DOI:
10.1111/jcpp.12711

Document Version
Peer reviewed version

Stress vulnerability in adolescents with chronic fatigue syndrome (CFS):

Experimental study investigating heart rate variability and skin conductance responses.

Journal of Child Psychology and Psychiatry:

http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1469-7610

Abbreviated title: Stress vulnerability in adolescents with chronic fatigue syndrome

Katharine A. Rimes, Kate Lievesley, Trudie Chalder

King's College London

Abstract

Background

Stress vulnerability has been implicated in adolescent chronic fatigue syndrome (CFS) but rarely investigated directly. This study compared psychological and physiological responses to a laboratory social performance task in adolescents with CFS with chronic illness (asthma) and healthy control groups.

Methods

Adolescents with CFS (n=60), adolescents with asthma (n=31) and healthy adolescents (n=78) completed questionnaires before and after a social performance task. Skin conductance responses (SCR; mean SCR and Max-Min) and heart rate variability (low frequency / high frequency; LF/ HF and root mean square difference of successive R-R intervals; RMSSD) was measured before, during and after the task.

Results

Baseline HRV (RMSSD) was significantly lower in the CFS and Asthma groups than the HC. During the speech, the CFS and Asthma groups had higher HRV (LF/HF) than the HC, adjusting for baseline LF/HF. Although the asthma group showed a subsequent reduction in HRV during recovery, the CFS group did not. Similarly, during recovery after the task, the CFS group showed a continued increase in skin conductance (Min-Max), unlike the Asthma and HC groups.

Compared to control groups, adolescents with CFS expected to find the task more difficult, were more anxious beforehand and afterwards, rated it as more difficult, evaluated their performance more negatively and had lower observer ratings of performance. Parents of adolescents with CFS expected that their child would perform less well in the task than parents of control participants.

Conclusions

Adolescents with CFS showed autonomic nervous system responses that are consistent with chronic stress vulnerability, difficulty coping with acute stress and slower recovery after acute stress. Self-report measures also indicated greater trait, pre- and post-task anxiety in the CFS group.

Keywords

Chronic fatigue syndrome, myalgic encephalomyelitis, adolescence, autonomic nervous system, fatigue, stress.

Chronic fatigue syndrome (CFS) is characterised by severe fatigue which is present for more than 50% of the time, not accounted for by organic illness and is disabling - affecting both physical and mental functioning. Other symptoms are common, such as headaches, sleep problems, difficulties with concentration and muscle and joint pain. In the UK, children and adolescents can be diagnosed after symptoms have been present for three months (Royal College of Physicians, 1996). This condition can be associated with significant school absenteeism (Crawley, Emond & Sterne, 2011 and potentially serious adverse effects on physical, emotional and intellectual development (Nijhof et al., 2016).

Many researchers have suggested that stress is a factor contributing to the aetiology and maintenance of CFS symptomatology, for example in terms of premorbid temperamental stress vulnerability (Lievesley, Rimes & Chalder, 2014), a persistent elevated stress response (Wyller, Malterud & Eriksen, 2009), a 'crash' in the neurobiological stress system (Houdenhove, Van Den Eeede & Luyten, 2009) or dysregulated stress signal sensitivity (Srahler, Skoluda, Rohleder & Nater, 2016). It has been proposed that chronic stress may be involved in the pathophysiology of CFS via mechanisms such as chronic low grade inflammation, sustained oxidative stress, mitochondrial dysfunction, impaired energy metabolism in the central nervous system and a hypometabolic state (Tanaka et al., 2015; Srahler et al., 2016; Naviaux et al. 2016).

Consistent with suggestions of stress system dysregulation, adolescents with CFS have lower daily cortisol output than healthy adolescents (Rimes, Papadopoulos, Cleare & Chalder, 2014), and hypocortisolism is known to be associated with chronic stress (Miller, Chen, Zhou, 2007). Adolescents with CFS have higher scores on anxiety questionnaires than both healthy and illness (rheumatoid arthritis) controls (Rangel, Garralda, Jeffs & Rose, 2003) and elevated depressive symptomatology (Bould, Collin, Lewis, Rimes & Crawley, 2013). Prospective studies indicate that psychological problems are a risk factor for chronic fatigue onset (Collin et al., 2015; Rimes et al., 2007; ter Wolbeek, van Doornen, Kavelaars & Heijnen, 2009). However, there is limited direct evidence of abnormalities in stress reactivity in adolescents with CFS.

Physiological responses to stress are very complex and are partly controlled by the sympathetic nervous system, which stimulates the 'fight or flight' response and interacts with the parasympathetic nervous system. One measure of sympathetic nervous system activity is skin conductance, which reflects sweat gland activity. Adults with CFS have been found to have higher skin conductance during a stressful task than healthy individuals (Rimes, Ashcroft, Bryan & Chalder, 2016). Skin conductance responses (SCR) to stress have not been previously reported in adolescents with CFS.

Another measure of nervous system activity, which can reflect both sympathetic and parasympathetic nervous system activity, is heart rate variability (HRV). HRV refers to variation in the time interval between heartbeats. Effective stress responsivity relies on rapid cardiac autonomic nervous system modulation. HRV disturbance has also been identified across numerous physical and psychiatric conditions (Koenig, Kemp, Beauchaine, Thayer & Kaes, 2016; Kemp & Quintana, 2013). It has been argued that HRV disturbance is a transdignostic psychophysiological marker of risk for physical and psychiatric health problems (Thayer, Ahs, Fredrison, Sollers & Wager, 2012).

The evidence is inconsistent in relation to HRV abnormalities in adolescents with CFS using the 'head-up tilt test' in which participants are tilted from a horizontal position. Some studies using this task have found HRV abnormalities in adolescents with CFS such as enhanced sympathetic and attenuated parasympathetic nervous activity (e.g. Wyller, Saul, Amlie, & Thaulow, 2007). In contrast, Wyller et al. (2014) did not find an abnormal response to standard version of this task, whereas when asked to *imagine* standing upright, adolescents with CFS showed a significantly stronger increase in sympathetic predominance compared to healthy controls. This indicates that abnormal responses to the head-up tilt task in adolescents with CFS are not purely the result of the gravitational challenge. However, previous HRV studies have not measured other possible contributory factors such as expectations or anxiety.

The current study investigated autonomic responses to a social performance task designed to induce stress, in adolescents with CFS compared to adolescents with another chronic condition (asthma) and

healthy adolescents. It was predicted that SCR would be significantly higher in the CFS group than the other two groups in anticipation of, during and after the task. For HRV it was expected that CFS participants would have higher LF/HF (reflecting high sympathetic and / or low parasympathetic heart rate control) and lower RMSSD HRV, indicating low parasympathethic heart rate control.

It was hypothesised that adolescents with CFS would report more anxiety, lower performance expectations and greater expected difficulty than the other two groups. Parental ratings of their expectations for their child's anxiety and performance were expected to show a similar pattern.

Method

Design

Adolescents with CFS were compared to an illness control group (adolescents with asthma) and a healthy control group. For the physiological measures, a group (CFS, asthma and healthy) by time (social task versus recovery period) design was used in which baseline scores were entered as covariates. For the self-report measures the design was group (CFS, asthma, healthy) by time (pre- and post-task).

Participants

Sixty adolescents who fulfilled the Oxford criteria for CFS (Sharpe *et al.*, 1991) were recruited from treatment waiting lists at King's College Hospital or Great Ormond Street Hospital in London. An additional participant decided not to undertake the task because he was too nervous and his data are not included here. Thirty one adolescents diagnosed with asthma and who used medication were recruited from general practitioners. All used inhalers (salbutamol or salmeterol plus fluticasone propionate); in addition five used cetirizine hydrochloride and two used Montelukast. Healthy individuals (n=78) were recruited from local schools. Individuals who had suffered with CFS or asthma in the past were excluded from the healthy control group. A history of psychiatric disorder was an exclusion factor for both control groups. All participants were aged 11-18 years. Participants

were asked to bring a parent with them; a parent attended with 56 of the adolescents with CFS, 21 of the adolescents with asthma and 60 of the healthy adolescents.

Procedure

Written informed consent was provided by adolescents and one of their parents prior to participation. Participants were sent questionnaires to complete beforehand. They attended the clinic with one parent who waited in a separate room. A baseline physiological recording was taken with the participant sitting in quiet room for five minutes, before task instructions were provided. Participants were asked to give a 3 minute speech on a topic of their choice to the experimenter, which was filmed, using the procedure by Rapee and Lim (1992). They were told that the experimenter would evaluate their performance and that the film was being made to allow a performance evaluation by independent raters later on. The task elicits a level of stress that is manageable for adolescents (Rapee & Lim, 1992). Before and after completing the experimental task, participants were asked to complete ratings of their expectations, performance, perceived difficulty and anxiety. At the end participants were debriefed and had the opportunity to talk about their feelings about the task.

Self-report questionnaires

Ethnicity information was collected in the standard format used in the clinic; due to small numbers of participants in groups other than White British, the minority ethnic group numbers were combined for group comparisons. All standardised questionnaires used (described below) have satisfactory validity and reliability in general population samples.

Children's Depression Inventory (CDI) (Kovacs & Beck, 1977): The CDI measures symptoms of depression during the past two weeks. The original form has 27 items (scored 0-2) with higher scores indicating greater depressive symptomatology. Here, items that referred to symptoms or common consequences of CFS were excluded (items 15, 16, 17, 19, 23).

State-Trait Anxiety Inventory for Children (STAI-C) (Spielberger, 1973): The 20-item trait anxiety sub-scale of the STAI-C was used here. Respondents indicate they generally feel by reporting the frequency of occurrence of anxiety-related feelings and symptoms; (1) almost never, (2) sometimes, (3) often, (4) almost always.

Social Phobia and Anxiety Inventory for children (SPAI-c) (Beidel, Turner & Morris, 1995): The SPAI-C is a 26-item scale assessing symptoms of social phobia and social anxiety in children and adolescents. The maximum score is 52 with higher scores indicating greater social anxiety severity. A clinical cut-off score of 18 or above is recommended.

Visual Analogue Scales –After the task instructions and after completing the task, participants completed 0-100 visual analogue scales regarding anxiety at that moment in time. They were also asked "How well do you think you are going to do on this task?" and "How difficult do you think you're going to find this task?" with higher ratings indicating higher anxiety, expected performance and expected difficulty. After the task they completed similar ratings regarding anxiety, performance and difficulty - "How well do you think you did on the task?" and "How difficult did you find the task?". After an explanation of the task by the researcher, parents were asked to make similar ratings on how they thought their child would feel and perform on the performance tasks. They made these ratings on the day of the experimental tasks, whilst the child was not in the room.

The Speech Evaluation Questionnaire (Harvey, Clark, Ehlers & Rapee, 2000) which included positive and negative indicators of performance (e.g. understandable, confident, clear voice, awkward) was completed by adolescents afterwards. (Due to administrative error the number completing this questionnaire is lower than for other questionnaires). Two independent raters separately rated each video using the Speech Evaluation Questionnaire. The raters were four research assistants who were blind to group membership.

Heart Rate Variability and Skin Conductance Response

Continual measurements of heart rate (HR) and skin conductance were recorded using Powerlab 26T hardware and LabChart Pro Software (ADInstruments; www.adinstruments.com).

Heart rate was measured using a finger pulse transducer on the second finger of the non-dominant hand, which was chosen as being less intrusive than chest ECG. The pulse signal was sampled at 200mV to ensure optimum resolution. HRV power spectra were calculated by means of fast Fourier transform. The low frequency / high frequency ratio (LF/HF) was calculated as a measure of frequency-domain HRV (Ori, Moni, Weiss, Sayhouni & Singer, 1992). The root mean square of successive differences in adjacent beat-to-beat intervals (RMSSD) was also derived, an index of HRV in the time domain, primarily reflecting parasympathetic modulation of the heart rate.

For skin conductance, electrodes were attached to the index and ring fingers of the non-dominant hand. The electrodes have a low, constant voltage AC excitation (22mVrms at 75 Hz). A minimum response amplitude of 0.05 μs was used. Mean skin conductance (μs) and the amplitude of the response (the "Max-Min response") were extracted.

The number of participants with usable HRV and / or SCR data (shown in Tables 3 and 4) was lower than for other parts of the study due to technical problems with the PowerLab or the data produced.

Physiological data was recorded in three blocks: Baseline (five minutes), during the social performance task (three minutes) and during recovery (30 minutes after the task, for 5 minutes).

Data preparation and Statistical Analyses

Analyses were completed using IBM SPSS Statistics version 22.0. No serious violations of normality were identified for all variables. To compare the groups on ratings of expectations, performance ratings, anxiety and parental ratings, one-way ANOVAs were conducted. Repeated measures ANCOVAs were used to investigate changes in variables over time, controlling for baseline scores.

Significant effects were investigated further with paired t-tests or one-way ANOVAs or ANCOVAs as appropriate. Bonferroni correction was used for multiple comparisons.

Results

Participant characteristics

Of the CFS group, 93.8% had been fatigued for 6 months or more; the remained had been fatigued for at least 3 months. There were no significant group differences for age, sex, ethnicity, main carer or social anxiety (see Table 1). The CFS group had significantly higher scores on measures of trait anxiety than the other two groups who did not differ significantly from each other. The CFS group and asthma group had higher depression scores than the HC but did not differ significantly from each other.

[Table 1]

Expectations, performance and anxiety

One-way ANOVAs were conducted to compare the groups on ratings of expectations, performance and anxiety (see Table 2). The healthy control group expected to perform better than either of the other two groups. The CFS group expected the social performance task to be more difficult than the other two groups. The CFS group had higher pre-task anxiety ratings than the other two groups. The healthy controls rated their performance more highly than the other two groups. The CFS group found the task more difficult and were more anxious post-task than both of the control groups. Self- and observer ratings of social performance on the SEQ were lower for the CFS participants than for the other two groups.

[Table 2]

Parental expectations for the child

ANOVAs (see Table 2) indicated that parents of the adolescents with CFS gave lower ratings for how well they expected their child to do on the task than parents for the asthma and healthy control groups.

Parents of adolescents with CFS and asthma expected their child to find the task more difficult than parents of healthy adolescents. Parents of adolescents with CFS expected their child to be feeling more anxious before the task than mothers of healthy children; the asthma group's parental ratings were not significantly different from the other two groups.

Group comparison for baseline skin conductance and heart rate variability

One-way ANOVAs indicated no significant differences in baseline skin conductance, HR, LF or HF power or LF/ HF ratio (see Table 3). There was a significant group difference in RMSSD. Post-hoc comparisons indicated that the CFS group had significantly lower RMSSD than the healthy adolescents. RMSSD for the asthma group did not differ significantly from the other two groups. The group difference in RMSSD remained significant when controlling for trait anxiety but when controlling for depression, it became non-significant ($F(2, 147)=2.9$, $p=0.06$).

[Table 3]

Physiological parameters before, during and after social performance task

Repeated measures ANCOVAs were conducted to compare the three groups on the physiological measures during the speech and in the recovery period, covarying for the baseline measure (see Table 4).

For *Mean SCR* there were no significant effects. For *Min-Max SCR* there was only a time by group interaction. Post-hoc analyses indicated that the CFS group showed a significant increase in Min-Max SCR between speech and recovery whereas the other groups showed no significant change.

HR and RMSSD both showed significant effects of time only. HR increased significantly between baseline and speech and then decreased significantly between speech and recovery. RMSSD also increased between baseline and speech but showed no significant change from speech to recovery.

For LF and HF, there were no significant effects.

For *LF/HF ratio* there were significant effects of time and group and also a time by group interaction. One-way ANOVAs and post-hoc comparisons indicated that during the speech phase, the HC had significantly lower LF/HF than the CFS and Asthma groups, which did not differ significantly from each other. There was no significant group difference in LF/HF during recovery. Post-hoc analyses indicated that Asthma group showed a significant decrease between speech and recovery whereas the other two groups did not.

When the ANCOVAs were repeated controlling for trait anxiety or depression, the effects described above remained significant.

[Table 4]

Discussion

Adolescents with CFS and asthma had lower baseline RMSSD HRV than healthy adolescents, a group difference which became just non-significant when controlling for depression. During the speech, both CFS and asthma groups had significantly greater LF/HF HRV than the healthy adolescents and this effect remained after adjustment for depression or trait anxiety. Unexpectedly, the skin conductance response in the CFS group continued to increase during the recovery period, unlike the other two groups. Self-report ratings showed lower performance expectations and post-task evaluations and greater anxiety in the CFS group relative to control groups.

The abnormally low HRV (measured by RMSSD) in the CFS group relative to healthy adolescents may indicate that the CFS participants have lower parasympathetic modulation of their heart rate. This could indicate a reduced ability to cope with stressors that tend to destabilise blood pressure. Although the group difference became non-significant when analyses were repeated controlling for depression

questionnaire scores, it should not be concluded that the abnormality is necessarily a result of depressive symptomatology. It has been argued that unusually low resting HRV reflects a transdiagnostic, general biomarker of reduced ability to adapt to stress (Beauchaine & Thayer, 2015). Therefore this may reflect a risk factor or set of risk factors that influence susceptibility to both CFS and depression. The lack of significance between the CFS and asthma group is likely to be a power issue.

During the speech task, LF/HF was significantly higher in the CFS group and asthma group relative to healthy controls. Although the group differences were not significant for HF power, the CFS participants had lower HF power during speech and recovery than at baseline whereas the other two groups showed the converse pattern. The current pattern of findings may indicate that adolescents with CFS had lower vagal modulation of heart rate during the stressful task, with increased sympathetic heart rate control also possibly playing a role. The HF and LF / HF changes in the current study are consistent with Wyller et al.'s (2007) finding of a greater increase in the LF/HF ratio and greater decrease in HF power in the CFS group compared to healthy adolescents when undergoing a head-up tilt test. This is the first study to demonstrate HRV abnormalities in adolescents with CFS in response to a socially stressful task, and after controlling for depression or anxiety.

When asked "how well do you think you will do at the task?", both chronic illness groups gave lower expectation ratings than those of the healthy controls, so their lower HRV during the speech task may reflect a greater perception of challenge for both illness groups. However, the CFS group expected to find the task more difficult than the other two groups and were more anxious beforehand. It is possible that this anxiety impaired their performance, as observers rated performance in the CFS group as lower than the other two groups. It is possible that the CFS participants had greater anticipated difficulty and anxiety because they believed their CFS symptoms would interfere with their ability to perform. However it is possible that anxiety tendencies were present premorbidly, with evidence from prospective studies that anxiety and depression are risk factors for chronic fatigue onset (e.g. Rimes et al., 2007; ter Wolbeek, van Doornen, Kavelaars & Heijnen, 2009). A prospective study would be

required to investigate whether differences in physiological and psychological responses to acute stressors predict subsequent CFS onset.

Although both the CFS and asthma groups had higher LF/HF during the speech task than the healthy controls, only the asthma group showed a significant subsequent decrease during the recovery period. The group by time interactions were not significant for LF and HF, but the CFS participants showed a decrease in HF between speech and recovery whereas the asthma group showed the opposite pattern. In contrast LF increased from speech to recovery in the CFS group but decreased in the asthma group. The findings may indicate that CFS adolescents had an impaired parasympathetic nervous system response during recovery from a challenging task, as well as possibly continued or increased sympathetic nervous system activity.. Similarly, the CFS group showed a continued increase in Min-Max SCR (a marker of sympathetic nervous system activity) during the recovered period unlike the other two groups. Furthermore, the CFS group reported greater anxiety both before and after the task than the other two groups. These are consistent with suggestions that CFS is characterised by *persistent* stress arousal (Wyller, Malterud & Eriksen, 2009). Future research could investigate whether psychological processes such as post-task rumination may contribute to persistence in arousal after a stressful event.

Parents of both the CFS and asthma groups expected that their child would find the task more difficult than parents of healthy participants. This may be because they anticipate their child's condition will interfere with their ability to do the task and / or to make them more anxious about the task. In support of the latter, expected anxiety ratings in the parents of the adolescents with CFS were significantly higher than those for the healthy controls; parental anxiety ratings for the asthma group were similar to the CFS group and probably did not differ significantly from the healthy controls due to insufficient power. In contrast, parents of adolescents with CFS expected that their child would perform less well in the task than parents of both control participants, and indeed this expectation was accurate with regards to lower observer ratings of performance for the CFS group. Future research could investigate in more detail parental understanding of why their children find social performance tasks difficult, any

impact of parental expectations on the adolescent and ways in which parents can best support their child.

Cognitive behaviour therapy is an effective treatment for pediatric CFS (Chalder et al., 2010) and stress vulnerability can be addressed within this framework. Prevention strategies to help improve stress awareness and management techniques in young people may not only help to reduce the risk of CFS but would have broader benefits as stress is implicated in many physical and psychiatric conditions.

Only participants able to travel to the hospital were included, due to the need to standardise testing conditions, and the results cannot be assumed to generalise to adolescents with CFS who are housebound. The group were mainly white British and further research is needed with more participants from other ethnic groups. Future studies could use a talking baseline task to match the speech condition. The speech task lasted three minutes to ensure the stress was manageable for participants, whereas the baseline and recovery recordings lasted five minutes; future research could use periods of identical duration. Another limitation was the smaller group size for the asthma participants due to recruitment difficulties. This may have limited the power to detect group differences in some analyses and meant it was not possible to apply more stringent adjustment of alpha values to account for the number of measures under investigation. Future studies should be sufficiently powered to support multivariable models and should use these findings to inform power analyses. Asthma participants had been required to take medication to help match for symptom severity but the adrenergic effects of this medication should be taken into account when interpreting the findings. Future research should include alternative illness control groups.

In conclusion, the baseline difference in RMSSD HRV in the adolescents with CFS relative to healthy adolescents may reflect *chronic* physiological difficulty adapting to stressors. The greater LF/HF HRV during the task in both CFS and asthma groups suggests impairments in coping with *acute* stress. This may in part relate to the lower pre-task performance expectations in both of these groups

compared to healthy individuals. Thirdly, the failure of the CFS group to show reductions in HRV during the recovery period, the continued increased in SCR, and the greater ratings of post-task anxiety may reflect slower *recovery* from stress compared to adolescents with asthma or healthy individuals. The role of disturbances in stress vulnerability in adolescents with CFS requires further investigation.

Acknowledgements

This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

We are very grateful to the participants and their parents. We would like to thank the staff at the CFS Units at King's College London and Great Ormond Street as well as local schools and general practice surgeries for all their help with recruitment. We are also grateful to Hannah Graham, James Gwinnutt, Egli Ioannou and Fatma Mehmet for their help with the video ratings.

Correspondence:

Dr Katharine A. Rimes, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF

Tel. +44 (0)20 7848 0430; Fax +44 (0)20 7848 5006

Email: Katharine.Rimes@kcl.ac.uk

References

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology, 98*, 338–350.

Beidel, D. C., Turner, S. M., & Morris, T. L. (1995). A new inventory to assess social anxiety and

phobia: The Social Phobia and Anxiety Inventory for Children. *Psychological Assessment, 7,* 73-79.

Bould H, Collin SM, Lewis G, Rimes, K.A., Crawley. E. (2013). Depression in paediatric chronic fatigue syndrome. *Archives of Diseases in Childhood, 98,* 425–428.

Bright AT, Alaynick WA, Wang L, Baxter A, Nathan N, Anderson W, Gordon E. Metabolic features of chronic fatigue syndrome. (2016). Proceedings of the National Academy of Sciences of the USA., 113, E5472-80. Doi: 10.1073/pnas.1607571113.

Chalder, T., Deary, V., Husain, K., & Walwyn, R. (2010). Family-focused cognitive behaviour therapy versus psycho-education for Chronic Fatigue Syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychological Medicine, 40,* 1269-1279.

Collin, S.M., Tilling, K., Joinson, C., Rimes, K.A., Pearson, R.M., Hughes, R.A., Sterne, J.A.C. & Crawley, E. (2015). Maternal and Childhood Psychological Factors Predict Chronic Disabling Fatigue at Age 13 Years. *Journal of Adolescent Health, 56,* 181-197.

Crawley, E., Emond, A. M. & Sterne, J. A. C. (2011). Unidentified Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *British Medical Journal Open, 1,* e000252. Doi:10.1136/bmjopen-2011-000252

Harvey, A. G., Clark, D. M., Ehlers, A., & Rapee, R. M. (2000). Social anxiety and self-impression: Cognitive preparation enhances the beneficial effects of video feedback following a stressful social task. *Behaviour Research and Therapy, 38,* 1183-1192.

Houdenhove, B.V., Van Den Eeede, F., Luyten, P. (2009). Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system? *Medical Hypotheses, 72,* 701-705.

Kemp, A. H. & Quintana, D. S. (2013). The relationship between mental and physical health: Insights from the study of heart rate variability. *International Journal of Psychophysiology, 89,* 288-296.

Koenig , J., Kemp, A.H., Beauchaine, T.P.,Thayer, J.F., Kaess, M. (2016). Depression and resting

state heart rate variability in children and adolescents — A systematic review and meta-analysis. *Clinical Psychology Review, 46*, 136-150.

Kovacs, M., & Beck, A. (1977). An empirical-clinical approach toward a definition of childhood depression. In J. S. A. Raskin (Ed.), *Depression in childhood: Diagnosis. Treatment and conceptual models* (pp. 1-26): Washington, DC: Department of Health, Education and Welfare.

Lievesley, K., Rimes, K. & Chalder, T. (2014). A review of the predisposing, precipitating and perpetuating factors in Chronic Fatigue Syndrome in children and adolescents. *Clinical Psychology Review, 34*, 233-248

Miller, G.E., Chen, E., Zhou, E.S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic pituitary–adrenal axis in humans. *Psychological Bulletin ,133*, 25–45.

Nijhof, L.N., Nijhof, S.L., Bleijenberg, G., Stellato, R.K., Kimpen, J.L., Hulshoff, H.E., van de Putte, E.M. (2016). The impact of chronic fatigue syndrome on cognitive functioning in adolescents. *European Journal of Pediatrics, 175*, 245-252.

Ori, Z., Monir, G., Weiss, J., Sayhouni, X. & Singer, D. H. (1992). Heart rate variability. Frequency domain analysis. *Cardiology Clinics, 10*, 499-537.

Spielberger, C. (1973). STAIC preliminary manual. Palo Alto, CA: Consulting Psychologists Press.

Rangel, L., Garralda, E., Hall, A., & Woodham, S. (2003). Psychiatric adjustment in Chronic Fatigue Syndrome of childhood and in juvenile idiopathic arthritis. *Psychological Medicine, 33*, 289-297.

Rapee, R. M., & Lim, L. (1992). Discrepancy between self and observer ratings of performance in social phobics. *Journal of Abnormal Psychology, 101*, 727-731.

Rimes, K.A., Ashcroft, J., Bryan, L., Chalder, T. (2016). Emotional suppression in chronic fatigue syndrome (CFS): Experimental study. Health Psychology. E-pub ahead of print. http://dx.doi.org/10.1037/hea0000341

Rimes, K. A., Goodman, R., Hotopf, M., Wessely, S., Meltzer, H., & Chalder, T. (2007). Incidence, Prognosis, and Risk Factors for Fatigue and Chronic Fatigue Syndrome in Adolescents: A prospective Community Study. *Pediatrics, 119*, 603-609.

Rimes, K., Papadopoulos, A., Cleare, A. & Chalder, T. (2014). Cortisol output in adolescents with chronic fatigue syndrome: Pilot study on the comparison with healthy adolescents and change after cognitive behavioural guided self-help treatment. *Journal of Psychosomatic Research, 77,* 409-414

Royal College of Physicians, Psychiatrists and General Practitioners. (1996). *Chronic fatigue syndrome: Report of a joint working group of the Royal College of Physicians, Psychiatrists and General Practitioners*. (Vol. Council Report CR54). London: Royal College of Physicians.

Sharpe M., Archard, L.C., Banatvala, J.E., Borysiewicz, L.K., Clare, A.W., David, A.S., …White, PD. (1991). A report – chronic fatigue syndrome: guidelines for research. *Journal for the Royal Society of Medicine, 84,* 118-121.

Strahler, J., Skoluda, N., Rohleder, N., Nater, U.M. (2016). Dysregulated stress signal sensitivity and inflammatory disinhibition as a pathophysiological mechanism of stress-related chronic fatigue. *Neuroscience & Biobehavioural Reviews, 68,* 298-218.

Stulemeijer, M., de Jong, W. A. M. L., Fiselier, T. J. W., Hoogveld, S. W. B., & Bleijenberg, G. (2005). Cognitive behaviour therapy for adolescents with Chronic Fatigue Syndrome: randomised controlled trial. *British Medical Journal, 330,* 1-5.

Tanaka. M., Tajima, S., Mizuno, K., Ishii, A., Konishi, Y., Miike, T., Watanabe, Y. (2015). .Frontier studies on fatigue autonomic nerve dysfunction and sleep rhythm disorder. *Journal of Physiological Sciences, 65*, 483–498.

Ter Wolbeek, M., van Doornen, L.J.P., Kavelaars, A. & Khiejnen, C.J. (2007). Predictors of Persistent and New-onset Fatigue in Adolescent Girls. *Pediatrics, 121,* e449-457.

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J. III, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 36, 747–756.

Wyller, B.B., Fagermoen, E., Sulkeim, D., Winger, A., Skovlund, E., & Saul, J.P. (2014). Orthostatic responses in adolescent chronic fatigue syndrome: contributions from expectancies as well as gravity. *Biopsychosocial Medicine, 8,* 22.

Wyller, V.B., Malterud, K., Eriksen, H.R. (2009). Can sustained arousal explain chronic fatigue syndrome? *Behavioural and Brain Functions, 5*, 10.

Wyller, V. B., Saul, J. P., Amlie, J. P., & Thaulow, E. (2007). Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. *Clinical Physiology and Functional Imaging, 27*, 231-238.

Table 1. Sociodemographic and clinical characteristics of the three groups

	Numbers in each group			**Chronic Fatigue Syndrome** (n=60)	**Asthma** (n=31)	**Healthy Controls** (n=78)	**Results of group comparison**
Age in years (Mean, SD)	60	31	78	15.6 (1.7)	15.5 (2.3)	15.1 (1.4)	F(2,164)=1.9, p=.161
Gender (number, % female)	60	31	78	38 (63.3%)	15(48.4%)	48 (61.5%)	χ^2 (2)=2.1, p=0.352
Ethnicity (number, % White British)	60	31	78	54 (90%)	24(77.4%)	67 (85.9%)	χ^2 (2)= 2.7, p=0.265
Main carer (number, %) both parents)	60	31	78	37 (61.7)	25 (80.6)	57 (73.1)	χ^2 (4) = 5.9, p = .204
Depression – CDI (Mean, SD)	59	31	78	11.0[a] (5.7)	8.7[a] (5.0)	5.8 (3.5)	F(2,167) = 20.6, p < .0005*
Trait anxiety (Mean, SD) – Spielberger	58	31	78	47.1 (10.3)	40.5[a](11.2)	37.5[a] (11.2)	F(2,166) = 13.2, p < .001*
Social anxiety – SPAI (Mean, SD)	53	28	78	13.2 (10.1)	10.8 (9.8)	10.1 (7.4)	F(2,158) = 2.0, p = .135
Proportion with SPAI score of 18 or above (number , %)	53	28	78	18 (34.8%)	7(25.0%)	14 (17.9%)	χ^2 (2) = 4.4, p = .112

* significant difference ; [ab] Values which share a subscript are not significantly different; CDI – Children's Depression Inventory with CFS-related symptoms removed; SPAI – Social Phobia and Anxiety Inventory

Table 2: Expectations, performance and anxiety; means, standard deviations and results of ANOVAs

	Numbers in each group	**Chronic Fatigue Syndrome**	**Asthma**	**Healthy Controls**	**Results of group comparison**
Child ratings	**CFS AS HC**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Anxiety: pre-task	60 31 78	46.0 (27.2)	34.9 (29.8)[a]	33.8 (25.6)[a]	F(2,166) = 3.8, p = .025*
Anxiety: post task	58 31 78	36.3 (26.7)	22.1 (20.6)[a]	26.1 (21.6)[a]	F(2,164) = 4.8, p = .010*
Performance expectations	60 31 78	45.1 (20.2)[a]	47.7 (25.7)[a]	61.2 (20.8)	F(2,166) = 10.5, p < .0005*
Performance evaluation	58 31 78	41.8 (22.1)	49.3 (29.4)[a]	58.6 (23.2)[a]	F(2,166) = 8.2, p < .0005*
Task difficulty expectations	60 31 78	55.1 (20.3)	37.4 (25.7)[a]	36.0 (24.1)[a]	F(2,166) = 12.6, p < .0005*
Task difficulty evaluation (post-task)	58 31 78	57.0 (24.8)	32.4 (26.8)[a]	39.4 (27.4)[a]	F(2,166) = 11.2, p < .0005*
Speech Evaluation Questionnaire (self)	51 24 63	77.1 (24.5)	88.6 (29.1)[a]	94.4 (26.0)[a]	F|(2,135) = 6.5, p = .002*
Observer –ratings Speech Evaluation Q.	59 17 75	85.0 (22.7)	94.8 (10.5)[a]	94.3 (17.0)[a]	F(2,149) = 4.5, p = .013*
Parental ratings					
How well do you think your child is going to do on this task?	56 21 60	64.8 (24.2)	73.7 (19.6)[a]	78.5 (19.2)[a]	F(2,134) = 6.0, p = .003*
How difficult do you think your child is going to find it?	56 21 60	43.8 (26.4)[a]	41.2 (34.6)[a]	25.6 (26.0)	F(2,134) = 6.9, p = .001*
How anxious is your child at this moment in time?	56 21 60	39.8 (24.6)[a]	35.7(28.7)[ab]	24.5 (23.4)[b]	F(2,134) = 5.7, p = .004*

[a] Values sharing a superscript do not differ significantly

Table 3. Baseline skin conductance and heart rate variability; means, standard deviations and ANOVA results

Physiological Parameters	**N for each group**			**CFS**		**AS**		**HC**		**Result (one-way ANOVA)**
	CFS	AS	HC	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Min-Max SCR	55	25	73	10.2	(6.1)	7.7	(4.2)	8.4	(6.2)	F(2,152) = 2.1, p = .131
Mean SCR	55	25	71	5.1	(4.5)	3.9	(2.0)	3.7	(3.3)	F(2,150) = 2.5, p = .085
Mean Heart Rate	51	28	73	82.2	(9.9)	80.9	(9.2)	79.9	(7.6)	F(2,149) = .99, p = .375
Low Frequency (LF)	51	28	73	1745.2	(1120.9)	2230.1	(1362.0)	2003.4	(1499.8)	F(2,149) = 1.23, p = .296
High Frequency (HF)	51	28	73	1034.8	(686.6)	1470.5	(1109.9)	1656.9	(2113.0)	F(2,149) = 2.31, p = .103
LF/HF ratio	51	28	73	2.0	(1.0)	2.2	(1.4)	1.9	(1.3)	F(2,149) = .69, p = .505
RMSSD	50	28	72	48.8[a]	(19.1)	61.4[ab]	(21.2)	62.9[b]	(35.4)	F(2,149) = 3.86, p = .023*

* indicates a significant difference

[a, b] Values sharing a subscript do not differ significantly

SCR – Skin Conductance Response

RMSSD – RMSSD – Root mean square difference of successive RR-intervals

Table 4. *Means, standard deviations and results of the repeated measures ANCOVAs to investigate differences from speech to recovery stage of the Social Performance Task, adjusted for baseline.*

	CFS Mean (SD)	**Asthma** Mean (SD)	**Healthy** Mean (SD)	**ANCOVA results**	**Effect size; partial eta squared** $\eta \frac{2}{p}$
Min-Max Skin Conductance Response (n=54 CFS; n=24 Asthma, n=73 Healthy)					
Baseline	10.2 (6.2)	7.7 (4.3)	8.4 (6.2)	Time[a]: F(1,147) = .4, p=0.519	.003
Speech	15.5 (8.4)	13.4 (8.6)	13.8 (7.3)	Group[b]: F(2,147) = .3, p = .732	.004
Recovery	17.5 (9.4)	13.3 (9.9)	14.1 (8.0)	Time by Group: F(2,147) = 3.6, p = .030*	.046
Mean Skin Conductance Response (n=53 CFS; n=22 Asthma, n=71 Healthy)					
Baseline	4.8 (3.7)	3.0 (2.1)	3.7 (3.3)	Time: F(1,142) = 1.5, p = .220	.011
Speech	14.7 (9.6)	12.5 (8.2)	12.7 (7.7)	Group: F(2,142) = .19, p = .831	.003
Recovery	15.8 (10.6)	12.4 (10.1)	12.9 (8.5)	Time by Group[c]: F(2,142) = .6, p = .547	.008
Heart rate (n=45 CFS, n=27 Asthma, n=70 Healthy)					
Baseline	81.0 (9.4)	80.7 (9.2)	79.6 (7.6)	Time: F(1,138) = 7.3, p=0.008*	.050
Speech	82.7 (8.4)	83.02 (9.3)	83.5 (8.2)	Group: F(2,138) = .073, p = .929	.001
Recovery	81.6 (7.5)	79.9 (8.3)	78.8 (8.5)	Time by Group: F(2,138) = 2.508, p = .085	.035
Low Frequency (LF) (n=39 CFS; n=23 Asthma, n=63 Healthy)					
Baseline	1786.7 (1200.7)	2138.3 (1260.4)	2041.5 (1529.2)	Time: F(1,121) = .2, p = .657	.002
Speech	1895.0 (1267.5)	3240.9 (3522.1)	2275.2 (2984.6)	Group: F(2,121) = 0.7, p = .520	.011
Recovery	2037.5 (1222.3)	3101.0 (6580.8)	5064.4 (1478.6)	Time by Group: F(2,121) = 1.1,., p = .326	.018
High Frequency (HF) (n=39 CFS; n=23 Asthma, n=63 Healthy)					
Baseline	1065.7 (695.7)	1613.8 (1166.3)	1726.2 (2233.7)	Time: F(1,121) = 2.9, p = .091	.023

Speech	984.7 (791.5)	2552.1 (5975.7)	2693.1 (6916.0)	Group: F(2,121) = 0.6, p = .551	.010
Recovery	982.98 (669.17)	5003.34 (1864.73)	2789.92 (6094.47)	Time by Group: F(2,121) = 1.452, p=0.238	.023
LF/HF ratio (n=39 CFS; n=23 Asthma, n=63 Healthy)					
Baseline	2.0 (1.0)	1.8 (1.0)	1.8 (1.3)	Time: F(1,121) = 9.9, p = .002*	.075
Speech	2.4 (1.3)	2.5 (1.6)	1.6 (1.0)	Group: F(2,121) = 3.8, p = .026*	.059
Recovery	2.3 (1.2)	2.0 (1.5)	2.0 (1.7)	Time by Group: F(2,121) = 3.2, p = .044*	.050
RMSSD (n=42 CFS; n=23 Asthma; n=62 Healthy)					
Baseline	50.6 (19.0)	60.9 (22.9)	63.5 (37.1)	Time: F(1,123) = 12.0, p=.001*	.089
Speech	52.0 (19.7)	70.9 (64.4)	79.0 (82.0)	Group: F(2,123) = .3, p = .764	.004
Recovery	51.8 (18.4)	82.8 (118.5)	91.7 (132.0)	Time by Group: F(2,123) <.05, p = .959	.001

* indicates a significant difference

[a] Change from speech to recovery. [b] Difference between the three groups [c] Interaction between Time (Speech to Recovery) by Group. Analyses adjusted for baseline measures. Effect size relates to the main effect or interaction on the same row.

RMSSD – Root mean square difference of successive RR-intervals

Key Points

- Stress has been proposed as a contributory factor for pediatric chronic fatigue syndrome (CFS) but there has been little experimental research.
- This study used a stressful social performance task and assessed heart rate variability and skin conductance responses as indicators of autonomic nervous system activity, as well as self-rated anxiety and performance expectations.
- Adolescents with CFS showed autonomic nervous system and self-report responses that are consistent with chronic stress vulnerability, difficulty coping with acute stress and slower recovery after acute stress.
- Health professionals should assess for stress vulnerability in young people with CFS and if needed, provide interventions to help them build their stress resilience.