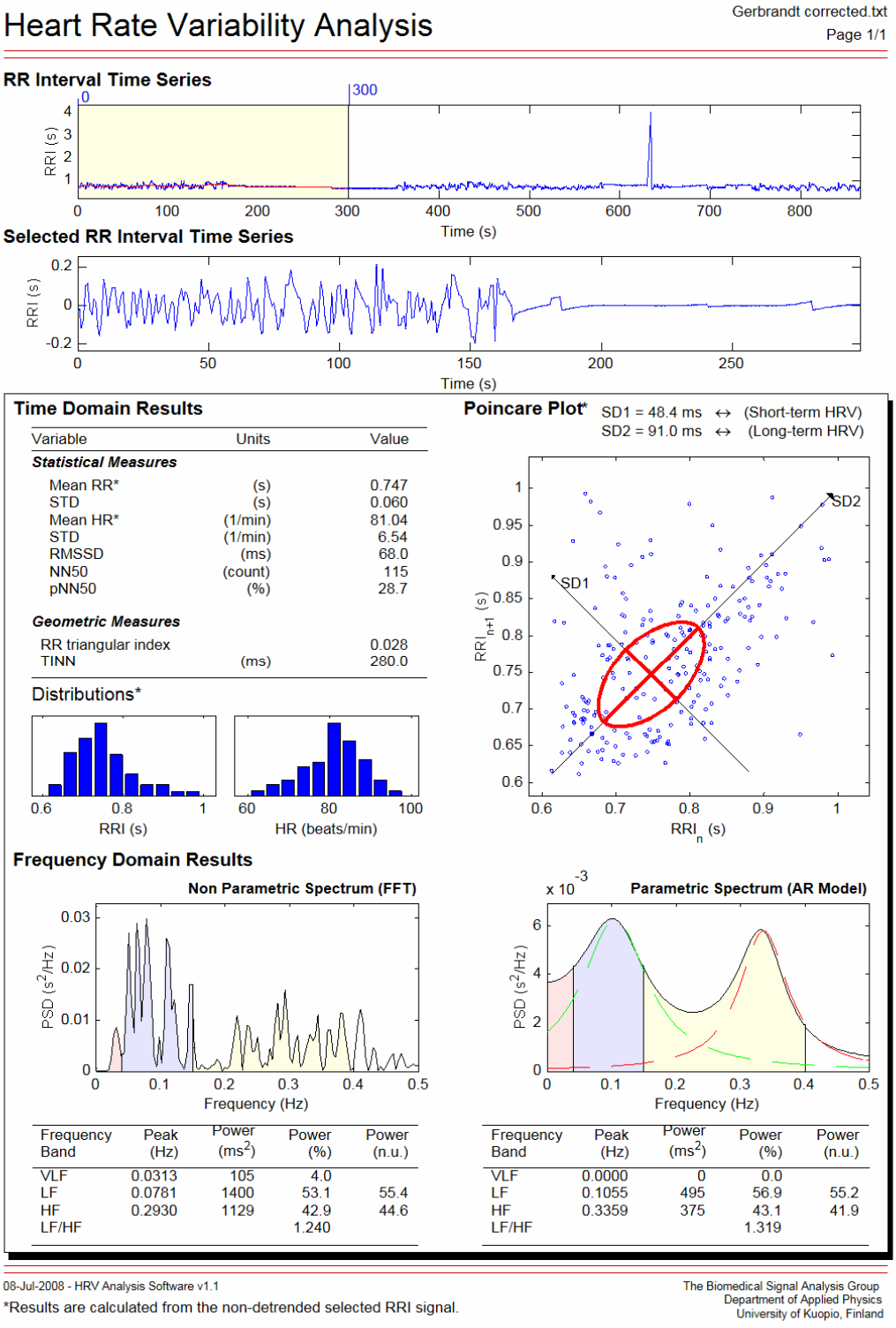

Figure A-89: Baseline HRV data for subject 09, tested while on stimulant medication

Subject 09 Focussed attention

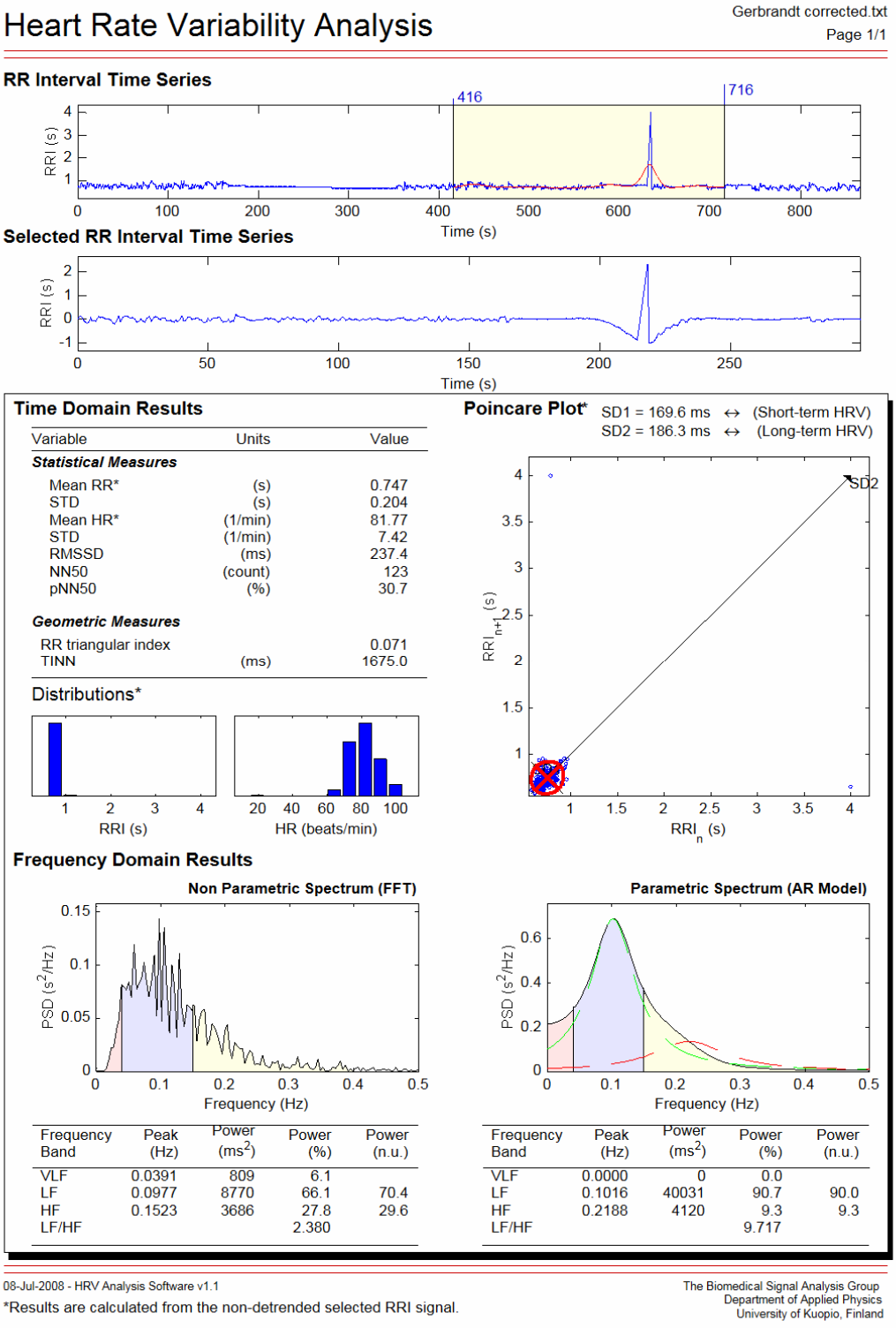

Figure A-90: HRV data during focussed attention for subject 09, tested while on stimulant medication

Subject 10 Baseline

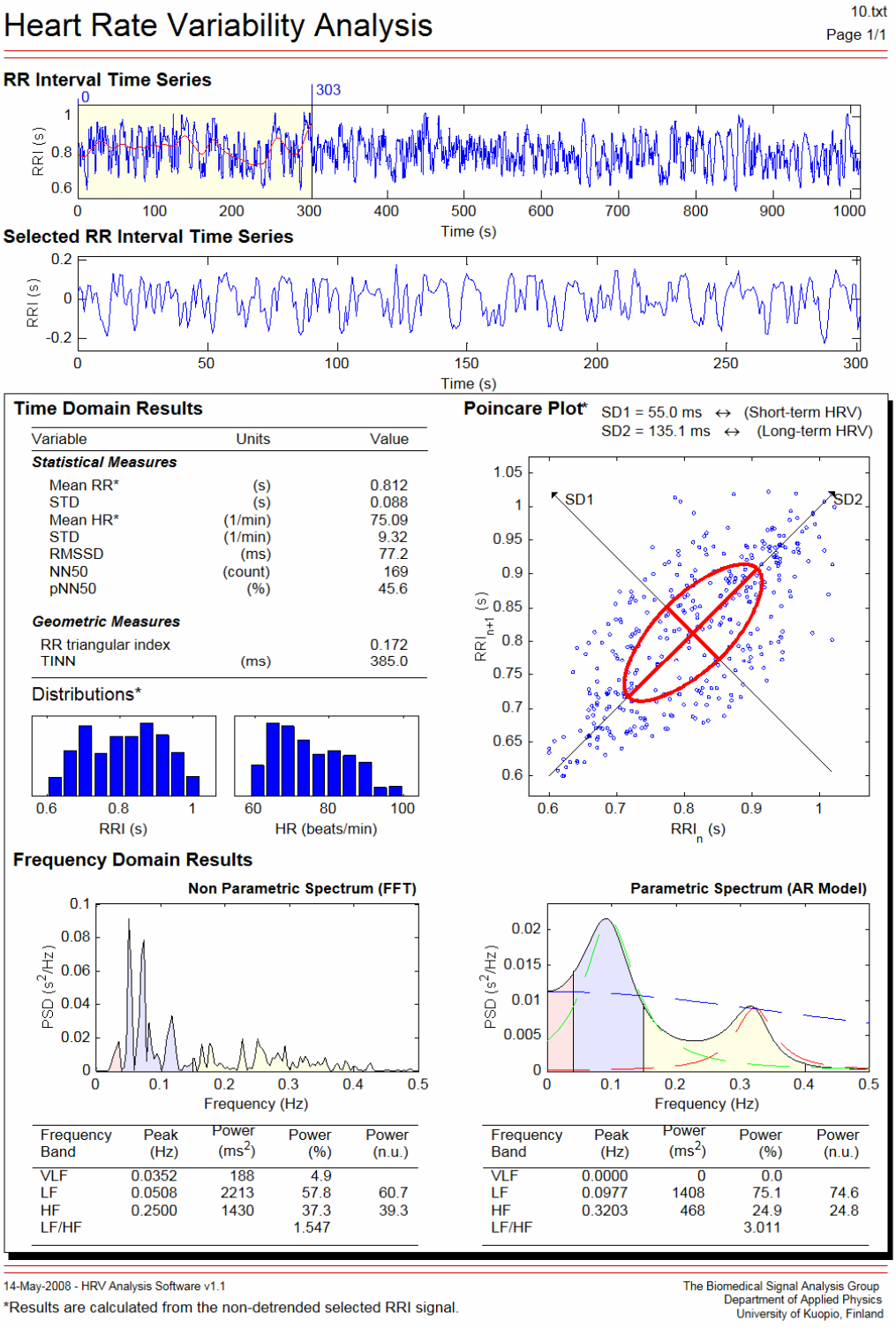

Figure A-91: Baseline HRV data for subject 10, tested while on stimulant medication

Subject 10 Focussed attention

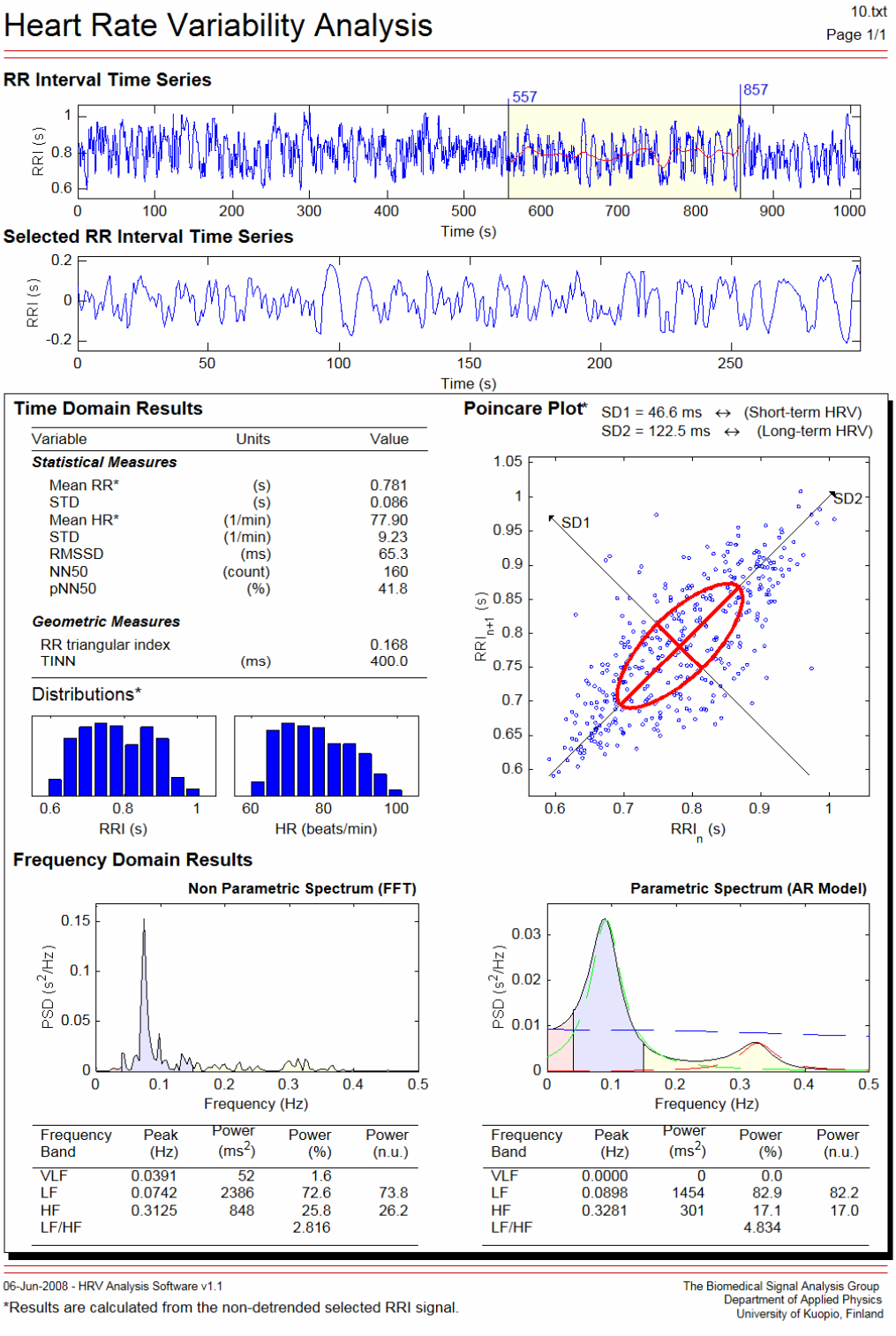

Figure A-92: HRV data during focussed attention for subject 10, tested while on stimulant medication

Subject 11 Baseline

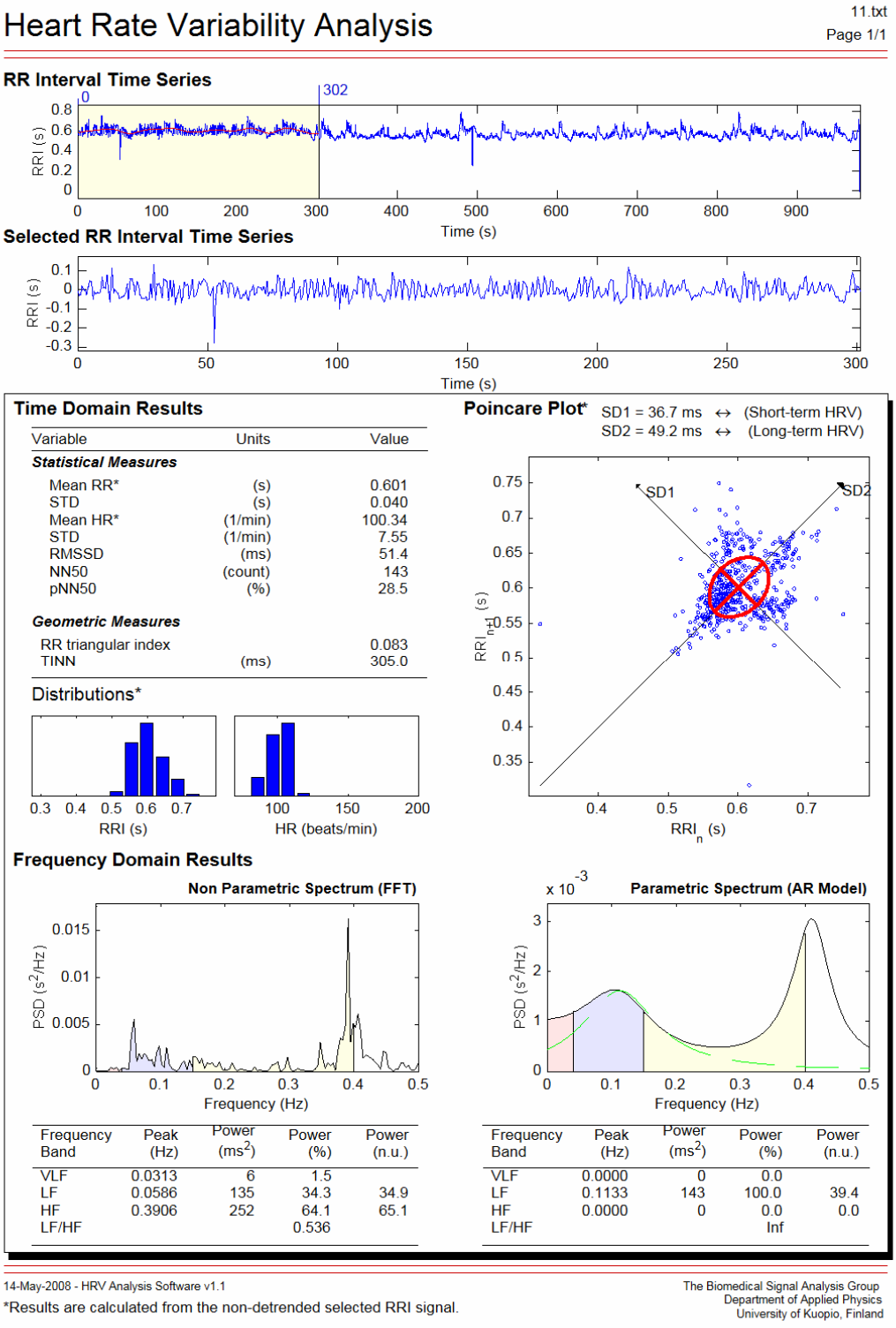

Figure A-93: Baseline HRV data for subject 11, tested while on stimulant medication

Subject 11 Focussed attention

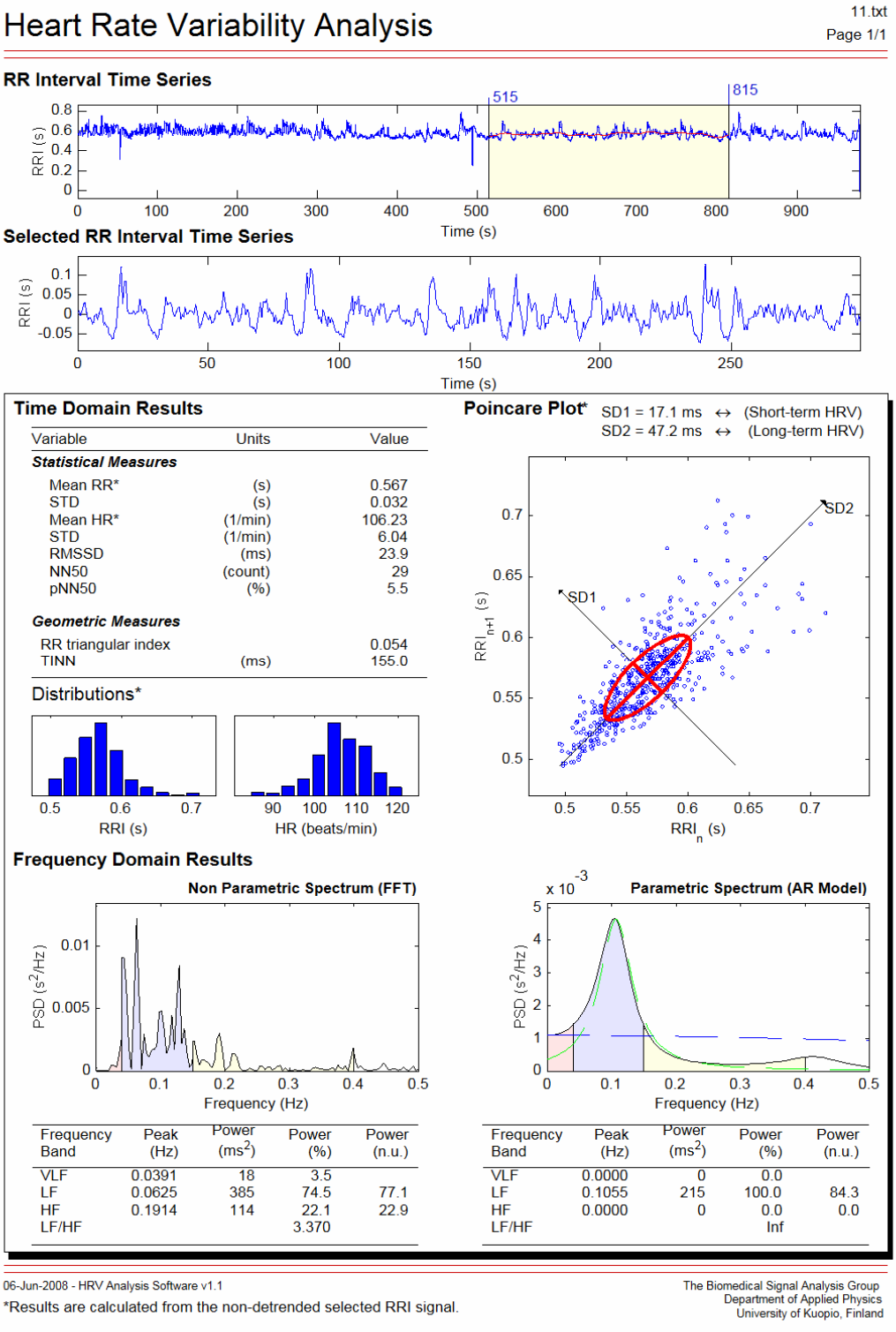

Figure A-94: HRV data during focussed attention for subject 11, tested while on stimulant medication

Subject 12 Baseline

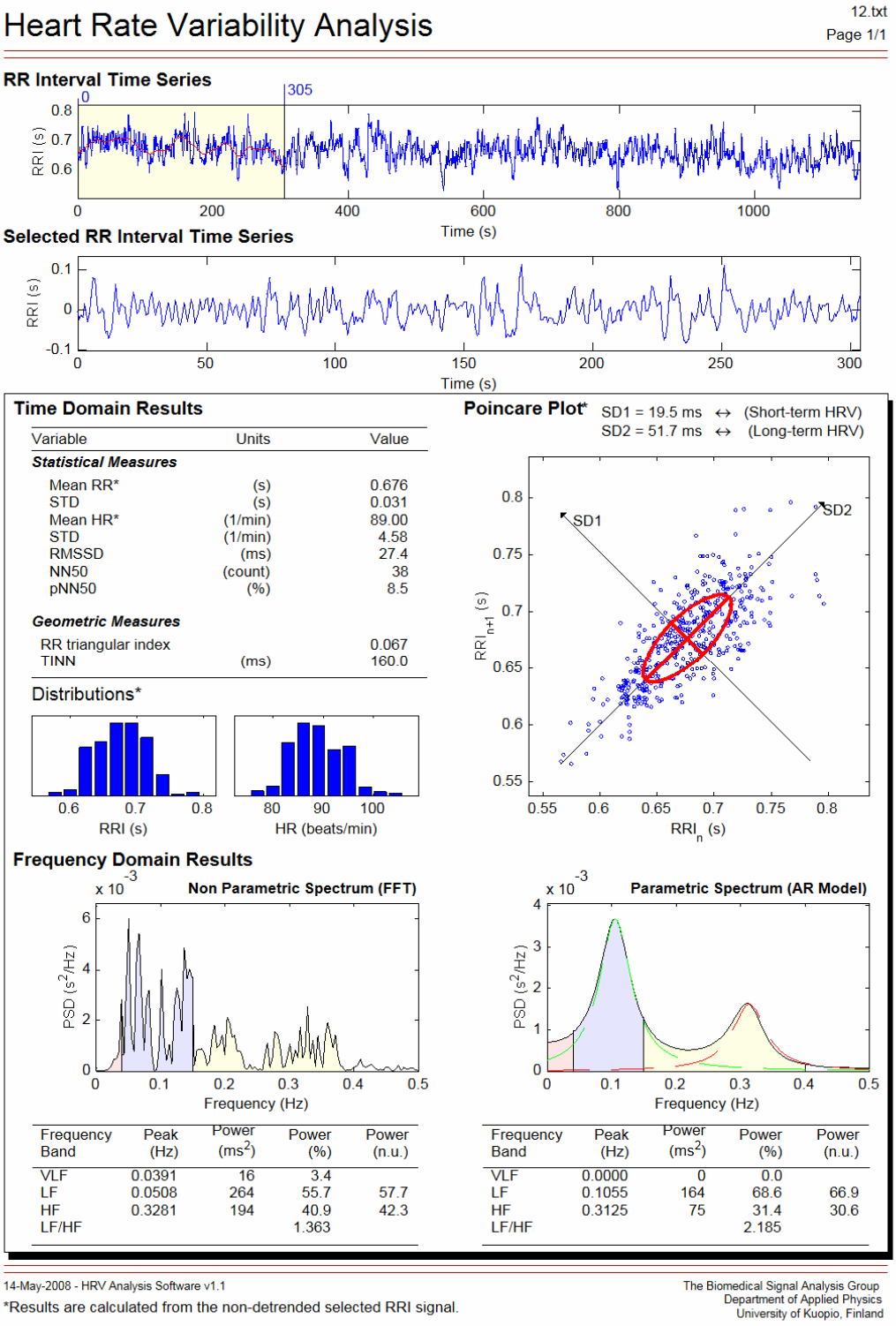

Figure A-95: Baseline HRV data for subject 12, tested while on stimulant medication

Subject 12 Focussed attention

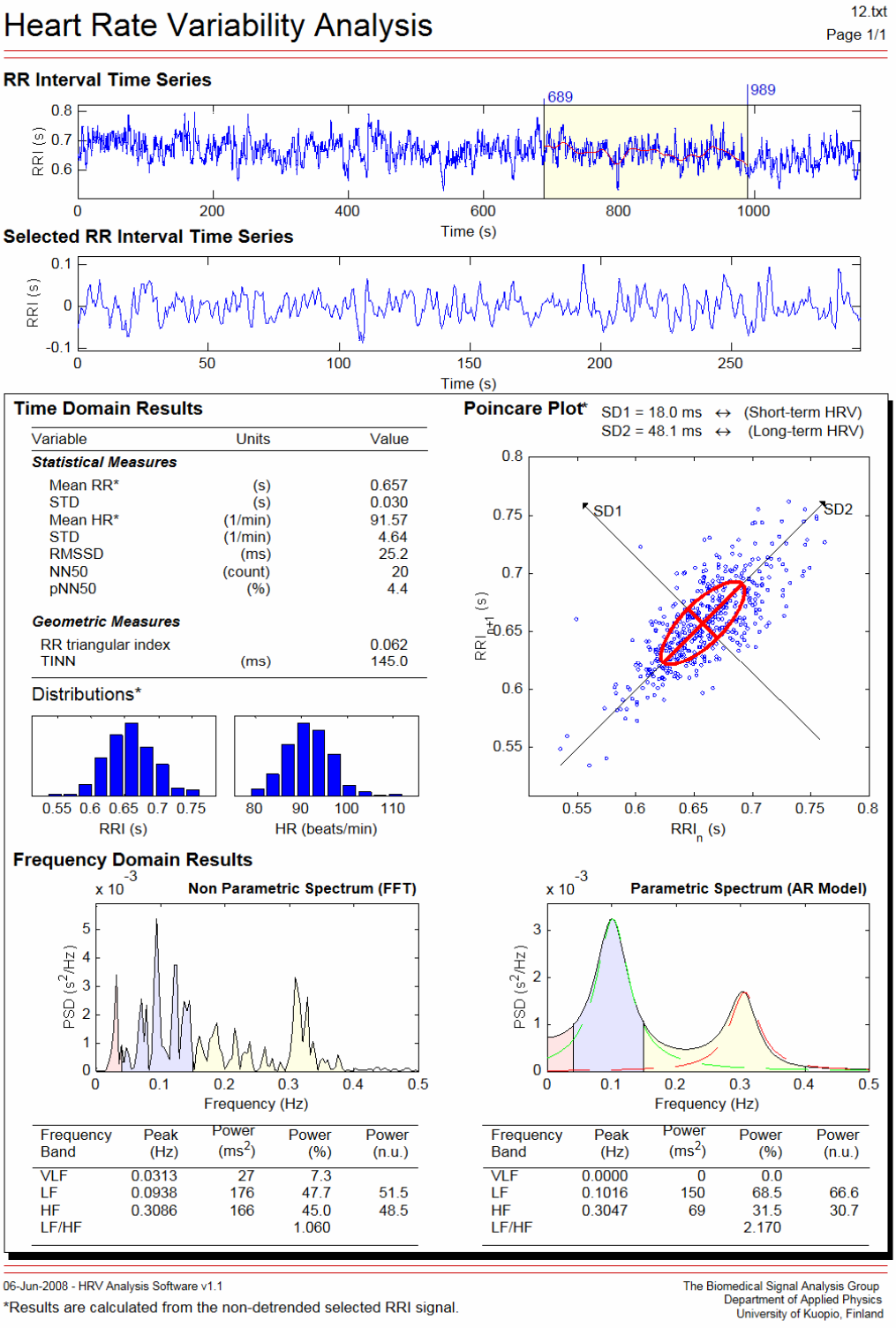

Figure A-96: HRV data during focussed attention for subject 12, tested while on stimulant medication

Subject 13 Baseline

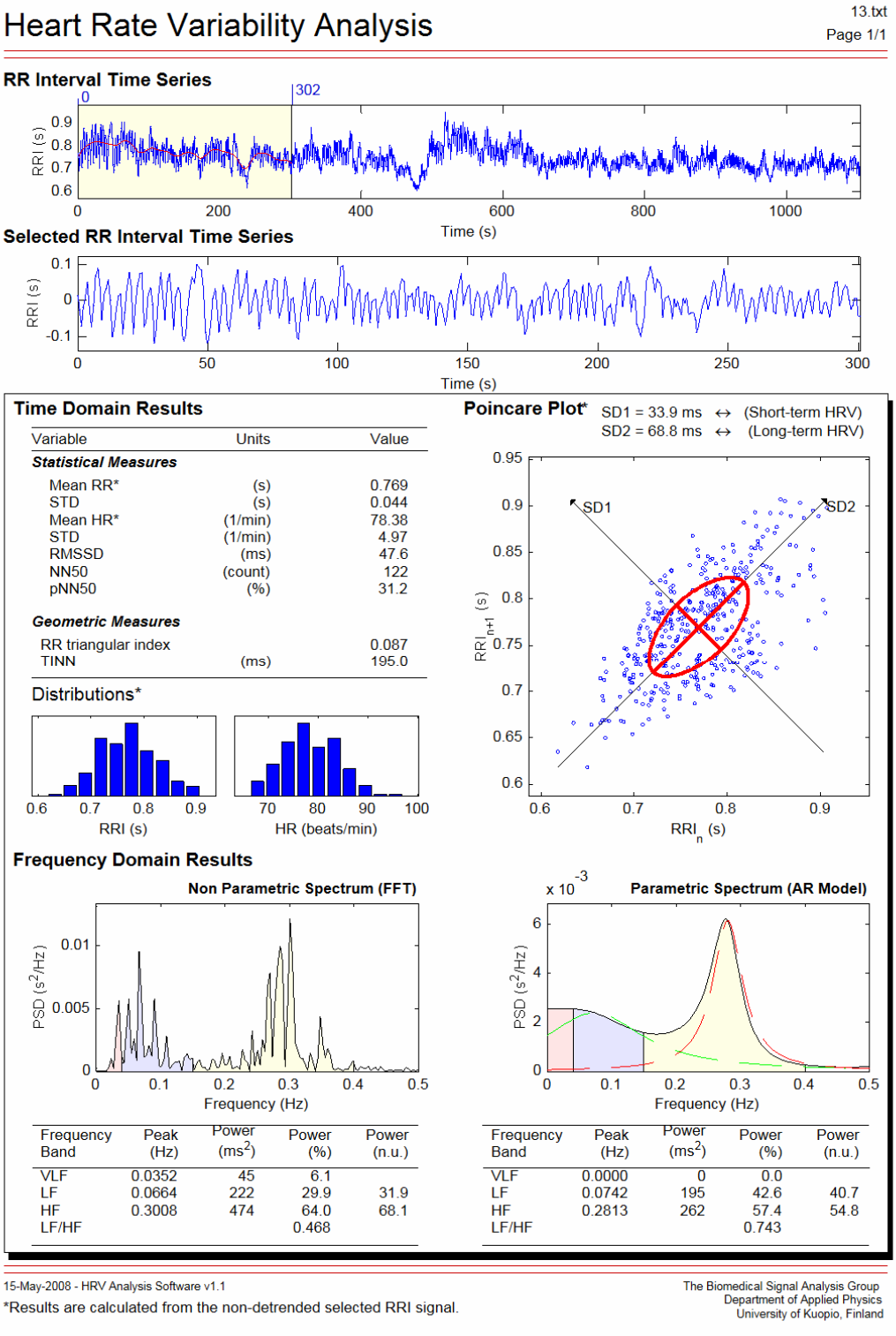

Figure A-97: Baseline HRV data for subject 13, tested while on stimulant medication

Subject 13 Focussed attention

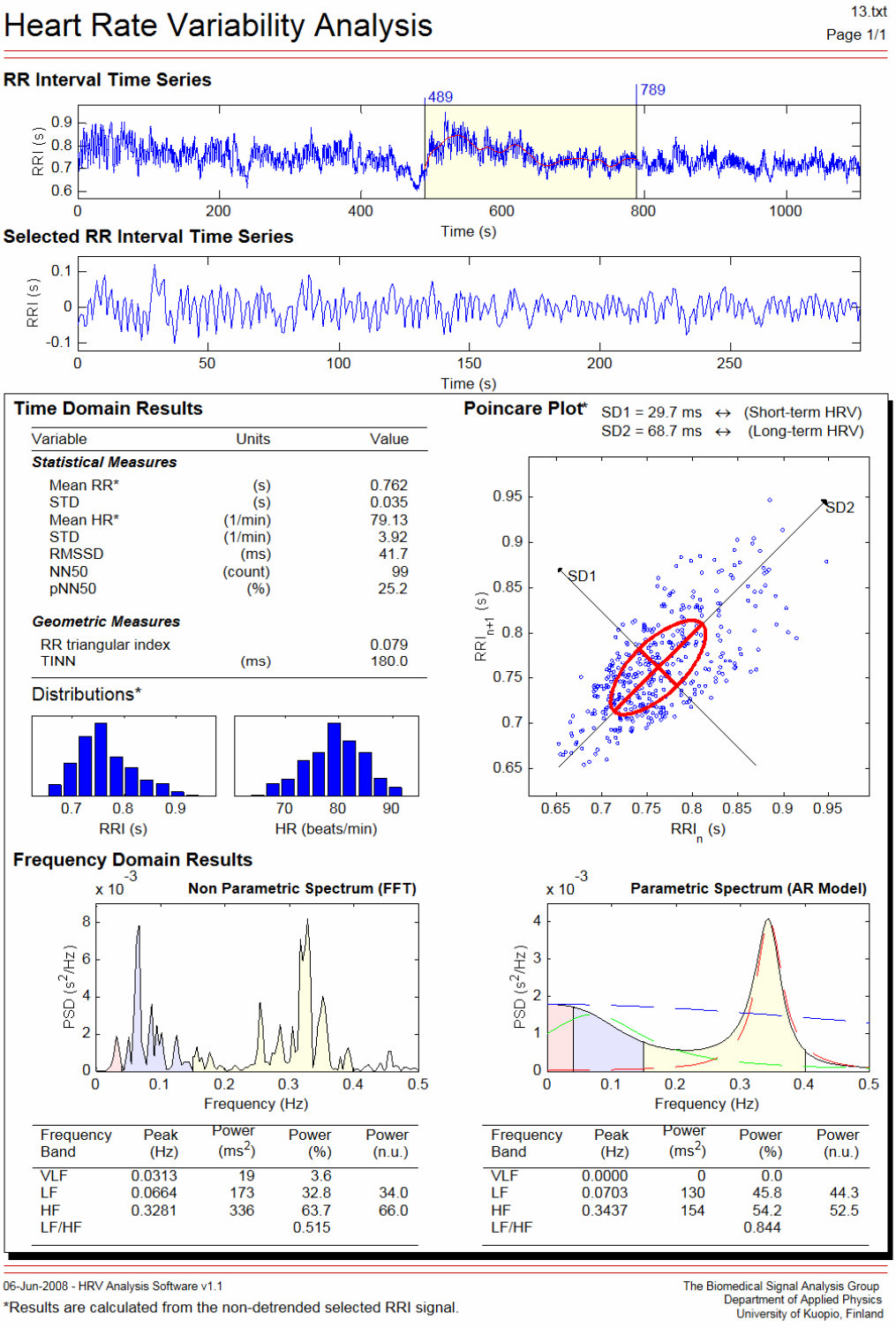

Figure A-98: HRV data during focussed attention for subject 13, tested while on stimulant medication

Subject 14 Baseline

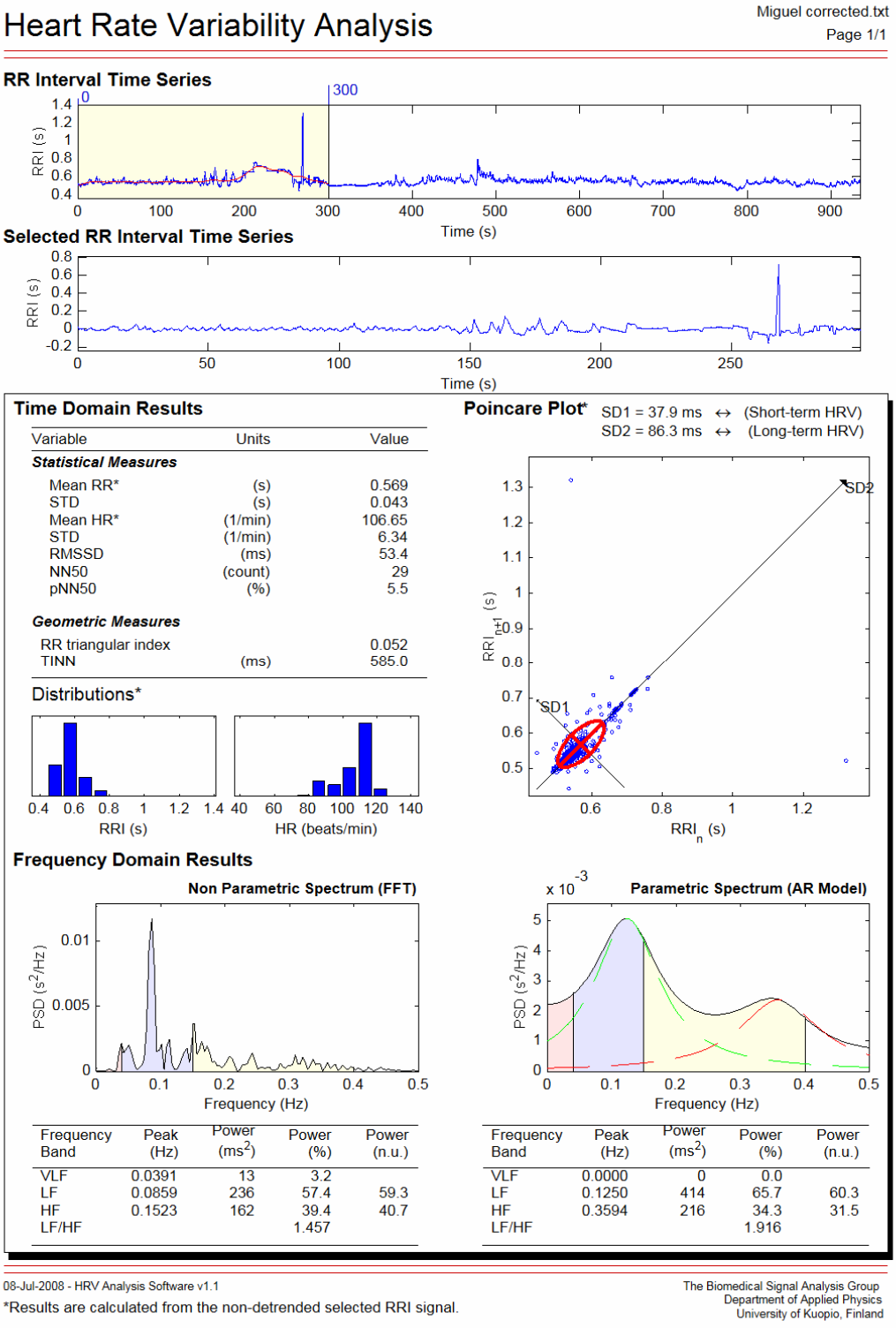

Figure A-99: Baseline HRV data for subject 14, tested while on stimulant medication

Subject 14 Focussed attention

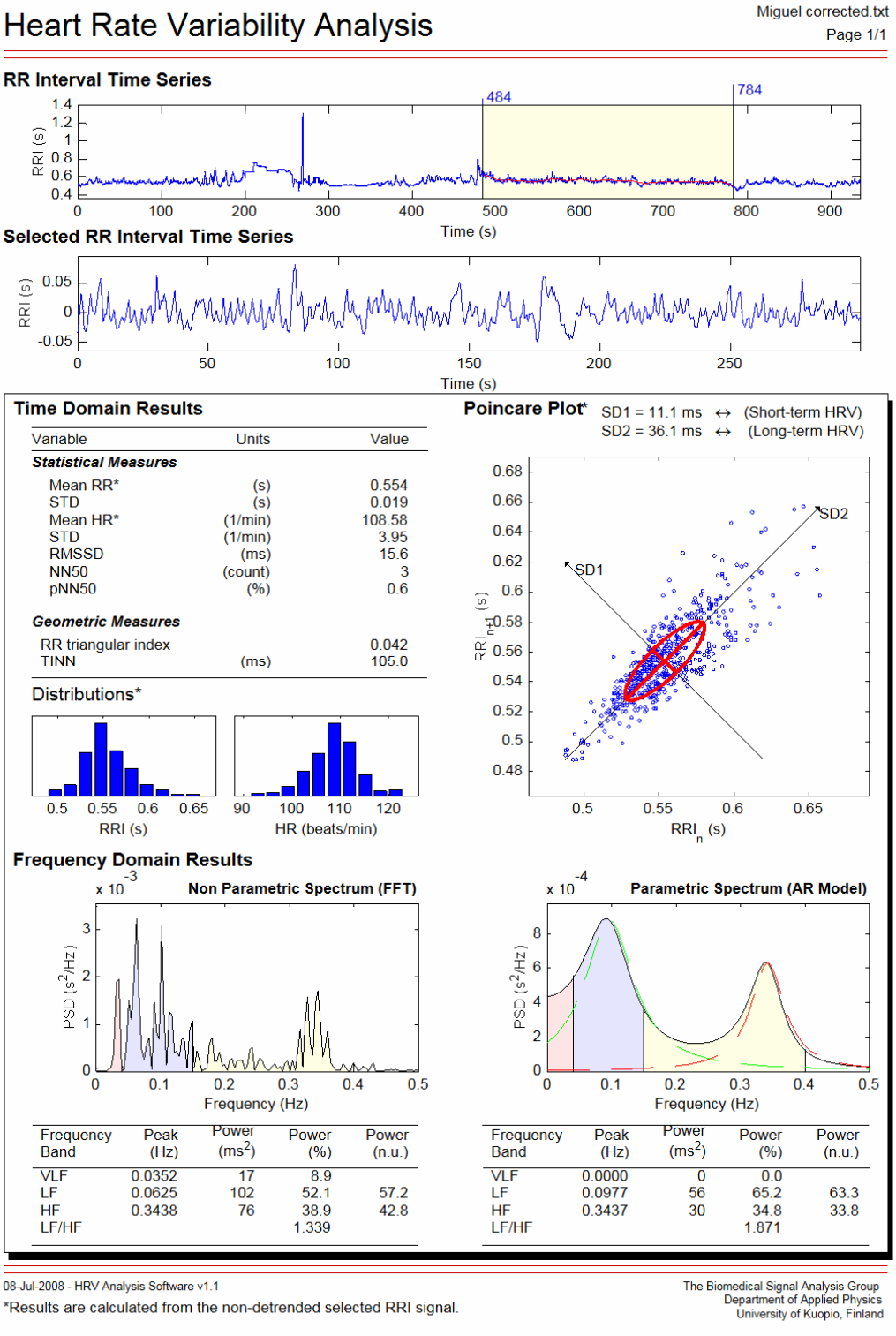

Figure A-100: HRV data during focussed attention for subject 14, tested while on stimulant medication

Subject 15 Baseline

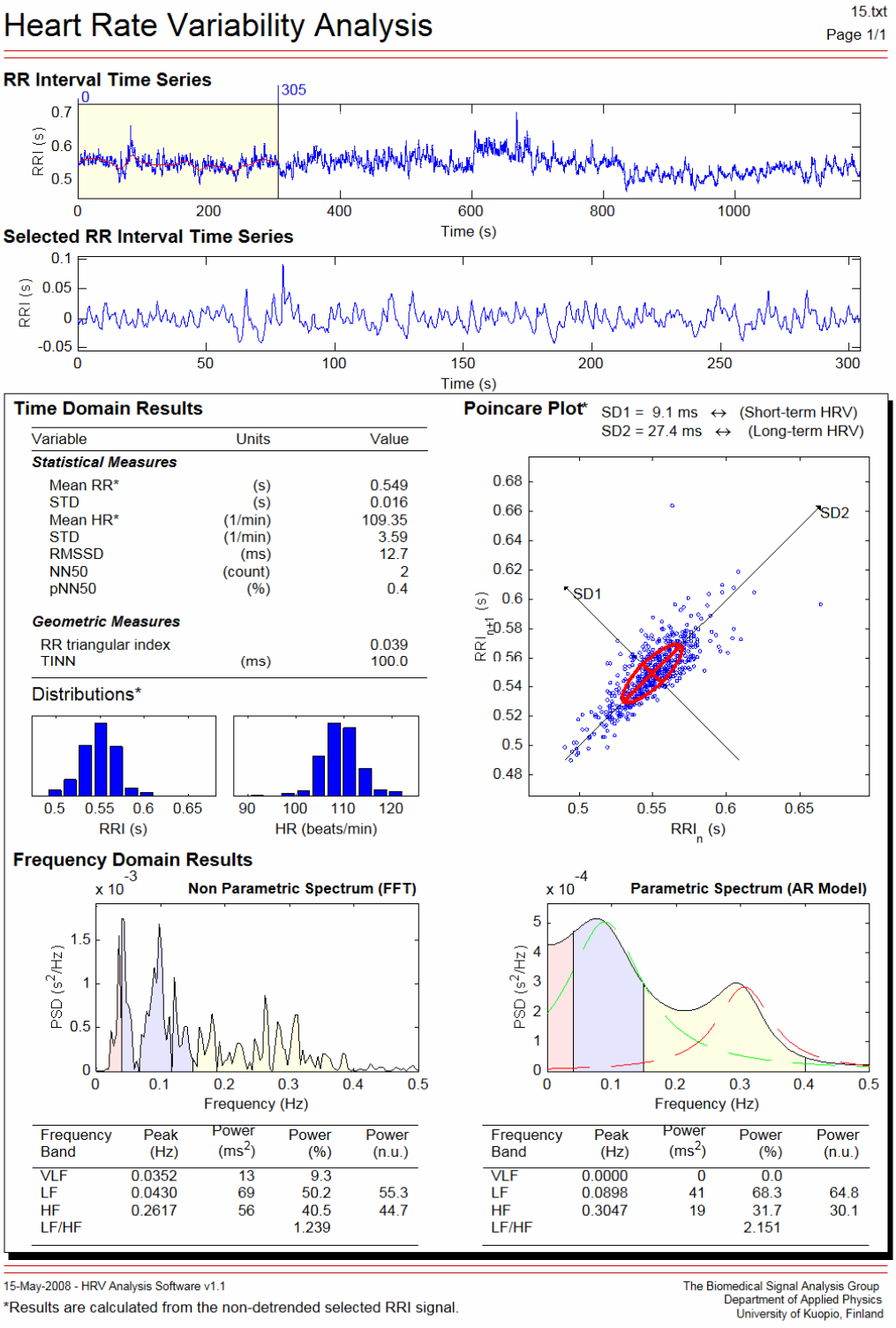

Figure A-101: Baseline HRV data for subject 15, tested while on stimulant medication

Subject 15 Focussed attention

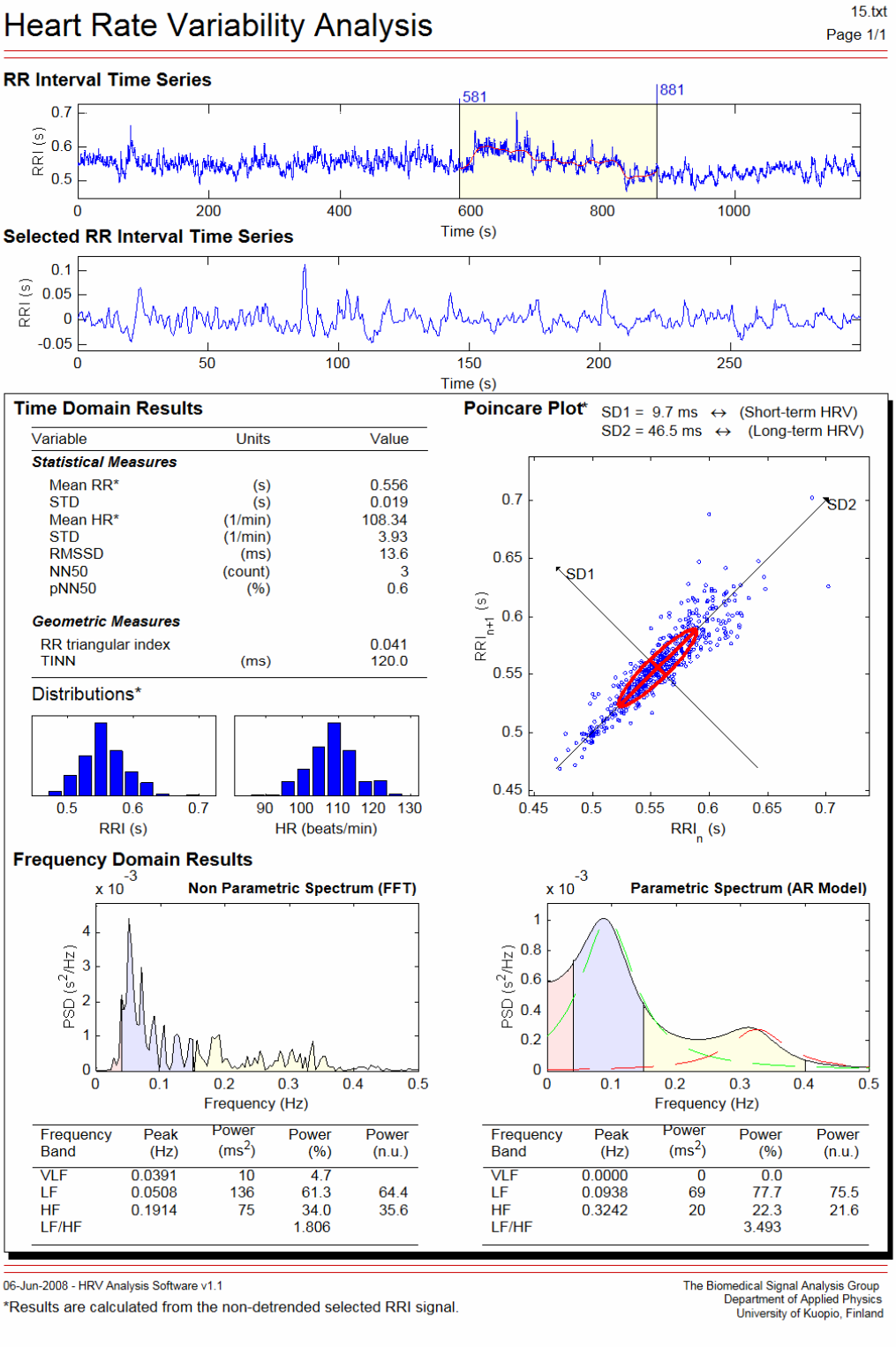

Figure A-102: HRV data during focussed attention for subject 15, tested while on stimulant medication

Subject 16 Baseline

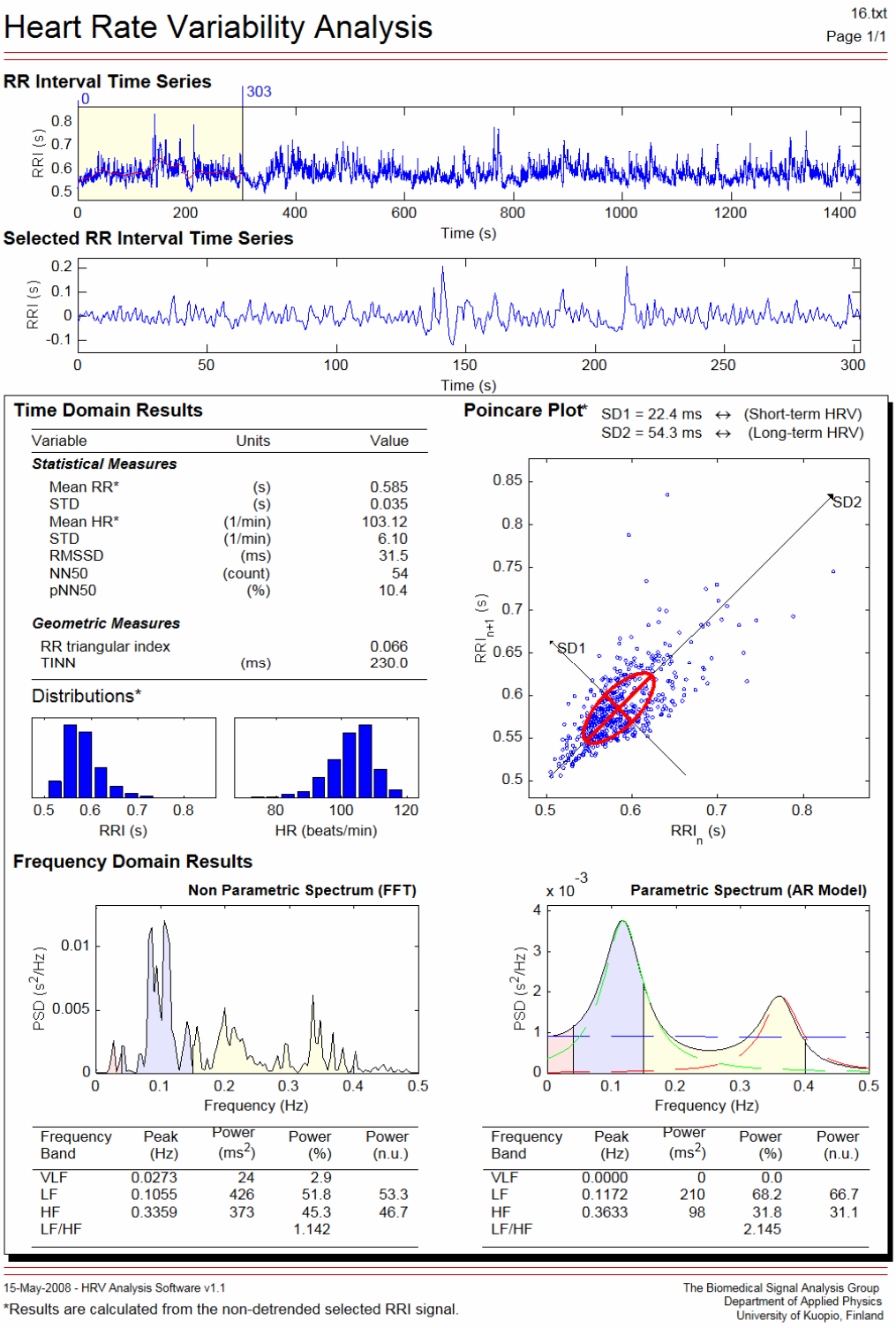

Figure A-103: Baseline HRV data for subject 16, tested while on stimulant medication

Subject 16 Focussed attention

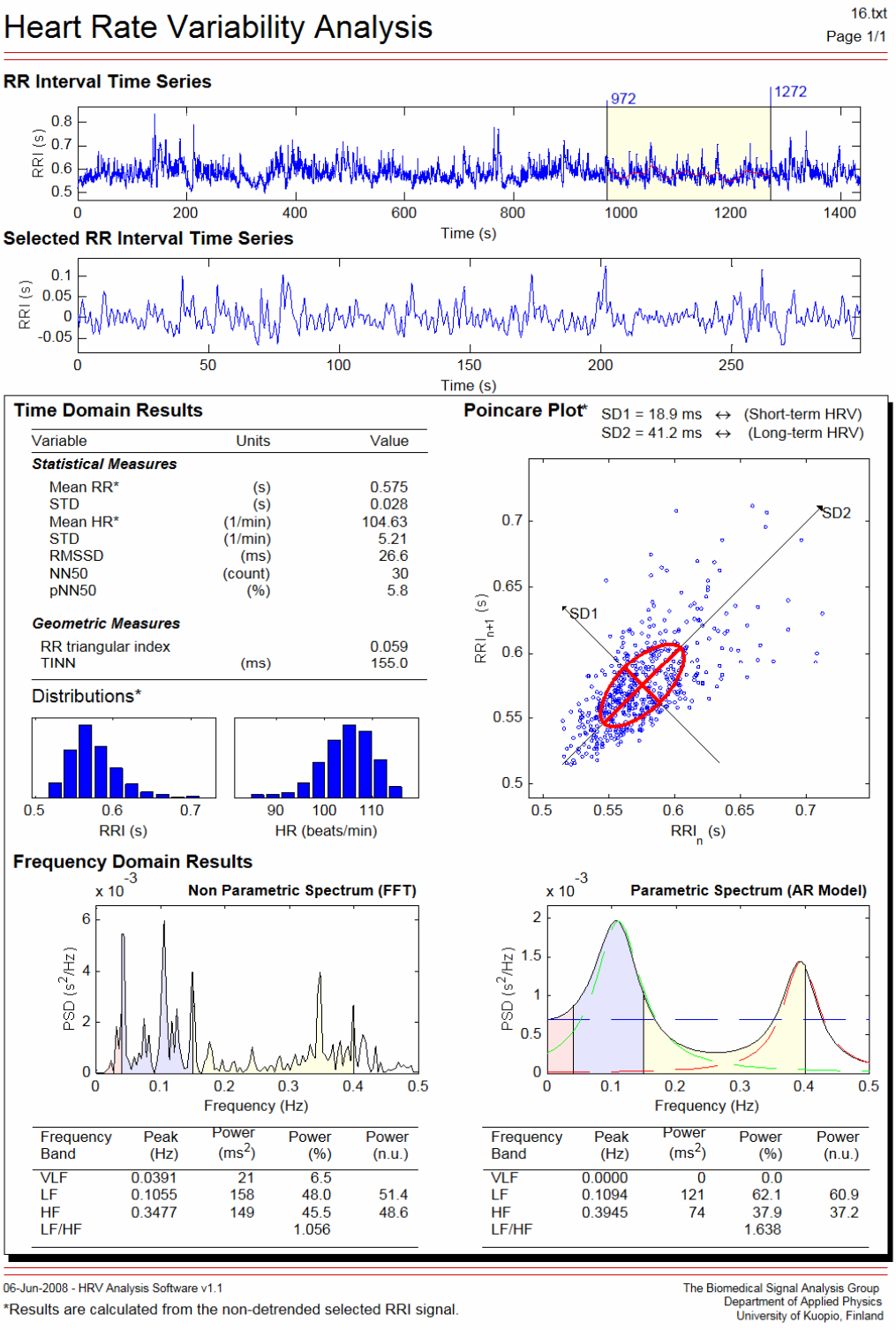

Figure A-104: HRV data during focussed attention for subject 16, tested while on stimulant medication

Subject 17 Baseline

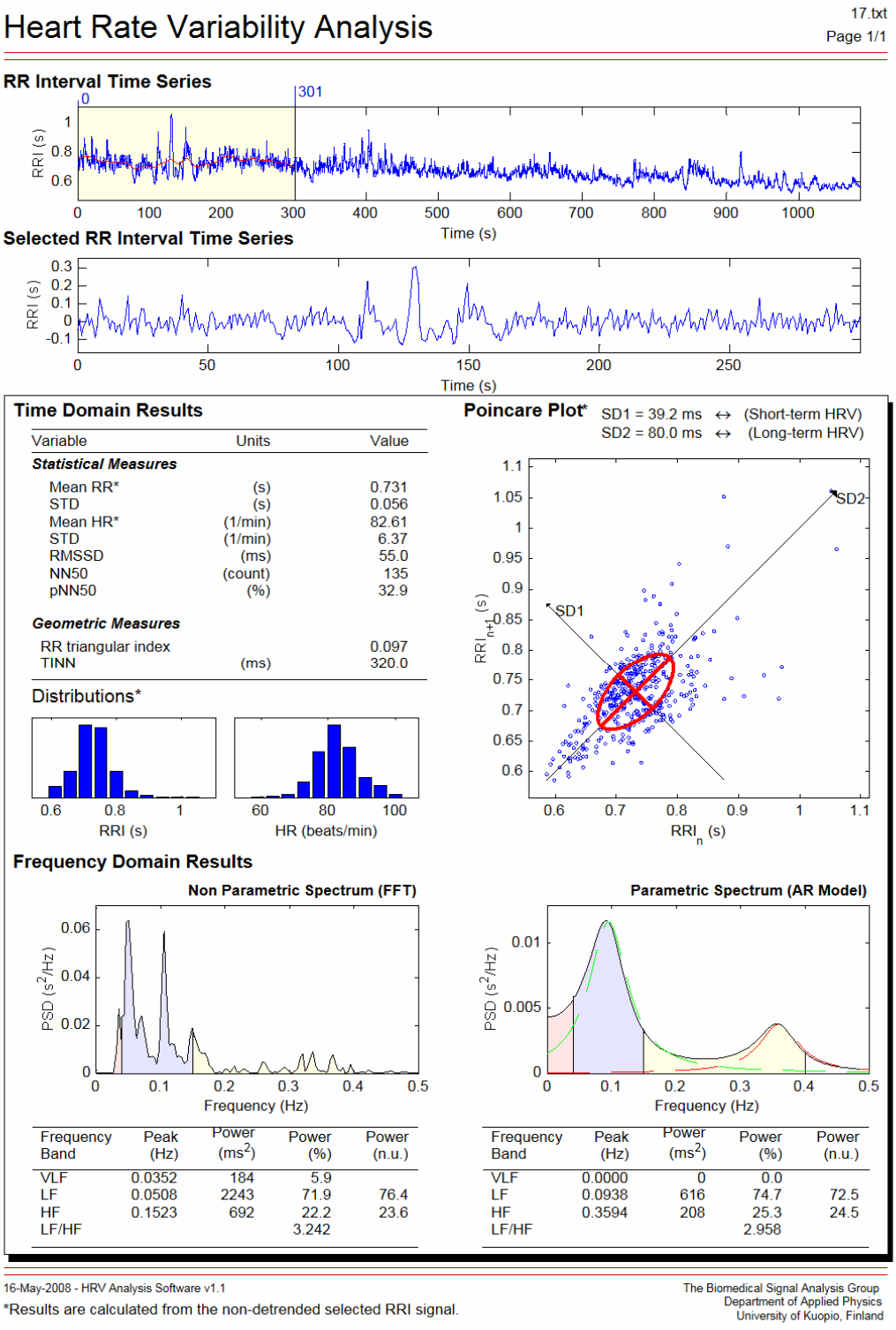

Figure A-105: Baseline HRV data for subject 17, tested while on stimulant medication

Subject 17 Focussed attention

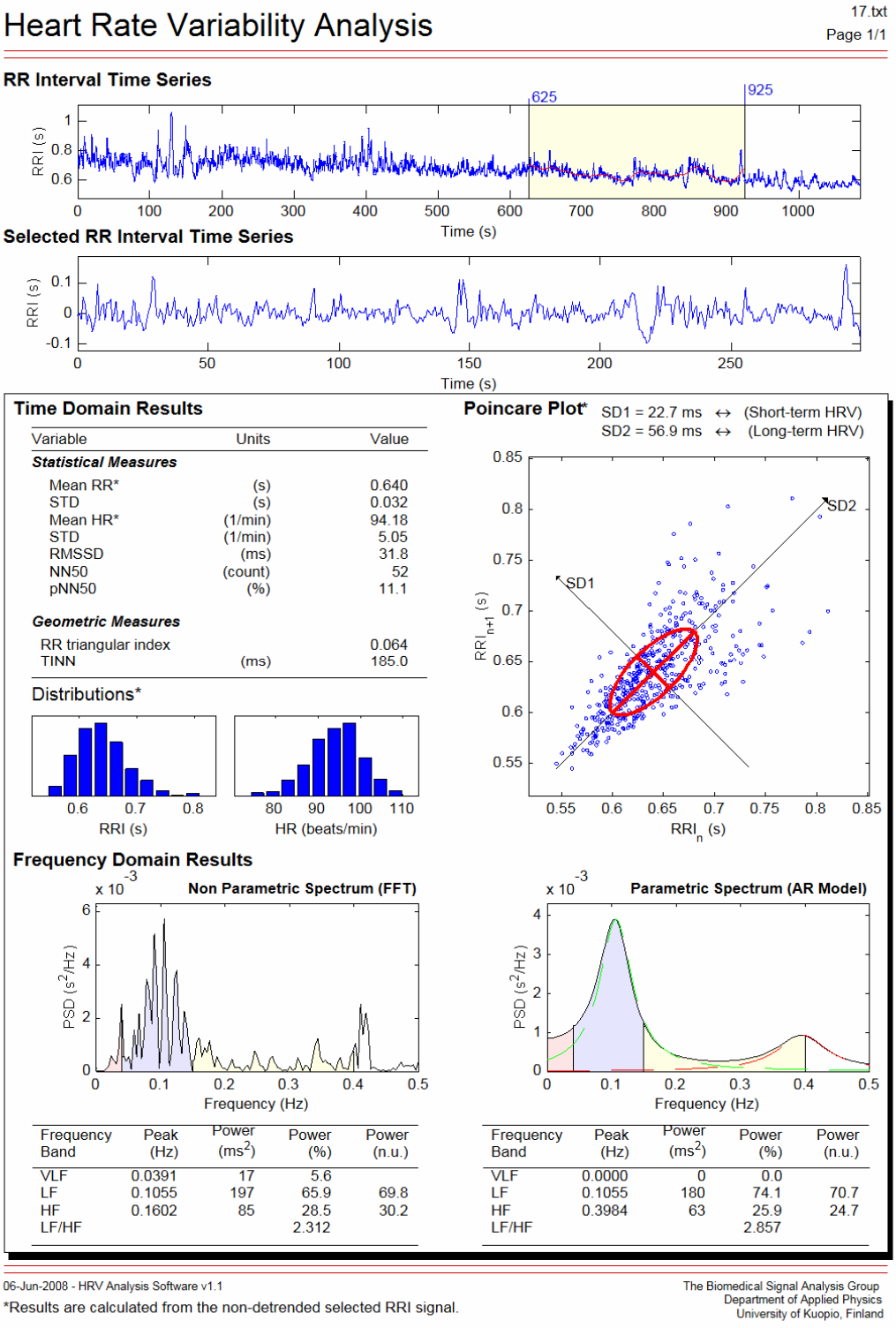

Figure A-106: HRV data during focussed attention for subject 17, tested while on stimulant medication

Subject 18 Baseline

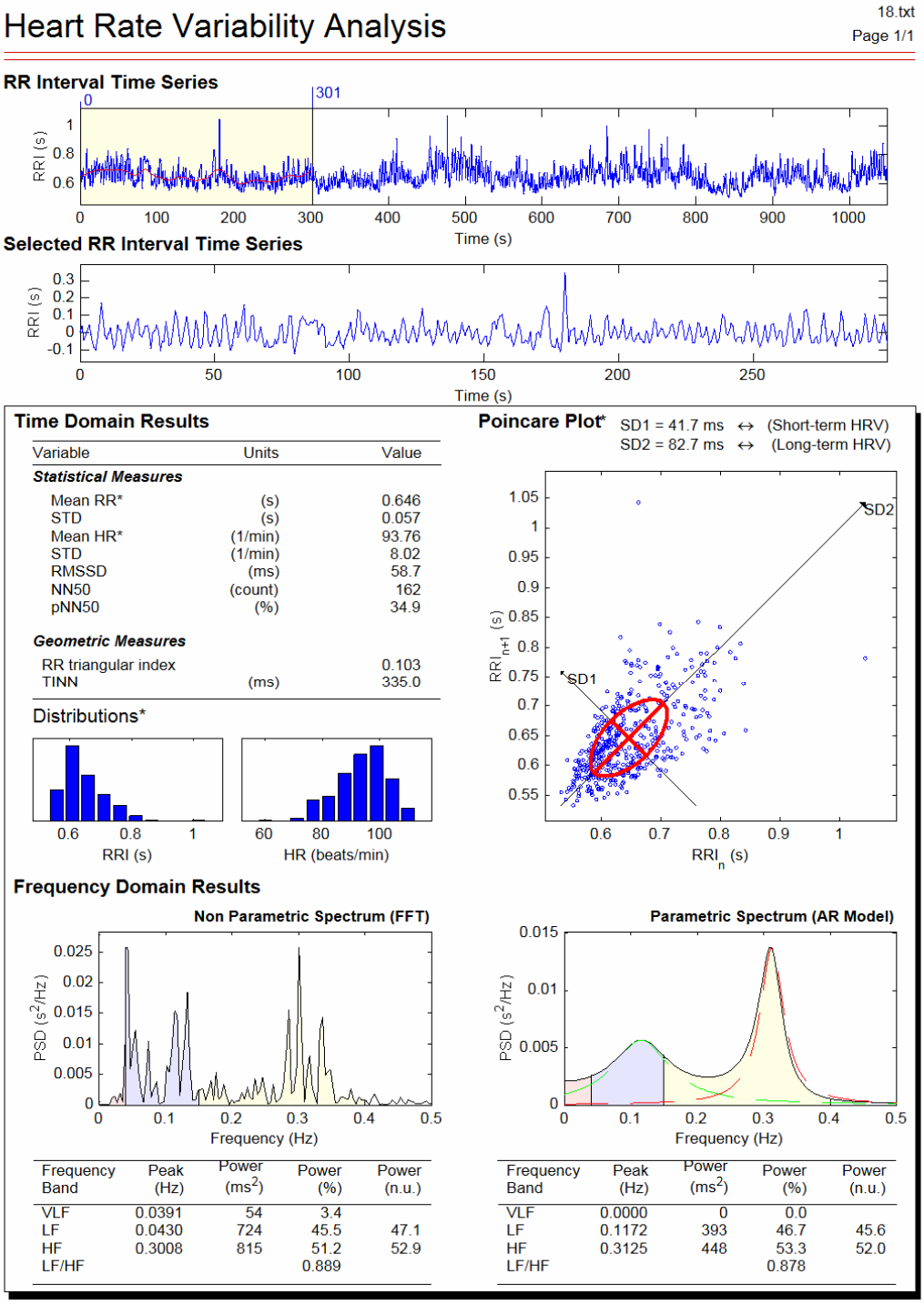

Figure A-107: Baseline HRV data for subject 18, tested while on stimulant medication

Subject 18 Focussed attention

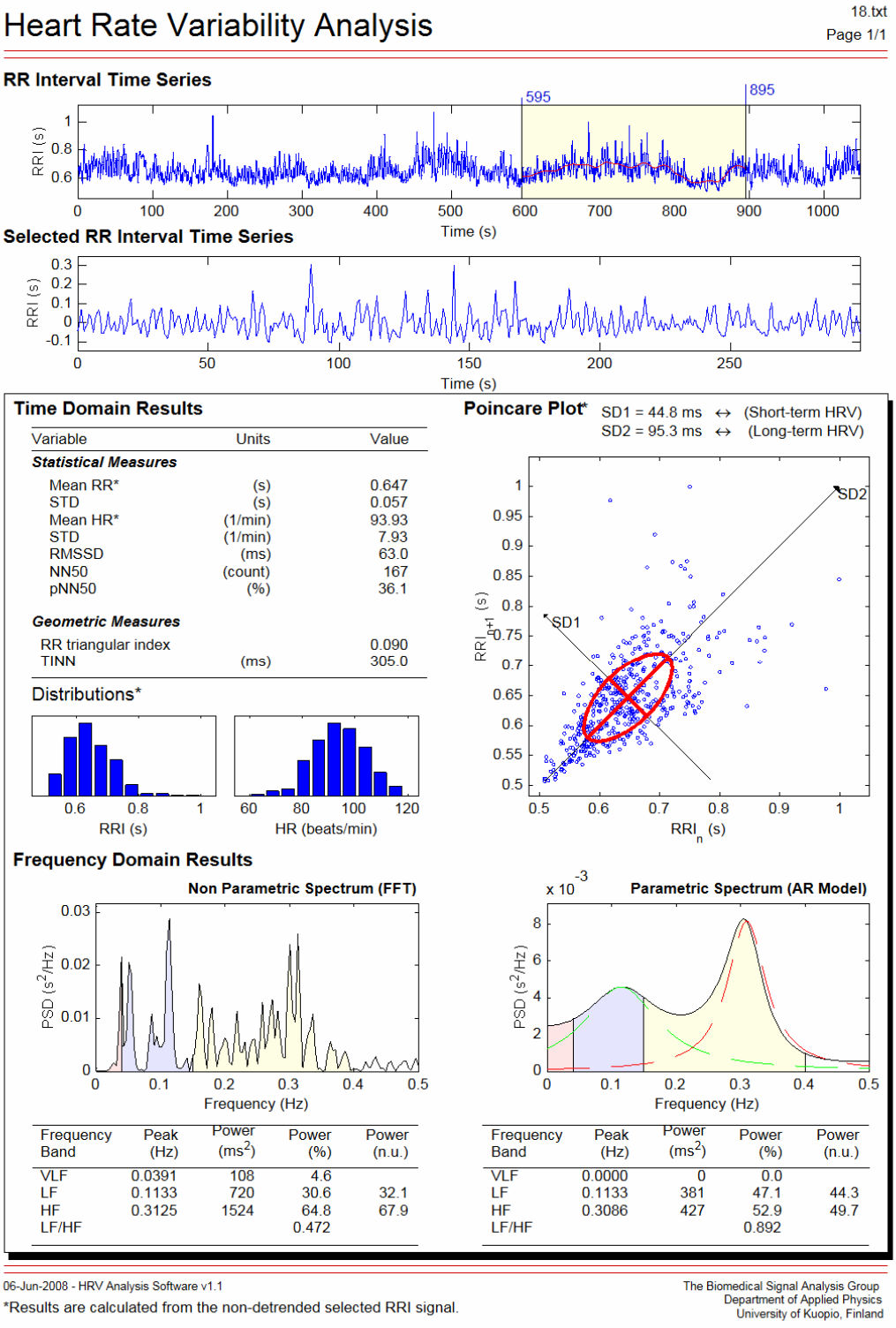

Figure A-108: HRV data during focussed attention for subject 18, tested while on stimulant medication

Subject 19 Baseline

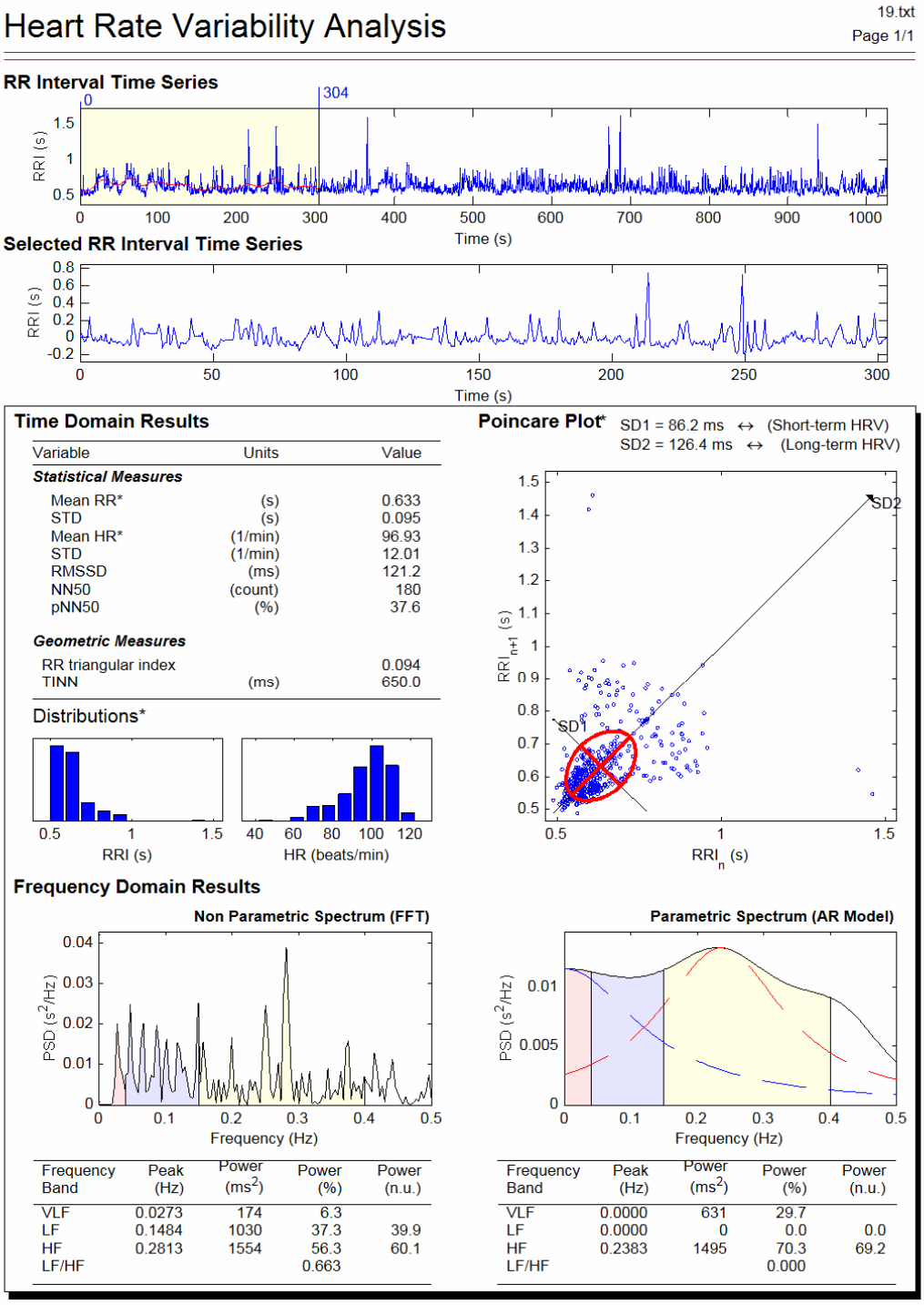

Figure A-109: Baseline HRV data for subject 19, tested while on stimulant medication

Subject 19 Focussed attention

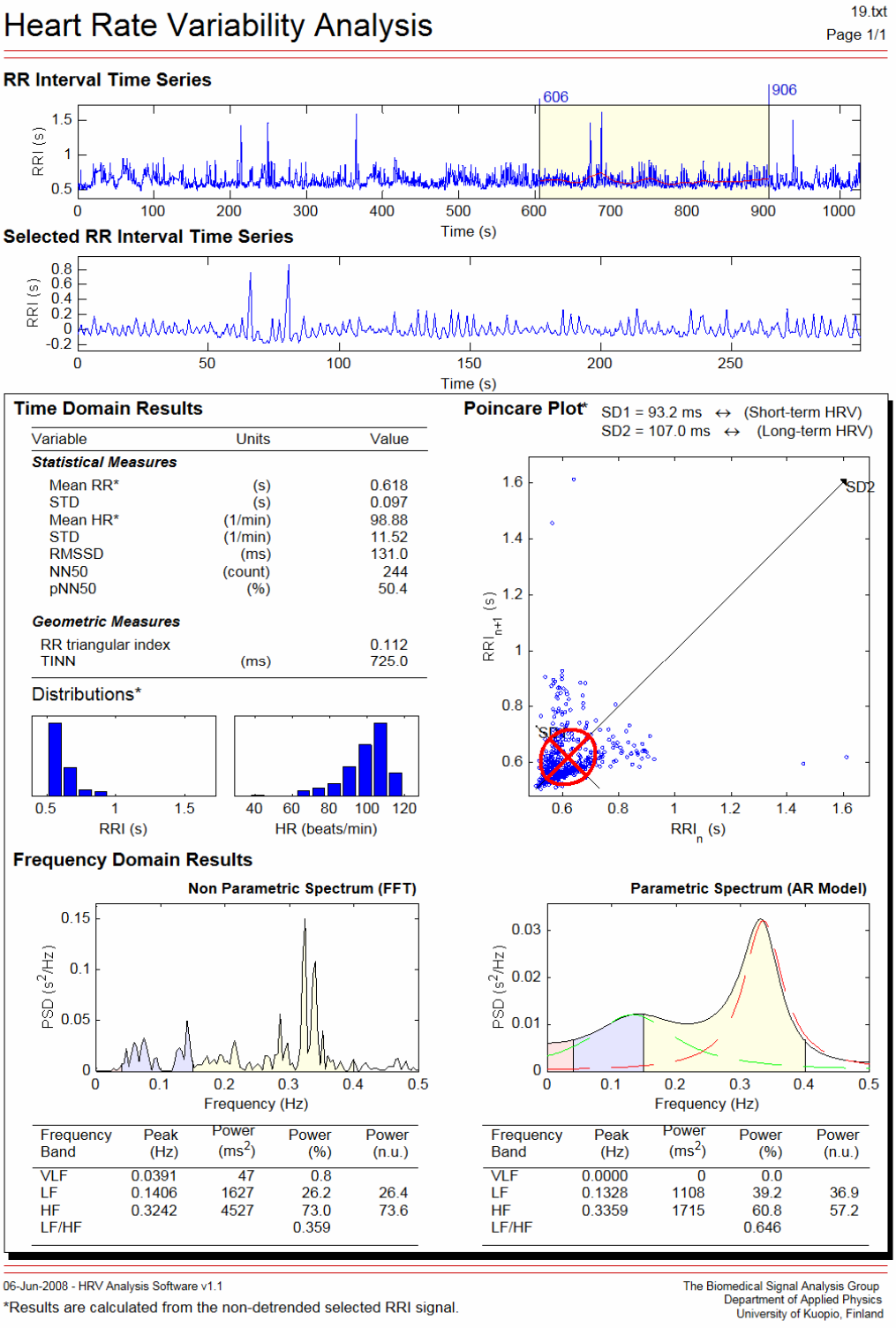

Figure A-110: HRV data during focussed attention for subject 19, tested while on stimulant medication

Subject 20 Baseline

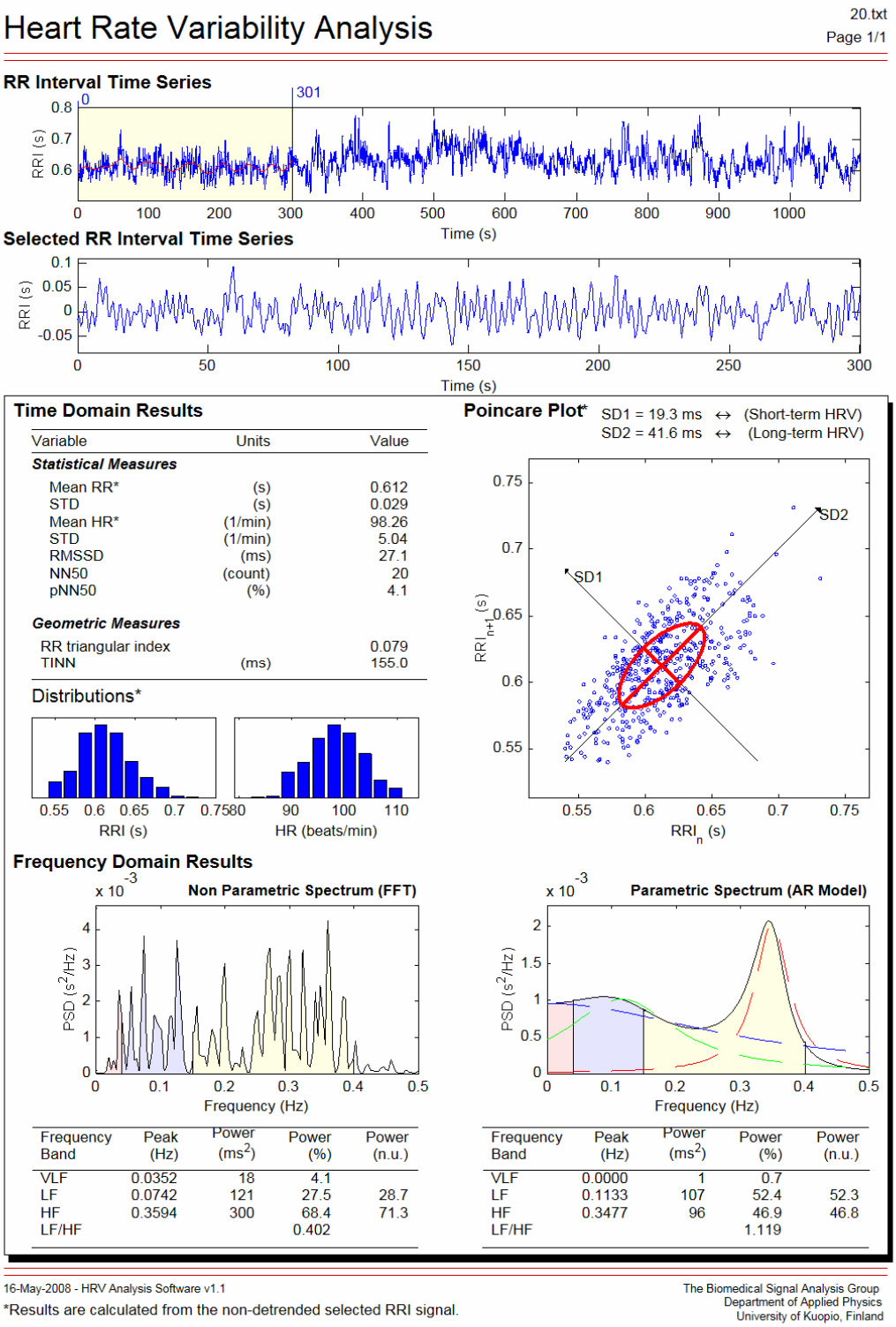

Figure A-111: Baseline HRV data for subject 20, tested while on stimulant medication

Subject 20 Focusssed attention

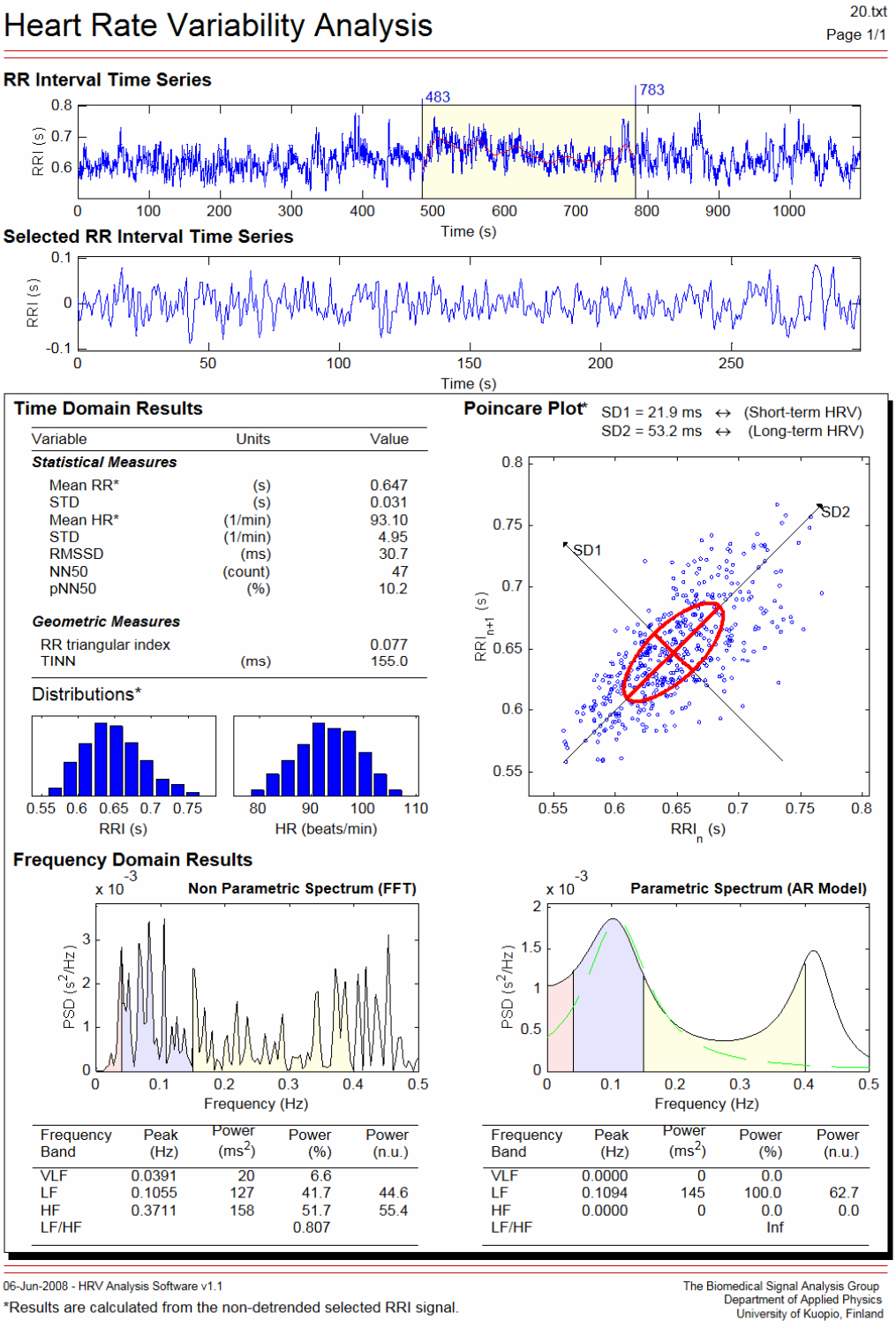

Figure A-112: HRV during focussed attention for subject 20, tested while on stimulant medication