Investigating the Link between Depression and Restless Legs Syndrome: A Controlled Comparison of Mood and Motor Restlessness in Restless Legs Syndrome, with Primary Insomnia and Good Sleeper Controls.

Clinical Research Portfolio

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I would like to dedicate this work to *my Papa*, Mr. John Murray (1924-2008).

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LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ASDA	American Sleep Disorders Association
BDI-II	Beck Depression Inventory, 2nd Edition
EMG	Electromyography
EPWORTH	Epworth Sleepiness Scale
ICSD	International Classification of Sleep Disorders
IRLS	International Restless Legs Syndrome Study Group RLS Severity Scale
IRLSSG	International Restless Legs Syndrome Study Group
ISI	Insomnia Severity Scale
MDS	Mean Sensory Discomfort
NRC	Non-restless control group
PANAS	Positive and Negative Affect Schedule
PI	Primary Insomnia
PLM	Periodic Leg Movement
PLMD	Periodic Limb Movement Disorder
PLMS	Periodic Leg Movements during Sleep
PLMW	Periodic Leg Movements during Wakefulness
PSAS COG	Pre-Sleep Arousal Scale Cognitive subscale
PSAS PHY	Pre-Sleep Arousal Scale Physical Subscale
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RLS	Restless Legs Syndrome
SE	Sleep Efficiency {TST/TIB × 100}
SF36MH	Short Form 36 Version 2 Mental Health Subtotal
SF36PH	Short Form 36 Version 2 Physical Health Subtotal
SIT	Suggested Immobilisation Test
SOL	Sleep Onset Latency
SOL	Sleep Onset Latency
TIB	Total Time in Bed
TST	Total Sleep Time
WAKE	Number of wakenings
WASO	Wake time after sleep onset

Systematic Review of the Methodologies Utilized in the Association between Restless Legs Syndrome and Depression Literature.

Running Title: RLS & Depression

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ABTRACT

Restless Legs Syndrome is a sensorimotor disorder that is also classed as a type of sleep disorder due to the RLS motor and sensory symptoms interfering with sleep. Over the last 20 years research investigating RLS has demonstrated that there is an association with depression or an increase in depressive symptoms. The purpose of this review is to critically assess the methods used to measure RLS severity and depression in the research literature and investigate the impact they have on the research findings. A number of important factors were identified: sampling; objective versus subjective measures; primary versus secondary RLS; reliability of measures; and responsiveness to potential confounds. These factors contributed to a quality rating scale devised to assess the quality of each of the papers included in the review. Following searches of electronic databases and key journals, 18 papers met inclusion criteria; nine epidemiological studies and nine clinical studies. The studies were reviewed in detail with respect to the methods they used and how these methods affected the level of association found between RLS and depression. The majority of studies utilised mainly subjective measures of RLS severity, sleep quality and mood. The reliability of the measure of depression was questionable in many studies. Factors which appeared to influence the association between RLS and depression were the methodology (e.g. subjective versus objective), the measure of depression, the RLS diagnostic criteria used, and the population participants were recruited from. It was unclear from the current literature how other factors such as medication and periodic leg movements during sleep influenced the level of association found. Recommendations for future research were then proposed.

Introduction

Professor Karl Ekbom first coined the term Restless Legs Syndrome (RLS) in 1944.[1] The International Classification of Sleep Disorders (ICSD-R) produced by the American Academy of Sleep Medicine (AASM) [2] classified RLS as a type of dyssomnia, which causes either excessive sleepiness or difficulties in initiating or maintaining sleep. RLS is categorized further as an intrinsic sleep disorder recognising that the difficulties in initiating or maintaining sleep are due to factors arising from within the body. RLS is more common in women than in men and age of onset is typically between 30-40years old, with increasing symptom frequency and intensity with age. The prevalence in western populations, such as Europe and America, is estimated between 5 and 15%. [3]

The essential features of RLS are uncomfortable sensations in the legs, usually occurring in the evening and when at rest, accompanied by an irresistible urge to move the legs. The ICSD highlights the characteristic feature of partial or complete relief from symptoms upon leg movement and return of the symptoms when legs movements stop.[2] The feelings usually occur in both legs between the ankle and knee, although, in some cases RLS can also present in the feet, thighs or arms. The symptoms can last for a few minutes or several hours prior to sleep and therefore can disturb sleep onset. Most people with RLS are usually able to sleep for several hours and generally do not complain of excessive daytime sleepiness.[2] However, RLS does appear to be associated with emotional distress and in the last 20 years there have been numerous studies investigating the impact of RLS on psychological functioning.

Association with Depression

In severe cases, RLS is associated with significant anxiety and depression. People have attributed negative psychosocial outcomes, such as divorce, to their RLS. One study showed that as many as 38% of RLS patients had suicidal thoughts in relation to their RLS. [4]

A review of the literature by Picchietti & Winkelman (2005)[5] found that depression symptoms are common in adults with RLS. However the relationship between RLS and depression is a complex

one. As many of the diagnostic criteria for RLS and depression overlap[1], this increases the importance of the methods used in studies to measure depression and RLS severity. Also antidepressants have been found to aggravate RLS symptoms and this creates a confound in this research. There have been no reviews to date that critically assess the methods used to measure RLS severity and depression.

Standard Diagnostic criteria for RLS

Minimal diagnostic criteria as outlined by the International RLS Study Group in collaboration with the National institutes of Health were published in 2003.[6] This publication is the result of a workshop attended by experts in RLS, epidemiology and questionnaire design. The group discussed and agreed upon four essential criteria for a diagnosis of RLS. Criterion1 is an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Criterion 2 requires that the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting. Criterion 3 states that the urge to move or unpleasant sensations are partially or totally relieved by movement, as long as the activity continues. And finally, Criterion 4 stipulates that the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

The participants in the above workshop also agreed upon 3 supportive clinical features which were not essential to a diagnosis of RLS but can help researchers and clinicians in making their decision. These are as follows: a family history of RLS; initial response to dopaminergic therapy; and periodic limb movements during sleep or wakefulness.

Primary versus secondary RLS

In order to elucidate the unique burden of RLS it is important for studies to distinguish between patients with primary and secondary RLS. Primary or idiopathic RLS is when the symptoms occur spontaneously, without an obvious medical complaint or injury that may account for the

[1] Of the 9 symptoms of depression listed in DSM-IV, 4 of them could be a consequence of RLS: insomnia/hypersomnia; fatigue; psychomotor agitation or retardation; and diminished ability to concentrate or indecisiveness

symptoms.[7] Conditions such as kidney failure, diabetes, arthritis, anaemia can also cause people to develop RLS symptoms.[3] RLS is also common in pregnancy.[8] If studies do not determine whether the RLS is primary or secondary then they cannot state that any elevated levels of psychological distress are due to the RLS as they could be partly or wholly resultant from a comorbid condition. For example diabetes is also associated with depression.[9] Similarly studies should aim to rule out RLS due to pregnancy (unless specifically looking at this) as this type of RLS is normally temporary and resolves once the mother gives birth and mineral levels return to normal.

Severity (population)

The population under investigation is understandably a significant factor in the level of severity of RLS reported. Studies have used a variety of methods to recruit participants. Many epidemiological studies recruit from random community samples. In doing so, they often include people with RLS who have not sought and do not intend to seek treatment. Other studies exclusively use participants that have been patients at a sleep centre or clinic. These participants are potentially experiencing symptoms at a greater frequency or increased intensity. This could introduce bias in terms of the impact that RLS has that may not generalise to the total RLS population. Therefore its is important to examine what time of sample was recruited as this will most likely have an impact on the level of incidence and the level of severity. This in turn may have an impact on the level of association with comorbid mood disorders found.

Medication

An important factor in RLS research is the involvement of pharmacological interventions for depression. Antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), have been shown to aggravate RLS symptoms.[10] The dopamingeric system is thought to play a role in both RLS and depression.[11,12] SSRIs act on the serotonin neurotransmitters to increase the levels of Serotonin in the synapse. In the acute phase of their use they also decrease the amount of dopamine.[13] A dopamine deficiency has been suggested as one of the biological causes of RLS. People with RLS nearly always show an initial positive response to either l-dopa or a dopamine-receptor agonist at low doses, although this initial response is not always maintained.[6]

It is important that any study looking at the association between RLS and depression takes antidepressant use into account, particularly if as suggested, people with RLS are more likely to be depressed, they may also be more likely to be prescribed anti-depressant medication.

PLMS and PLMD

Periodic Leg Movements during Sleep (PLMS) are described as extensions of the big toe followed by dorsiflexions of the foot sometimes with flexion of the knees and hips and they occur in 80% of people with RLS.[14,15] These movements can also be observed whilst awake during periods of inactivity. PLMS and periodic legs movements during wakefulness (PLMW) are usually measured by surface electromyogram (EMG) channels placed on the right and left anterior tibialis muscle during a Suggested immobilization Test (SIT).[16] Not all people with RLS experience PLMS and PLMS are a feature of other disorders such as Periodic Limb Movement Disorder (PLMD).[2] Often studies will combine RLS and PLMD; however PLMD does not have the same subjective sensations and associated urge to move. Therefore any possible psychological impact of these two disorders may not necessarily be a result of a common mechanism. Support for this suggestion is provided in a study by Inhoue et al[17], which employed polysomnography (PSG) and the SIT and compared subjective sleep quality in RLS with PLMD. They found that scores on the Pittsburgh Sleep Quality Inventory (PSQI) were much higher (reflecting poorer sleep quality) in the RLS group than in the PLMD group ($p<0.01$). On the PSG variables, the PLM-arousal index was significantly higher in the group with both PLMS and RLS compared with the group with PLMD ($p<0.01$) despite similar PLM index values between the two groups. Consequently, it would be helpful for studies to measure PLMS, where they occur in conjunction with the subjective sensations of RLS, especially as they are classed as a supportive clinical feature of RLS.[6]

Objective & Subjective measures of RLS Severity

Laboratory measures, namely PSG and SIT have been used as a method of determining RLS severity. The PLM index during sleep (PLMs per hour of sleep) and wakefulness (PLMs during an hour of voluntary immobilisation) are used as indicators of RLS severity. A new method has been

developed to measure PLMS with actigraphy which is less intrusive to patients. This technique involves the patient wearing two actigraphy watches on each of their feet, at home, for a period of three nights and excellent sensitivity and specificity has been reported (Sensitivity, 100%; Specificity, 97.1%).[18]

The IRLSSG[19] have developed a rating scale to measure self-reported severity or RLS – the International Restless Legs Study Group Rating Scale (IRLS). Garcia-Borreguero et al[20] performed initial validation studies of the measure and found that the IRLS correlated significantly with PLMS and PLMS-arousals during PSG, as well as PLMW during the SIT(all $r=0.4$; $P<0.01$). This promising finding adds support to the IRLS and its use in clinical trials. Ideally however, studies should strive to measure both objective and subjective RLS severity whenever possible.

Measure of depression/ reliability of diagnosis

Depression and in particular in relation to a specific condition such as RLS is likely to be multifaceted. There may also be alternative factors in the construct due to the new context of dealing with a motor disorder that feels out of the person's control and has a detrimental impact on their sleep and social lives. Therefore it would be advantageous for studies in this area to use multiple modalities to assess depression.

The diagnostic criteria used are also important. Some studies may use the DSM-IV (Diagnostic Statistical Manual, 4th Edition) whilst others may rely solely on inventories that assess the self-report components of depression. A clinical interview by a trained clinician would be useful to explore whether there is an adequate correlation between the measures as you would expect if there are truly measuring the same construct.

Depression in adults has been studied extensively using multiple modalities. Preferred methods that have been widely used are self-report measures such as the Beck Depression Inventory[21] and clinician rating scales, such at the Hamilton Rating Scale for Depression[22]. The use of standardised

assessment measures has its advantages and disadvantages. Each of these measures has already been tested and reliability and validity are easily discovered.

In any study, measures should be selected following consideration of the construct that the investigators are hoping to assess, the psychometric properties of a measure and the sensitivity of the measure to detect change. It is also an important consideration when measuring a construct such as adult depression is whether to use obtrusive and reactive measures, self-report inventories generally fall into this category, or unobtrusive measures such as medical records. The awareness of the participant that they are being assessed can modify their performance on a particular measure and is said to be reactive.[23] It can help to reassure participants that their answers will remain anonymous and this may increase their openness about their symptoms. Unobtrusive measures have increased external validity as they are not based on laboratory, contrived situations, instead a snap shot of real-life circumstances. In particular medical records have the advantage of not being subjected to the bias of both the participant's own motivations and the experimenter's hypothesis. [23]

Aims

The present review aims to systematically gather and evaluate the literature which investigates the association of depression and restless legs syndrome. There are two questions of particular interest given the issues outlined above:

1. How does the methodology of the studies affect the reported levels of association found between RLS and depression?

2. Do specific methodological issues have a positive effect on the level of association reported between RLS and depression?

With a growth in the research being conducted within the area of RLS and its correlates, it is important to explore in more depth the evidence surrounding an increased risk of depression. Looking critically at the methods used should aid development of a strategy for measuring the

prevalence of depression in RLS, which will help to answer the questions surrounding the different theories that account for the association.

Methods

Search strategy

The following databases were search electronically using the terms [Depression] or [Depressive symptom$] or [psychological distress] linked to [Restless legs$] or [RLS] or [Periodic leg movement$]: Ovid MEDLINE (R) [1980 to 2007], All EBM Reviews, CINAHL [1982 to 2007], EMBASE [1980 to 2007], PsycINFO [1985 to 2007], ScienceDirect [1980 to 2007]. Key journals were electronically searched, including *Sleep Medicine Reviews* and *Sleep*. The reference section of each article meeting criteria was checked for additional sources. Additionally, studies which had cited included studies were identified and examined.

Types of Studies

Epidemiological and clinical studies investigating the association between restless legs syndrome and depression or depressive symptoms were considered. Studies were selected for entry according to the inclusion and exclusion criteria outlined in Table 1.

INSERT TABLE 1

Assessment of Study Quality

To assess the methodological quality of each study, data were extracted from each articles and rated on a 20-item scale (see table 2) which was devised using items adapted from the Scottish Intercollegiate Guidelines Network (SIGN) number 50[24] and the Newcastle-Ottawa Assessment Scale[25]. The majority of the items had a 3-point scoring system of 0, 1 or 2 which were allocated if studies did not meet, partially met, or did meet quality criteria respectively. The items related to the measurement of RLS and depression were rated separately, based on the measures and diagnostic criteria that were employed by the study. Each item was of equal weighting and total scores expressed as an integer between 0 and 1. The quality assessment process was repeated by an

independent reviewer and differences in ratings were resolved through discussion. The total scores from both reviewers were entered into a SPSS Version 15 database and the inter-rater correlation coefficient calculated using Spearman's Rho (r_s= .93) which indicated that inter-rater reliability was high.

Results

The electronic search retrieved 370 studies of which 340 were discarded based on the title and/or the abstract. Figure 1 illustrates the results of the study selection process. A summary of the excluded studies and the reasons for exclusion can be seen in Table 3.

Of the remaining studies that were included in the review, nine were epidemiological studies[26-34] (see Table 4) and eight were clinical studies[35-42] (see Table 5). Of the clinical studies, only 3 were case-control studies. Finally there was a study by Winkelmann et al (2006)[43] which reported results of an epidemiological survey and a sub-sample of laboratory based findings. Further breakdown of the quality rating scores into the areas covered in the instrument can be seen for epidemiological and clinical studies in Tables 6 and 7 respectively.

Epidemiological studies

The total of all samples in the epidemiological studies is 50,520 (See Table 4). The age range of these studies is 18-83. Unfortunately there were insufficient data to calculate the gender distribution of the overall sample. The mean quality rating score for the epidemiological studies was .47 (range=.20-.775; see Table 6). Each of these studies will now be examined.

Alattar et al[26] found that in a primary care sample (n= 1943), those people suffering symptoms suggestive of RLS were significantly more likely to have experienced depression in the previous 10 years (OR, 2.84; $p<0.001$). This study used a brief screening questionnaire aimed at categorising patients based on their answers into various sleep disorder symptoms. It is not clear from their findings how many of the patients endorsing the RLS symptoms were also endorsing symptoms related to other sleep disorders. The population in this study were asked to fill in the questionnaire

when attending their primary care physician. Therefore this sample may have elevated levels of depression compared to a community sample. The study only achieved a 65.3% response rate but did not make comparisons between the participants and non-participants to establish their similarities or differences. It is not clear from the study whether they have ruled out secondary RLS or in fact include this within their sample of people with symptoms suggestive of RLS. Diabetes (17.8%) and arthritis (33.3%) are just some of the health conditions present in the sample. Thus some of the RLS could be secondary. The authors use a single question to assign patients to the RLS symptom group which only includes one of the IRLSSG's criteria for RLS. The authors concluded that the study demonstrated that people with depression were at increased risk of RLS and should be questioned for its symptoms. However a third of the sample responded positively to the RLS question which is far greater than the prevalence rates found in other studies and could be indicative that the specificity of the measure was questionable. There is no information on the sensitivity and specificity of the questions employed. They use self-report of depression over the last 10 years which may be subject to a response bias and does not give a current measure of level of depression. The study does include a question related to days in the previous month were mental health was poor but this is not specific to depression. Table 6 shows that the study scored no points for the clinical or outcome measures. This study is interesting as it employed a primary care population in which one might expect an increase in many of the conditions they screened for but unfortunately the design of the study makes it impossible to isolate and sensitively classify the separate sleep disorders, thus only making general conclusions possible.

Two studies[27,28] presented in Table 4 originate from the RLS Epidemiology, Symptoms, and Treatment (REST) program which investigated the impact of the RLS symptoms on individuals who where classified as having RLS and deemed most likely to seek treatment. Both of these studies scored disappointingly low on the quality rating scale (See Table 4). Allen et al[27] report their findings from a large multinational population study which used current diagnostic criteria for RLS. They used a panel or RLS experts to define a subset of "RLS sufferers" who were likely to warrant medical treatment, as those whose symptoms occurred at least twice weekly during the past twelve months and were reported to be moderately or extremely distressing. Using this method of

classifying people with RLS, they identified 2.7% of the population as warranting medical treatment. Twenty-six percent of this subset of the sample reported a tendency to become "depressed/low" in mood, although only 2.6% of the sample reports this as the most troublesome symptom. The study obtained a very high response rate (95%) but fails to exclude secondary RLS and the authors do not screen for other sleep disorders such as sleep apnoea.

Hening et al[28] conducted the companion REST study which focuses on the impact of RLS in a primary care population in the same countries as the Allen et al study. They recruited 23,052 patients into the study from 182 primary care physicians over a two week period. Using similar RLS criteria as the Allen et al study they found that 59.9% of those who were presumed to require treatment for RLS (n=551) reported a tendency to become low or depressed. The lack of standardised criteria for either RLS or depression, as well as confounding factor not being considered in the design gives this study the lowest quality score (See Table 4). However an interesting addition to this study is the physician screening questionnaire. From this data they found that of the people presumed to have RLS, only 209 were reported to have discussed these symptoms to with their physician and from those consultations only 24.9% were given a diagnosis of RLS and 5.3% were diagnosed with depression. This indicates that some diagnoses of depression may in fact be due to physicians misdiagnosing RLS. This study does not separate those with secondary and idiopathic RLS and as a result the figure of 59.9% of depression may be elevated, especially given the primary care sample.

The results of a National Sleep Foundation (NSF) poll conducted in the United States in 2005 was reported by Phillips et al[29], focusing on the prevalence and correlates of RLS (see Table 4). Unfortunately the authors do not state the level of association that they found between RLS and depression. They conclude that the presence of depression was associated with the endorsement of RLS symptoms ($p<0.05$) but do not elaborate of the strength of this association. They do not use all the diagnostic criteria in their telephone interview, omitting the criteria related to symptoms being worse during periods of inactivity and being relieved by movement. This study, although a random sample of the general population, does not reliably give estimates of the prevalence of RLS, nor

does it give sufficient details of any of the correlates they investigated, accordingly the quality rating score for this study is low (.225) (see Table 6). A positive aspect of the study was the inclusion of a measure of risk of sleep apnoea but again they did not use this to isolate the RLS group by excluding sleep apnoea and look at the association with mental health issues.

Rothdach et al[30] conducted a population-based survey of older adults in Germany, using two RLS-trained physicians to assess the prevalence of RLS in face-to-face interviews. They found that older adults (66-83years) with RLS had significantly higher scores on the Center for Epidemiological Studies Depression Scale (CES-D) than those without RLS (11.6 vs. 7.8; $p<0.01$) (see Table 4). However, the mean scores did not reach clinical the suggested clinical cut-off of 16. The authors also found that there was a significant association between RLS and depression using the CES-D but only in men (OR, 13.06; $p=0.01$). The authors state that their study in the first to apply minimal diagnostic criteria for RLS. All of the participants in the study were given a full neurological examination to test for Parkinson's Disease and information on their medical history was gathered. Investigators also noted use of cigarettes and alcohol, as well as BMI. However they do not appear to include screening items to rule out comorbid sleeping disorders which could confound the results. They took note of the medications that participants were prescribed and found that the use of medication was not significantly different between people with and without RLS.

The overall sample is fairly small (n=369) with a response rate of 60% and therefore the number of people identified as having RLS was only thirty-six: 12 men; 24 women. These numbers are quite small for a population based survey, however the study scored highly on the study population component of the quality rating scale suggesting that this was a fairly representative sample (see Table 6). This sample is different from other studies though in the age of participants. Therefore the lack of an association of depression with RLS in females could perhaps be due to the different experiences of the older generation. They are not required to get up for work at a set time and therefore sleep disturbance caused by RLS may not have the same impact on daily functioning and mood. People also require less sleep as they get older and this could also be factor in the results. Despite only finding an association between men with RLS and depression, the authors concluded

that RLS is a frequent syndrome in the elderly with considerable impact of self-perceived mental health.

Another of the epidemiological studies utilised face-to-face interviews and carried out neurological examinations on a Turkish community sample of adults aged over 17 years. Sevim et al[31] conducted a sample size justification based on previous prevalence studies and weighted the randomisation according to gender, age and residence (e.g. a town or city population). They then employed neurologists, who were also trained in the Hamilton Rating Scale for Depression (HAM-D) to conduct all the interviews. They achieved a high response rate (92.4%) with 3234 people out of the 3500 approached participating in the study. The authors give details of the reasons for non-participation and it appears unlikely that there was any bias in the selection of the sample. The neurologists assessed participants for differential diagnoses such as other neurological disorders that can mimic the symptoms of RLS. The results of the interviews, which took place over a 6month period, identified 103 people with RLS. An age and gender matched control group was taken from the same district as those diagnosed with RLS. The results on the HAM-D of these two groups were compared and a significant difference was found with those with RLS scoring higher on the scale than controls (9.27 vs. 5.88; $p<0.001$). This study was the highest rated on the quality rating scale (see Table 4) and demonstrated a medium to large effect size in comparing depression scores between people with RLS and healthy controls (Cohen's $d = 0.67$). [44]

The HAM-D has been a gold standard clinician rated measure for depression since its development in 1960, however some have criticised the psychometric robustness of the measure, questioning its reliability and validity.[45] Sevim and colleagues[31] do not report on the inter-rater reliability for the HAM-D in their study. However they do report that the 4 questions based on the IRLSSG diagnostic criteria enjoyed excellent levels of agreement between the 4 raters (Intra-class Coefficient = 0.92, $p<0.001$). This study also used the IRLS and found a significant correlation with scores on the HAM-D ($r= 0.201$, $p=0.04$), which accounts for 4% of the variance. They also took into account co-morbid disease, such as diabetes mellitus, finding that depression scores did not vary with the presence of comorbid disease, or indeed smoking or socioeconomic status. The

quality score for this study was high indicating the strengths in design and procedure of the study. The authors' conclusions state that RLS was probably the major determining factor for the depression scores, with higher scores correlating with more severe RLS. However despite the important findings of this study, the lack of data on the onset of depressive symptoms in relation to the onset of RLS means that they cannot make conclusive statements regarding causality.

A Dutch epidemiological study by Spoormaker & van den Bout[32] randomly targeted 800 homes throughout the Netherlands according to geographical distribution. They sent a postal survey to be completed by the first adult of the household. The survey consisted of: the SLEEP-50, a scale devised by the authors and in the preliminary stages of validation; the Dutch version of the SCL-90; and a self-rating scale for PTSD. The SLEEP-50 was reported to have good overall sensitivity and specificity however they do not report the predictive validity of the measure in identifying those with RLS. They also do not mention whether the scale component related to RLS is based on the ICSD or IRLSSG criteria. The main analysis of the study is focused on the correlation of the various sleep problems assessed by the SLEEP-50 and the mental health complaints reported on the SCL-90. Unfortunately the authors do not report how many of the 402 respondents were classified as having RLS. The study suffered from a poor response rate (50.3%) and this limits the reliability of the results. The shortcomings of their sampling procedure were reflected by a low score on the study population component of the quality rating scale (see Table 6). No significant correlations were revealed between RLS and mental health complaints, including depression. Importantly, they do not state whether the SLEEP-50 has any items regarding medication. It appears that this has not been taken into account in this study and given low returns it may be that those who replied had already obtained a diagnosis and may have been receiving treatment. This is of course speculative but highlights the importance of medication in studies investigating the impact of RLS.

A further epidemiological study by Sukegawa et al[33] was conducted using a sample derived from all the elderly residents belonging to a Seniors Association in Izumo City, Japan. This study scored above average on the quality rating scale (see Table 6) which is attributable to the researchers investigating the differences between those with and without depressive symptoms. The authors do

not report the response rate, however only 25% (n= 2023) of the sample responded to *all* items on the questionnaires distributed, which included the Japanese versions of the PSQI and the Geriatric Depression Scale (GDS). They divided the respondents into two groups based on their responses to the GDS; the depressive group consisted of those who scored ≥11 (n= 634) and the control group scoring < 11 (n= 1389). The depressive group were found to be 2.5 times more likely to suffer from RLS ($p<0.05$). Following a multiple logistic regression, dividing the groups by age and gender, only the younger elderly men (65-74years) showed a statistically significant association of RLS with depression. These results are consisted with those of Rothdach et al[30] . A difficulty with this study was the use of some but not all the criteria for classification of RLS. The respondents were only required to endorse one of the diagnostic criteria with an element of symptom frequency added. The authors attempted to manage this by saying that RLS was only "probable". However this increases the likelihood that many of the people classed has having probable RLS may not in fact have the syndrome. They also do not rule out other health conditions that could be causing the symptoms, thus placing doubt over the validity of their results.

The last study presented in Table 4 by Ulfberg et al[34] investigated the prevalence of RLS in a random sample of 4000 men, aged 18-64 years, living in central Sweden. As part of their study they also investigated the association between RLS and neuropsychiatric and somatic disease. A total of 2608 men responded to the questionnaire giving them a low response rate of 66%. The main method involved a postal survey; however 10% of non-responders were contacted by telephone to determine the prevalence of RLS among them. They calculated that 5.8% of the sample had RLS using questions based on the ILRSSG diagnostic criteria and translated into Swedish. They employed a crude measure in relation to the presence or absence of depressive symptoms, asking the men "are you affected by depressed mood without any recognisable reason?" Using multivariate logistic regression they found that men responding positively to all 4 RLS diagnostic questions were 2.6 times more likely to report depressed mood (OR, 2.6; $p<0.05$). They also found a significant association with social isolation (OR, 2.6; $p<.05$). Unfortunately they did not screen for conditions that increase the risk of secondary RLS. Therefore it is unclear whether the RLS respondents were suffering from any other conditions which may cause RLS symptoms

and also affect their ability to cope with sleep disturbance, a common side effect, confirmed by the sample (problems initiating sleep OR equals 3.2). Unfortunately, like many of the other epidemiological studies, the authors did not take into account use of medication. They did not exclude another important confounding variable – the presence of sleep apnoea. However they did include witnessed apnoeas along with smoking and alcohol consumption in the multivariate analyses. Ulfberg et al[34] concluded that although their high figure of depressed mood was based solely on self-report and not secured by an independent diagnosis, they demonstrated that RLS was associated with several somatic and neuropsychiatric symptoms. They avoid drawing conclusions specifically on the association between RLS and depression.

Conclusions from epidemiological studies

Eight out of nine of the epidemiological studies found an association between RLS and Depression.[26-31,33,34] Examining the differences between Spoormaker et al's[32] study, which did not find an association, and the other studies revealed a unique difference in the way people with RLS were recruited to the study. The authors employed a new measure which focused on sleep disorders generally, lacking established reliability and validity and it is unclear whether they incorporated internationally recognised criteria for RLS.

The two largest studies, one of a community sample[27], and the other of a primary care sample[28] demonstrated using the same criteria for RLS, and marginally different measures of low mood that the percentage of people in the primary care RLS group reporting depressed mood was double that of the community RLS group. It is likely that both of these studies overestimated the level of depression due to the absence of a defined nosology. However the results of these studies demonstrate that people with RLS presenting at their primary care centres are more likely to report depression than a community sample. Given the same strict criteria for RLS used in both studies was regarded as selecting those who would be likely to require treatment, the difference in depression scores are unlikely to be due to a difference in severity of RLS but rather a combination of the other medical problems that people may affecting their quality of life.

Other studies failed to differentiate between primary and secondary RLS. The design and methodology of the majority of epidemiological studies prevented elucidation of spontaneous symptoms and those with a known aetiology. Only one of the studies[31] carried out a neurological examination to test for conditions that could mimic RLS. Whilst they did not exclude people with relevant comorbid conditions, (e.g. diabetes, renal disease) they analysed whether the presences of a cormobid condition changed the level of depressive symptoms. This was not the case. There is a dearth of population based studies which include only primary RLS in order to discover the unique burden of the syndrome in a community sample. The results of the Sevim et al[31] study suggests that there will be elevated levels of depression even when secondary RLS is excluded. This study also demonstrated a medium to large effect size. Further population based studies identifying those with primary RLS are needed.

Medication was taken into account in only two out of the nine studies.[28,30] However they did not compare results of those currently taking medication, for example psychotropic or hypnotic medication, with those who were medication free.

Unsurprisingly none of the above population based studies applied laboratory based measures or actigraphy as this would almost certainly have been too expensive. It is of note here that a further study[43] (see table 5) has used both a population based survey and selected a quasi-random subset of the sample to partake in laboratory assessments which provides a potential solution to the problem of cost. This study shall be discussed in a later section of the review.

With regards to subjective RLS severity, the majority of the studies use symptom frequency as a measure of severity. However this says nothing about the intensity of symptoms. Only one study used the IRLS[31] and found a positive correlation between IRLS and a standardised measure of depression. Although statistically significant, this association was small and the correlation coefficient corresponds with a below medium effect size. The remainder of the studies do not directly compare severity, however measured, with the level of depressive symptoms.

All of the studies used obtrusive and therefore possibly reactive measures of depression/low mood. Just under half of the studies used standardised measures of depression. However, none of the measures were developed specifically for people with RLS and yet none of the studies report the reliability of the measures for their own data. Furthermore, they do not use more than one method of assessing depression and low mood. This would be impracticable in population based studies, although not impossible. Single measures prevent verification of the construct validity of the study.

The standardised measures appear to give a more conservative estimate of depression in RLS groups. Studies using the CES-D found significant differences between the RLS and non RLS groups, yet the means of both these groups failed to reach the clinical cut off points. Single questions regarding mood may vastly overestimate the psychological distress in this group as they are often quite vague and could be misinterpreted as enquiring about normal fluctuations in mood; state rather than trait.

Certainly from the above examination of these studies it appears that the measure of depression is an important factor to the level of association found between RLS and depression. The population recruited from is also important. It is encouraging that two studies[30,33] which used similar criteria for RLS, and a similar sample (older adults), found a similar pattern of significance on a standard measure of depression. They demonstrated that the adjusted OR was only significant in men. This is not replicated in the adult sample (18-65yrs), which could imply that age is also a factor in the level of association between RLS and depression. Both women and men of working age with RLS are found to have elevated levels of depression, whereas in the older sample only men appear to have an elevated level of depression.

Clinical Studies

Together the clinical studies yield an overall sample size of 741(range of n=39-218) (See Table 5). Three of the clinical studies are case-control studies[35,40,42], whilst the remainder are uncontrolled cross-sectional studies[36-39,41,43]. The mean quality rating scores for the case-control and uncontrolled clinical studies were .63(range=.55-.675) and .48(range=.275-.625) (see Table 7).

Case-control studies

The first of the clinical studies presented in Table 5 by Banno et al[35] compared RLS patients who attended a sleep clinic with 4 age, gender and socioeconomic matched controls taken from the Province of Manitoba Health Database. The total number of RLS patients was 218 and there were 872 controls. The methodology of the study was reliant on an unobtrusive measure - medical records, thus reducing the influence of social desirability. Patients were diagnosed with RLS according to the ICSD criteria. The investigators looked at all diagnoses that had been given to at least 4 people of each gender, giving them a total of 81 diagnoses for men and 94 women. This was a large number of comparisons and a Bonferroni correction was applied in the analyses. All diagnoses in the database were based on the ICD 9CM. The results demonstrated that male RLS patients were 5.3 times more likely to have a positive history of diagnosis of affective psychosis, depressive disorder not otherwise specified and neurotic disorder, whilst female RLS patients were 2.9 times more likely to have the same diagnoses (both ORs were significant at the 0.001 level). However the inclusion of several diagnostic categories makes comparison with other studies difficult.

An advantage to the design of this study was the access to reliable information on prescribed medication. Fourteen of the male RLS patients were prescribed antidepressants and thirty-one of the female patients were also prescribed anti-depressants. However this was not entered into the analyses to see what impact if any it might have had on the results. Conversely a problem that arises from the design in this study is that they are unable to establish that controls are not cases. Given the well-documented under recognition of RLS by primary care physicians[28] it could be that a proportion of the controls have RLS and it is yet to be diagnosed; although the use of 4 controls for each patient should help to circumvent this problem. The population of RLS patients in this study had been referred to a sleep clinic due to their sleep problems and therefore the results of the study may not be generalisable to other experiencing RLS at a less severe level. This problem with sampling is reflected in the study's low score on the study population component of the quality rating scale (see Table7). In spite of this issue, Banno et al[35] conclude that the results of this study

suggest that RLS patients are more likely to have been diagnosed with depression and that patients presented with depression should be have a sleep history assessment as they may require treatment for RLS.

The second case-control study was of good quality (see Table 5), particularly in their use of objective laboratory measures for assessing the RLS patients. Saletu et al[40] compared 33 RLS patients with age and sex-matched healthy controls. All patients underwent a complete neuropsychiatric and general medical evaluation, including serum chemistry and laboratory tests. Patients were excluded is there was evidence of a medical or psychiatric disorder that might account for the primary complaint. Importantly, patients with sleep apnoea, signs of secondary RLS, pregnant woman, patients with a history of drug abuse, patients requiring psychoactive medication, were all excluded from the study. Therefore the patients in this study are likely to have the idiopathic form of the condition. They also used standard criteria for the diagnoses of RLS (ICSD) and a standardised measure of depression – the Zung Self-Rating Depression Scale (SDS). The results of the SDS scores revealed a significant difference between RLS patients and controls (39.9 vs. 29.6; $p<0.001$). Calculations derived from these results revealed a large effect size (Cohen's $d = 1.5$). A further part of the study involved a subset of the patients and controls who underwent EEG mapping techniques. An interesting finding from these investigations was that the greatest difference between RLS patients and normal controls occurred in those EEG measures that in depression showed the highest correlations to the HAM-D. They state that the EEG findings are characteristic of the dissociated vigilance changes described in depression. The authors fail to report how patients and controls were recruited therefore it is unclear whether they came from comparable populations and whether there were any other differences between the groups in relation to socioeconomic status or smoking and alcohol intake. These issues were reflected in the scores obtained on the quality rating scale (see Table 7). The conclusions drawn from this relative thorough investigation were that EEG mapping revealed neurophysiological correlates of depression in RLS which were further confirmed by the self-ratings on the SDS.

The final case-control study, conducted by Winkelmann et al[42], scored very similarly to Saletu et al[40] on the quality rating scale (see Table 7). They investigated the rates of depression and anxiety according to DSM-IV criteria in 130 patients with idiopathic RLS compared to controls from a community sample. To control for non-specific effects of somatic illness on the rates of mental disorder the controls were selected if they had one or more diagnoses of physical health problem. Controls were excluded from the study if they had any diagnoses of neurological or kidney problems because of the association with secondary RLS. Telephone interviews were used to gather data on previous inpatients and outpatients at the Max Planck Institute Movement Disorder Unit. The control subjects were selected from the German National Health Interview and Examinations Survey, which contained the same information with regards to diagnoses on the DSM-IV. They found that the RLS patients reported higher 12-month rates (OR, 2.6; $p<0.05$) and higher lifetime prevalence rates (OR, 3.30; $p<0.001$) of any depressive disorder, suggesting that RLS has a greater impact that other somatic illnesses. Furthermore the study analysed age-of-onset of depressive disorders and found that in the majority of RLS patients, the onset of RLS preceded the onset of mental health problems. They also compared those in the RLS group who were receiving pharmacological treatment of their RLS (n=103) and those who were not (n=23) They did not find any significant differences in the level of depression or anxiety between these two groups however the authors acknowledge that their analysis was exploratory and lacks the power needed detect subtle changes.

A shortcoming of this study is that the patients and control samples were recruited from different populations and the procedure also differed for each group. The controls were not contacted for this study but the information was obtained from a previous population survey. They authors try to manage this problem by using a weighting programme to account for the differential sampling probabilities. They also adjusted the analyses for age and gender as these were not matched. Another problem stemming from the different methods of sampling is that it cannot be established that the control group does not also contain those with RLS. The authors balance this with their view that excluding the controls with a neurology or kidney problem reduced the likelihood of RLS symptoms being present in this group. The authors conclude that despite their strict comparisons,

patients with RLS have significantly higher rates of depression than others with other somatic disorders.

Conclusion from case-control studies

Each of the case-control studies uses a different methodology. Again these differences have an impact on the level of association found. However the measures of depression and whether authors are looking at incidence or lifetime prevalence of depression could well account for this difference. Saletu et al[40] is the highest rated study in terms of quality and used standard self-report measures and EEG to confirm a diagnosis of depression (although not a standard clinical technique). Banno et al[35] used an unobtrusive measure of previous diagnoses listed in medical records of patients and controls and found the highest level of association. Winkelmann et al[42] used a diagnostic interview and found that the level of association was somewhere in the middle. Thus one could speculate that the reactivity of the measure contributes to the level of depression, with the more reactive measures estimating a lower level. However Banno et al[35] also did not rule out secondary RLS which might create bias in the sample.

Comparing any clinical sample with a healthy control group on measures of depression will normally produce an effect. The Winkelmann et al[42] study is unusual in this area as it compares people with RLS to people with other somatic conditions. Despite the observed association between somatic illnesses and reduced quality of life, a large effect size was obtained, suggesting that RLS has a distinctive impact on patients. It would therefore also appear to suggest that the issue of primary vs. secondary RLS does not have a major influence on the levels of association found between RLS and depression.

As with the previous section conclusions, there are a number of factors that do appear to influence the association between RLS and Depression; the methodology, the measures of depression, RLS criteria, and the population are significant. It is less clear if and how other factors, such as, medication, PLMS and severity of RLS affects the level of association.

Non-controlled clinical studies (observational studies)

This next section of the review considers studies that are uncontrolled and employ a clinical sample in the form of patients attending a sleep disorder clinic. Two of these studies[39,41] are looking at a number of other sleep disorders, of which RLS is one. The quality of the studies was variable and largely determined by sampling procedures and the diagnostic strength in relation to RLS (See Table 7).

Bassetti et al[36] assessed consecutive RLS patients who attended their sleep clinic over a 7year period. During this time only 81 out of 1284 patients received a diagnosis of RLS, however only 55 of them, who met all four diagnostics criteria for RLS, were included in the study. Patients were interviewed either by telephone or during a routine clinic visit by the authors and the presence or absence of depression was determined by a single question, the exact wording of which was not provided. They divided the group into those with idiopathic RLS and symptomatic RLS. Thirty-five percent of the idiopathic RLS group reported depression. The authors concluded that neuropsychiatric symptoms were relatively common in patients with RLS. This study aimed to test whether distinct clinical forms of the condition existed based on age of onset, presence of insomnia or recognised aetiology. As a result the association of RLS with depression was not looked at in depth. They also do not look at other covariates such as smoking and alcohol intake. Consequently this study scored poorly on the quality rating scale (see Table 7) and does not add substantially to the evidence of an association between RLS and depression.

Another clinical study which took place at the University of Pennsylvania Sleep Centre was conducted by Cuellar et al[37] (see Table 5), and employed a sample of older adults with a diagnosis of RLS (n=39) according to IRLSSG standard diagnostic criteria. This study was cross-sectional in design as they stratified the RLS group by symptom severity using the RLS severity scale[19]. The used the CES-D as a measure of depression and reported the reliability of the measure for their specific group was 0.76. The authors recognise that this may have been higher if they had used a measure that was developed specifically for older adults such as the Geriatric Depression Scale (GDS). Although scores in the severe RLS group were higher than those in the mild/moderate

group, these differences did not reach statistical significance. The data produce a medium effect size of 0.46, suggesting that the study was under powered to detect differences in level of depression between these two groups. The primary outcome measure of this study was the PSQI and therefore the sample size justification had been based on detecting differences in this measure. Nevertheless the mean scores for the CES-D did not reach the clinical caseness in either of the groups. They did however find a significant difference on a measure of emotional well-being (RLS-QLI) and concluded that severity of RLS not only affects sleep quality but also emotional well-being. Overall however this study does not provide strong support for an association between RLS and depression in older adults.

Hornyak et al[38] retrospectively evaluated completed self-report questionnaires of untreated, idiopathic RLS patients seen at their Sleep Disorders Unit. They looked at sleep quality (PSQI), severity of RLS (IRLS), and depressive symptoms (BDI). The level of depressive symptoms found is reported in Table 5. The authors excluded patients whose RLS symptoms may have been secondary to another medical condition and those on anti-depressants. They also reported that all patients underwent a physical and psychiatric examination and polysomnography; however it did not appear that this information was used in the analysis. The results were therefore based entirely on subjective self-report measures. The finding that RLS severity correlated with sleep quality ($r=0.281$, $p=0.007$) and not depressive symptoms ($r=0.119$, $p=0.237$) could have been due to patients' reluctance to disclose mental health issues. Furthermore patients prescribed anti-depressant medication were excluded from the study. This potentially could mean that the people most severely affected by their RLS were not included, underestimating the possible association between RLS severity and mood. An additional difficulty with this study was in the reporting of their findings. They report that the majority of their sample fell within the moderate to severe range on the IRLS however they do not give numbers or percentages. When they later report that 17% of the 'moderate to severe' RLS sample was depressed, this is misleading as they did not explicitly state how many of their sample this included.

The following two studies[39,41] looked at the level of mood disorder and depressive symptoms in patients attending a sleep centre. They created groups based on the diagnosis of sleep disorders such as narcolepsy, sleep apnoea and insomnia. Both studies contain groups of people with RLS which were combined with people with periodic legs movements during sleep.

Mosko et al[39] reported on two studies, one assessing mood at presentation to the sleep disorders centre, and the other monitoring changes in mood as a measure of treatment outcome. From the 233 patients attending their clinic, 12 were diagnosed with RLS. Patients underwent polysomnography, which included leg electromyograms of the anterior tibialis muscles. They were also tested for sleep apnoea and narcolepsy. However due to the small numbers, the RLS group (n=12) was combined with the PLM group (n=12). The authors used the Profile of Mood States (POMS) self-rating scale to measure mood states. One of the subscales is called Depression/Dejection. At the time of the study there were limited available norms for the POMS in order to enable comparison. However, they did tentatively report that the level of pathology in their sample was one or two standard deviations above a previous sample of healthy males. They also recorded the number of depressive symptoms that the patients reported according to the DSM-III, stating that at least four symptoms were required to be present for at least 2 weeks for a diagnosis of major depressive disorder. They found that 71% of the PLM/RLS group had four or more symptoms. However they did not give details regarding the nature of the symptoms they reported. These symptoms could be accounted for by the RLS/PLM. For example, people with RLS may complain of insomnia; fatigue; psychomotor retardation and diminished ability to concentrate or indecisiveness. All of these symptoms could be mistaken for symptoms of depression. However one could argue that prolonged occurrence of the above symptoms could lead to depressed mood and anhedonia.

The second part of the Mosko et al[39] study looked at changes in the POMS as an outcome measure for treatment. A subset of the RLS/PLM group from Study 1 was treated with clonazepam following an initial 2-week medication-free period. POMS were repeated at 4 weeks, 8 weeks, and again after a 4-week withdrawal period. They found that Fatigue as measured by the POMS was significantly less at 8weeks and increased again after withdrawal of the clonazepam. They also

found a significant treatment effect on the POMS factor A, which measured Anger. Anger was significantly increased following treatment and remained at this level even after withdrawal of the medication. There was no significant change on the Depression/Dejection factor after treatment with clonazepam in the RLS/PLM group. The authors concluded that high rates of self-reported depression were present in all sleep disorder patients and that their investigation indicated that the nature of the relationship between sleep disorder and mood disturbance was probably unique to each sleep disorder. This study may also suggest that it is not only the sleep disturbance that adds to the ratings on the depression scale, but perhaps the frustration regarding the uncontrollable urge to move their legs.

Mosko et al[39] is the oldest study considered within this review and therefore difficulties arose with respect to the advances that had been made in diagnostic standards for both depression and RLS. There have been two revisions of the DSM since their study was published and one significant change is that there needs to be 5 out of nine symptoms present for at least two weeks for the diagnosis of Major Affective Disorder. Also since Mosko et al's study the criteria for RLS have been revised and agreed upon following work by the IRLSSG[6]. However this study was strengthened by the use of objective laboratory based measures in the confirmation of the diagnoses and scored above average on the quality rating scale (see Table 7).

Vandeputte et al[41] combined 154 patients from their Sleep Disorders Clinic that met ICSD criteria for RLS or PLMD. They assessed level of depressive symptoms with the Beck Depression Inventory (BDI) completed by the patients between two nights of PSG recordings in their own home. They found that 53% of those with the RLS/PLMD diagnosis had some form of depression (using a clinical cut-off score of <10). They pointed out that as they excluded all patients with a primary diagnosis of depression, these results are indicative of depressive feelings that are secondary to the sleep problems. It is unclear from their description of the sample how many of the RLS/PLMD group were on antidepressants, they also did not give details of which other pharmacological interventions this group were receiving. They did not report information on smoking, alcohol intake or BMI which are important confounding factors. Also combining PLMD

and RLS made it difficult to draw conclusions about how each of these disorders is related to mood disturbance. There could be different factors in the aetiology of mood disturbance in these two distinct groups. For example people with only PLMD do not experience the creeping-crawly tingling sensations accompanied with the uncontrollable urge to move their legs. RLS could have a very different psychological impact in view of this different subjective experience. These issues were reflected in the low scores on components of the quality rating instrument dealing with sampling and potential confounds, however this study did score relatively highly on the clinical measurement aspect of the scale (See Table7).

The final study is both an epidemiological study and clinic based (see Table 5). Winkelmann et al[43] utilised data from the prospective Wisconsin Sleep Cohort study in order to assess prevalence of RLS and to determine associations with mental and physical heath, daytime sleepiness, and specific medical conditions. From the initial sample (n=2821) a prevalence rate of 10.6% was found for RLS symptoms of at least weekly frequency. A subset of the sample (n=898) were invited to the laboratory for PSG assessments within a two year timeframe from the original survey. Data on Mood, daytime sleepiness and cardiac problems was collected during the laboratory visit. The authors coded those with a score <50 on the 20-item Zung Depression Scale (SDS) and those currently taking anti-depressant medication as depressed. Although this subset of participants had undergone PSG the authors did not report the results of these tests. However they did take into account possible confounding variables such as age, gender, BMI smoking, diabetes and sleep apnoea and included them as covariates in the analysis. They found that people with *Daily RLS* symptoms (OR, 2.17; 95%CI=1.20-3.95) and *Frequent RLS* symptoms (OR, 1.80; 95%CI=1.00-3.24) were more likely to be depressed than those with no RLS symptoms.

However there were several limitations that must be considered. The way in which this study encoded people as depressed, may lead to an artificially elevated level of people with depression. The use of antidepressants could be due to doctors misdiagnosing the RLS symptoms as depression. The authors did indicate that they have analysed the data to check that rates of depression remain elevated in the RLS symptom group after controlling for hypnotic

antidepressants and taking away the questions on the SDS that relate to sleep and motor restlessness. Unfortunately they did not report the results of this analysis but stated that levels of depression do in fact remain elevated. Another limitation of the study is that the data on mood and RLS symptoms were gathered at different times which, as the authors conceded, may have introduced bias into the associations between RLS symptoms and this measure. This study also did not use the standard criteria for RLS. Instead of a requirement of symptoms to worsen at night, in order for people to be classed as having RLS symptoms they had to report problems of sleep disturbance related to the RLS. This may have actually underestimated the rate of RLS present in the sample as this latter symptom would only be found in those with a severe form of the disorder. The authors inferred that there were elevated levels of depression in individuals with RLS but also stated that it is impossible to elucidate from their data whether there is a causal link between them.

Conclusions from uncontrolled clinical studies

The highest levels of association between RLS and depression or depressive symptoms were found in studies that did not separate RLS and PLMD. Both of these studies[39,41] looked at all patients attending a sleep disorder clinic and therefore RLS was not a specific focus of their work. As previously discussed these are two distinct disorders with some overlapping symptoms. The difference in subjective experience of these disorders could be crucial and therefore future studies should aim to separate them. These studies might also therefore suggest that the presence of PLMS could increase the likelihood of mood disturbance.

Unfortunately although two-thirds of the clinical studies discussed in the above section of the review included the use of objective measures such as 24-hour PSG, none of them used these findings in the analysis. Therefore it remains unclear the impact of the presence of PLMS on levels of association found between RLS and depression. As this could be a mediating factor it is essential that researchers who have the means (i.e. availability of equipment) include this in their design in order to help explain how RLS impacts on mood.

Cuellar et al[37] and Hornyak et al[38] both utilised the IRLS as a subjective measure of RLS severity. Apart from the aforementioned difficulties with reporting in the Hornyak study, these studies can also not be compared due to the fact that they categorised the samples differently. Hornyak et al[38] create a 'moderate to severe" RLS category whilst Cuellar et al[37] break the sample up into 'mild/moderate' and 'severe/very severe'. Cuellar et al[37] did not find any significant differences in the depressive symptoms of their two groups and breaking the sample up further was out of the question. Further studies with greater numbers are needed so that the level of subjective severity and its impact can be investigated more thoroughly.

Hornyak et al[38] was the only uncontrolled clinical study to investigate a solely idiopathic RLS sample. They found no association between RLS severity and depression. However, perhaps if PLMS play a mediating role then measures of subjective severity would not detect this as patients are not always aware that they have PLMS. Again, objective data would have been advantageous here.

Bassetti et al[36] included both people with primary and secondary RLS. However, they separated the two types and found that there was no significant difference in the level of depression found between them (35%) (See Table 5). This suggests, along with the Sevim et al[31] study, that the level of impact of RLS on mood in primary RLS is analogous to that in secondary RLS.

Although the majority of the studies detail the use of medication in the demographic of their samples, none of them make direct comparisons between those taking medication and those who are medication free.

The population, measure of depression and diagnosis of RLS again all appear to play a part in the differences in the level of association found. However due to a dearth of studies also examining the effects of medication use, RLS subjective severity and objective measures – the impact of these methodological issues on the level of association found cannot be determined.

Discussion

There appears to be strong evidence that an association exists between RLS and depression. However the focus of this review was to examine how the methodology of studies impacts the level of association found. Whilst a quantitative analysis was not possible, a qualitative evaluation of the included studies resulted in the above outlined conclusions. This review set out to determine how the methodology of the studies affects the reported levels of association found between RLS and depression and what factors were important to predict the association of depression with RLS. A number of overarching conclusions from the three types of study discussed will now be outlined. These conclusions are synthesised into a number of recommendations for future research.

Depression Measures

Studies employing unobtrusive measures of depression found a greater association between RLS and depression. Some studies looked at current incidence of depression, whilst others examined lifetime prevalence rates, making comparison difficult. All of the studies used only one modality to assess level of depression and the majority of studies only used self-report measures. None of the studies employed an independent clinician assessment to diagnose depression. Nearly half of the population-based studies failed to use a recognised nosology.

Research Agenda:

Future studies should try to use medical records/independent clinical assessment where possible. They should include a standardised measure of symptom severity and have a question regarding symptom onset.

RLS Diagnosis

Studies which did not use recognised diagnostic criteria or adapted criteria from the ICSD or IRLSSG, did not find a strong association between RLS and mental health problems. Subjective severity of RLS was not routinely measured in a standardised way. Whilst many of the clinical studies employed objective measures such as PSG, these were only used to confirm diagnoses and the PLM index was not reported.

Research Agenda:

Future studies should use IRLSSG criteria and have a subjective measure of severity such as the IRLS. Clinical studies should report PLMS parameters and examine whether these should be added to the statistical analysis as a covariate. Where possible, studies should measure subjective sleep quality, SIT and (PSG) PLMS. Not only will this help to categorise RLS and rule out other sleep disorders but it will also bring us closer to understanding the link between RLS and Depression and the influence of sleep disturbance on this association.

Population

Population based studies have shown that the association between RLS and depression is greater in primary care than community samples. However these studies lacked standardised measures of depression. There was tentative evidence that the presence or absence of comorbid conditions such as diabetes or kidney disease do not impact the level of association found between RLS and depression. Whilst it appears that the presence of comorbid medical conditions may not have a great influence, the impact of sleep disturbance could be investigated further. Studies of older adult populations have found that the association between RLS and depression exists only in men and the only clinic-based study[37] did not find high levels of depression in a sample of older adults attending a sleep clinic. There was a dearth of case-control studies investigating older adult samples. However it appears that the age of the sample did have a bearing on the level of association found.

Research Agenda:

Follow-up research should be carried out using a control group consisting of people with psycho-physiological insomnia to control for the effects of sleep disturbance. Further studies of older adult samples are required and control groups would be helpful to control for the social and environmental circumstances of the elderly.

Medication

It remains unclear the impact that pharmacological treatment for RLS has on the level of depressive symptomatology.

Research Agenda:

Studies should include in the design a measure of pharmacological treatments and investigate the impact these have on the level of depression found in those receiving treatment.

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Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Studies that measure RLS and level of depression (or other related mental health problems). • Studies that measure sleep disturbance and PLMS or PLMW in RLS • Outcome studies investigating the effects of pharmacological treatment of restless legs syndrome on measures of psychological distress. • Epidemiological and clinical studies • Studies including adults • Studies written in English	• Studies with people < 18 years • Studies looking at secondary RLS, for e.g. uraemia, pregnancy and peripheral nerve injuries • Studies grouping RLS with co-morbid sleep disorders (e.g. OSA) • Non English language studies

RLS: Restless legs syndrome; PLMS: Periodic leg movements during sleep; PLMW: Periodic leg movements during wakefulness; OSA: Obstructive Sleep Apnoea.

Table 2. Quality Rating Scale

Quality of Methodology Checklist

Reviewer:_____Article No:_____Score: _____

Study design: _____

Cohort, prospective
Cohort, retrospective
Cross-sectional
Case-control
Case reports or case series

Possible responses to Questions 1-10 & 14-19**:** **YES (=2) PARTIAL (=1) NO (=0)** **N/A**

Study Question:

1. Was the study question sufficiently described?___

Study population

2. Were participants appropriate to the study question?____
3. Were control participants used? ____
4. Were participants and controls taken from comparable populations? ____
5. The same exclusion criteria are used for both cases and controls?____
6. Comparison is made between participants and non-participants to establish their similarities or differences? ____
7. Cases are clearly defined and differentiated from controls? ____
8. It is clearly established that controls are non-cases? ____

Demographic details:

9. Were demographic details of participants reported? ____
10. The main potential confounders are identified and taken into account in the design and analysis? ____

Clinical Characteristics:

11. How was RLS diagnosis ascertained?
    a. Independent assessment (Objective measures: EMG, PSG, Actigraphy)(= 2)____
    b. Medical Records (= 1)____
    c. Clinical interview(= 1)____
    d. Self report (e.g. IRLSSG rating scale)(= 0) ____
    e. No description(= 0)____
12. Were the IRLSSG diagnostic criteria used? (= 2) ____

Outcome measurement:

13. How was level of depressive symptomatology ascertained?
    a. Independent assessment(= 2)____
    b. Medical records(= 1)____
    c. Clinical interview(= 1)____
    d. Self report(= 0)____
    e. No description(= 0)____
14. Was a valid assessment/screening tool used (e.g. BDI)? (= 2) ____

Statistical analysis

15. Was there a sample size justification before the study? ____
16. Were post-hoc power calculations or confidence intervals reported for statistically non-significant results? ____
17. Were the statistical analyses appropriate? ____
18. Were the statistical tests stated? ____
19. Were the exact p values or confidence intervals reported for each test? ____

Funding or sponsorship

20. Was this study independently funded? (i.e. not funded by a drug company) ____

Table 3. Excluded Studies

Study	Reasons for Exclusion
Aikens et al 1999	Not investigating RLS.
Allen et al 2003	Report from IRLSSG conference paper
Cuellar et al 2006	All Secondary RLS
Dickel and Mosko 1990	Not investigating RLS
Herraez et al 2006	Not Written in English
Kushida et al 2004	Looking at RLS Quality of life
Kushida et al 2007	Looking more generally at Quality of life
Philips et al 2000	No specific measure of mental health problems or depression
Picchietti & Winkelmann 2005	Review Article
Rodrigues et al 2007	Not Written in English

Table 4. Population based studies examining the prevalence and correlates of RLS

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	Limitations	Authors Conclusions
Allattar et al. 2007	Cross-sectional	0.425	Patients attending their Primary Care Practices in North Carolina, USA.	n= 1934	Questionnaire; either self-report or via interview.	Screened by question: "At night, how often do you feel unpleasant, tingling, creeping, or restless feelings in your legs while trying to sleep?	Question related to health problems experienced over previous 10 year period.	NS	ODDS RATIO (adjusted for race, age and gender)	2.84 times more likely to have suffered depression in last 10 years.	Do not use IRLSSG criteria; No measure of Depressive symptom severity;	Mental disorders were significantly associated with sleep disorders.
Allen et al. 2005	Cross-sectional	0.275	Randomly selected population based sample in UK; France; Germany: Italy; Spain; USA.	n= 15,391	Telephone or face-to-face interview.	4 questions addressing IRLSSG diagnostic criteria & questions regarding frequency of symptoms. RLS sufferers were defined as those whose symptoms occurred at least twice weekly in last 12 months	Percentage reporting tendency to become "depressed/ low"	NS	None	26.2 % reported tendency to become depressed	Do not use valid measure of Depression. Do not rule out other sleep disorders.	Clinically significant RLS is common, is under diagnosed and significantly affects sleep and quality of life.

RLS Criteria: The diagnostic clinical criteria employed; Mx: Whether medication taken into account - NS: Not stated; Y: Yes; free: participants were all medication free; RLS: Restless legs syndrome; PLMD: Periodic limb movement disorder.

Table 4 cont. Population based studies examining the prevalence and correlates of RLS

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	limitations	Authors conclusions
Hening et al. 2004	Cross-sectional	0.2	Primary care sample in UK; France; Germany: Italy; Spain; USA.	N= 23053 RLS n= 551 (likely to require tx)	Screening questionnaire completed by patient and physician during 2 week enrolment period	Same as the Allen et al study	Question related to impact of RLS symptoms	Y	Chi-squared for categorical data; t-tests for quantative data	59.9% of reported tendency to become low/ depressed.	Primary care sample will have elevated levels of comorbid health conditions. Do not separate primary & secondary RLS. Do not use standard methods for RLS diagnosis. Do not have a measure of depression.	RLS significantly impairs patients' lives, often by severely disrupting sleep.
Philips et al. 2006	Cross-sectional	0.225	USA adults	n=1506	Telephone survey	Standard question developed by IRLSSG	Self-report of previous diagnosis by doctor of Depression	NS	Stepwise multiple logistic regression models	NS (Significant association found but no details of level)	Not all IRLSSG criteria are used. Did not exclude people with comorbid Sleep apnoea from analysis	RLS is significantly associated with medical and psychiatric conditions.

Table 4 cont. Population based studies examining the prevalence and correlates of RLS

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	limitations	Authors conclusions
Rothdach et al. 2000	Cross-sectional	0.750	Germany; Older Adults aged 65-83 years.	n=369	Face-to-face interviews	Questions using the IRLSSG standard diagnostic criteria	The Center for Epidemiologic Studies Depression (CES-D).	Y	T-test and logistic regression.	RLS positives have significantly higher CES-D scores(11.6 vs 7.8; p=0.01). Significant association between RLS and depression for males only (OR, 13.06; p=0.01)	Did not use objective laboratory based measures to confirm diagnosis of RLS. Does not rule out other sleep disorders.	RLS is a frequent syndrome in the elderly with considerable impact of self-perceived mental health
Sevim et al 2004	Cross-sectional & case-control	0.775	Community sample of adults aged over 17years; Mersin; Turkey.	N = 3234 RLS n = 103	Face-to-face interview, neurological examination, questionnaires	IRLSSG Criteria	Hamilton Rating Scale for Depression (HAM-D)(Turkish Version)	ns	t-test and correlation.	Significant difference between RLS and controls on HAM-D; A positive correlation between depression and RLS severity (r=0.201; p=0.04)	Higher rate of smokers in RLS group. Issues with the HAM-D scoring and classification due to modification by authors.	RLS more anxious & depressed than controls. HAM-D scores were directly related to increased IRLSSGRS scores. Taken together RLS was probably the major determining factor for dep scores, with higher scores correlating with more severe RLS.

Table 4 cont. Population based studies examining the prevalence and correlates of RLS

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	Limitations	Authors Conclusions
Spoor-maker et al. 2005	Cross-sectional	0.35	Community sample of adults over 18 years old. Netherlands.	N= 402	Postal survey	SLEEP-50 which provides subscales for the impact of sleep complaints on daily functioning.	Dutch version of the SCL-90	NS	Correlation	RLS did not correlate with any mental health complaints	Low response rate (50.25%). Response bias present. Reliability of SLEEP-50 unclear.	Authors do not mention RLS in discussion. Do conclude that other sleep complaints are related to depression and anxiety
Suke-gawa et al. 2003	Cross-sectional	0.575	Elderly residents in Seniors Association (age <65 years): Izumo City; Japan	N=2023, sub-divided by scores of depressi on measure DEP group n=634, control group n=1389	Self-report questionnaires	Questions based on IRLSSG diagnostic criteria with also measures of symptom frequency.	Geriatric Depression Scale (GDS)	NS	X^2 test for association of variables with the depressive group & Logistic Regression	OR, 2.5 ($p<0.05$) in total sample. i.e. Depressed group 2.5x more likely to have RLS. In younger males Adjusted OR, 3.9 ($P<0.05$)	Not all Criteria needed e.g. RLS "probable". Failed to rule out or take account of co-morbid disorders in either group.	Restless legs syndrome was significantly associated with depression in younger men.
Ulfberg et al. 2001	Cross-sectional Epidemiol ogical	0.65	Random sample of male population aged 18-64 years: Sweden	N = 2608, RLS = 181.	Postal survey, followed by telephone contact of 10% of non-responders	Questions devised and translated using the IRLSSG standard diagnostic criteria.	Yes/no question: "are you affected by depressed mood without any recognisable reason".	NS	Multivariate logistic regression.	RLS responders were more likely to report depressed mood (OR, 2.6; 95% CI, 1.8-3.8)	Do not report demo-graphics. Do not rule out secondary causes (e.g. primary vs. secondary RLS). Low response rate.	It is hypothesized that RLS may be associated with several somatic and neuro-psychiatric symptoms.

Table 5. Clinic-based studies examining the association between RLS and Mood Disorder

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	limitations	Authors conclusions
Banno et al. 2000	Case-control	0.55	Patients from a sleep disorder center in Manitoba, Canada. Controls taken from Manitoba Health Database	n=218 RLS patients each with 4 age & gender matched controls.	Medical record evaluation	ICSD criteria for RLS.	Positive history of Diagnosis of Affective psychosis, depressive disorder not elsewhere classified and neurotic disorder.	Y	Mantel-Haenszel χ^2; logistic regression Bonferroni correction.	OR = 5.3 for males ($p<0.001$) OR = 2.9 for females ($p<0.001$)	Not clearly established that controls are not cases. No measure of symptom severity.	RLS patients are more likely to have been diagnosed with depression.
Bassetti et al. 2001	Cross-sectional	0.275	Patients diagnosed with RLS at sleep clinic; Switzerland.	N = 55	Telephone interview	1995 IRLSSG diagnostic criteria	Question related to presence or absence of depressive symptoms (exact wording not given)	Y	Proportions reported.	35% of those with idiopathic RLS (n=37) reported depression.	Do not make comparison between participants and non-participants. Do not take into account possible covariates such as smoking, alcohol intake and weight.	Neuro-psychiatric symptoms were relatively common in patients.

RLS Criteria: The diagnostic clinical criteria employed; Mx: Whether medication taken into account - NS: Not stated; Y: Yes; free: participants were all medication free; RLS: Restless legs syndrome; PLMD: Periodic limb movement disorder.

Table 5 cont. Clinic-based studies examining the association between RLS and Mood Disorder

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	limitations	Authors conclusions
Cuellar et al. 2007	Cross-sectional	0.55	Older adults (aged >65) University of Pennsylvania Sleep Centre and RLS support groups in surrounding area.	n=39	Self-report Questionnaires	IRLSSG standard diagnostic criteria. Group stratified by RLS severity using IRLS	The Center for Epidemiologic Studies Depression (CES-D). (Reliability 0.90)	Y	Power analysis provided.	Mean scores for both mild/moderate (9.2) and severe (13.1) groups did not reach clinical cut-off.	Small sample size. No control group. Not using the geriatric depression scale.	Severity of RLS affects not only sleep quality but emotional well-being.
Hornyak et al. 2005	Cross-sectional	0.50	Sleep Disorder Unit, Germany	n=100	Retrospective evaluation of questionnaire data including laboratory data and PSG results.	IRLSSG Standard diagnostic criteria	Beck Depression Inventory (BDI)	Y	Spearman's Rho	17% of RLS patients complained of mild to moderate depressive symptoms. Severity of RLS not correlated with self-reported depression symptoms (r=0.119, p=0.237)	Patient selection: patients on Anti-depressants were excluded. BDI may underestimate severity.	RLS associated with some depressive symptoms but not full spectrum of a depressive disorder.

Table 5 cont. Clinic-based studies examining the association between RLS and Mood Disorder

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	Limitations	Authors Conclusions
Mosko et al. 1989	Cross-sectional	0.575	Patients at Sleep disorder Centre at the University of Califonia.	n=233 RLS = 12 but was combined with PLM group for analysis RLS/PLM= 35	All night PSG which included leg electromyo-grams; MSLT; self-report questionnaire	Prior to IRLSSG criteria were published.	Profile of Mood States (POMS); No. Of DSM-III Sx of Depression.	Y	One-way ANOVAs	71% of those with RLS/PLM had 4 or more Dep Sx.	POMS not well validated at time of publication. Did not rule out concomitant medical problems or primary affective disorders	High frequency of self-reported sx of major depression in patients at presentation, irrespective of subsequent sleep disorders diagnosis.
Saletu et al. 2002	Case-control	0.675	RLS & PLMD patients at Sleep centre and age and gender matched normal healthy controls; Vienna, Austria.	RLS = 33 & 33 controls PLMD = 26 & 26 controls	EEG mapping and questionnaires	ICSD Criteria For RLS	The Zung Self-Rating Depression Scale (SDS)	free	Mann Whitney U-test; Significance probability mapping based on independent sample t-tests. Correction due to multiple tests	Significant difference between RLS and Controls on Zung Depression Scale (39.9 vs. 29.6)	Not clear how participants and controls were recruited.	EEG Mapping revealed neuro-physiological correlates of depression in RLS which were confirmed by self ratings of symptoms.

Table 5 cont. Clinic-based studies examining the association between RLS and Mood Disorder

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	Limitations	Authors Conclusions
Vandeputte et al. 2003 (Brief Communication)	Cross-sectional	0.375	Patients attending a sleep disorders clinic, excluding those with primary diagnosis of depression.	Total N = 917 PLMD/ RLS n = 154	24hr polysomno-graphy recordings at home. History taking. Self-report questionnaire	ASDA international classification of sleep disorders.	Beck Depression Inventory (BDI)	NS	Not stated	53% of those with RLS diagnosis had some form of depression.	May reflect those presenting to a sleep clinic and not generalise to RLS population as a whole. Other info not reported such as smokers or alcohol intake, weight etc. Combines RLS and PLMD.	In PLMD/RLS some form of depression occurred in more than half of patients. Use of a depression scale recommended for routine practice in sleep medicine.
Winkelmann et al. 2005	Case-control	0.675	Patients of Movement Disorder Clinic at the Max Planck Institute of Psychiatry; Munich, Germany. Controls were selected from a Health Database, only subjects with one or more somatic diagnoses were included. Aged (18-65years)	RLS n = 130, Controls n= 2265	Telephone interview.	Diagnosis of idiopathic RLS previously given. Methods or criteria used not stated.	Munich-Composite International Diagnostic Interview for DSM-IV	Yes [1]	Logistic regression. Every control subject had a weighting factor to account for differential sampling probabilities.	RLS patients reported higher 12-month rates of any depressive disorder (OR, 2.5, 95% CI = 1.5-4.4). Lifetime prevalence rates were also higher in RLS group (OR,3.30, 95% CI = 2.1-5.0)(p<0.001)	Controls not clearly differentiated from patients.	Patients with RLS are at higher risk of Psychiatric disorders than patients with other somatic disorders.

[1] Comparison between those receiving medication and those not for RLS; No significant differences were found between the groups.

Table 5 cont. Clinic-based studies examining the association between RLS and Mood Disorder

Study	Type of Study	Quality score	Population & appropriate control group	Sample size	Main methods	RLS criteria	Depression measure	Mx	Analysis	Level of Depressive symptoms found	Limitations	Authors Conclusions
Winkelmann et al. 2006	Cross-sectional Epidemiological	0.625	Community based sample; Wisconsin, USA.	N = 2821. N= 898 had in-laboratory tests	Postal Survey, a subset completed further in-laboratory tests and questionnaires.	Devised own questions. In recognition that the criteria were not identical to the standard diagnostic criteria they use the term 'RLS symptoms' rather than RLS.	Zung Self-rating Depression Scale (SDS) and those on Antidepressants were coded as depressed.	Y	Logistic regression using 'no RLS symptoms' as the baseline group.	People with Daily RLS symptoms (OR, 2.17, 95% CI = 1.20-3.95) and Frequent (1-6/week) RLS symptoms (OR,1.80, 95%CI = 1.00-3.24) were more likely to have depression.	Primary diagnoses of Depression not excluded. Do not report p-value for significant OR. Data concerning depression symptoms were not gathered at the same time as the RLS symptoms.	Found elevated depressions scores in individuals with RLS symptoms. It is unclear whether there is a causal link between RLS symptoms and symptoms of depression.

Table 6. Epidemiological Studies

Component (maximum points available):	Study								
	A	B	C	D	E	F	G	H	I
Study question (2)	2	2	2	2	2	2	2	2	2
Study population (14)	3	4	2	2	12	11	2	10	11
Demographic/confounding factors (4)	4	1	1	1	4	3	2	1	2
RLS Diagnosis (2)	0	0	0	0	1	1	0	0	0
RLS standard diagnostic criteria used (2)	0	2	0	0	2	2	0	0	2
Outcome measurement (2)	0	0	0	0	0	1	0	0	0
Valid assessment/screening tool used (e.g. BDI-II) (2)	0	0	0	0	2	2	2	2	0
Statistical analysis (10)	6	2	3	4	5	7	4	6	7
Funding or sponsorship (2)	2	0	0	0	2	2	2	2	2
Total (40)	17	11	8	9	30	31	14	23	26
Quality Score	0.425	0.275	0.200	0.225	0.750	0.775	0.350	0.575	0.650

A. Allattar et al 2007
B. Allen et al 2005
C. Hening et al 2004
D. Phillips et al 2006
E. Rothdach et al 2000
F. Sevim et al 2004
G. Spoormaker et al 2005
H. Sukegawa et al 2003
I. Ulfberg

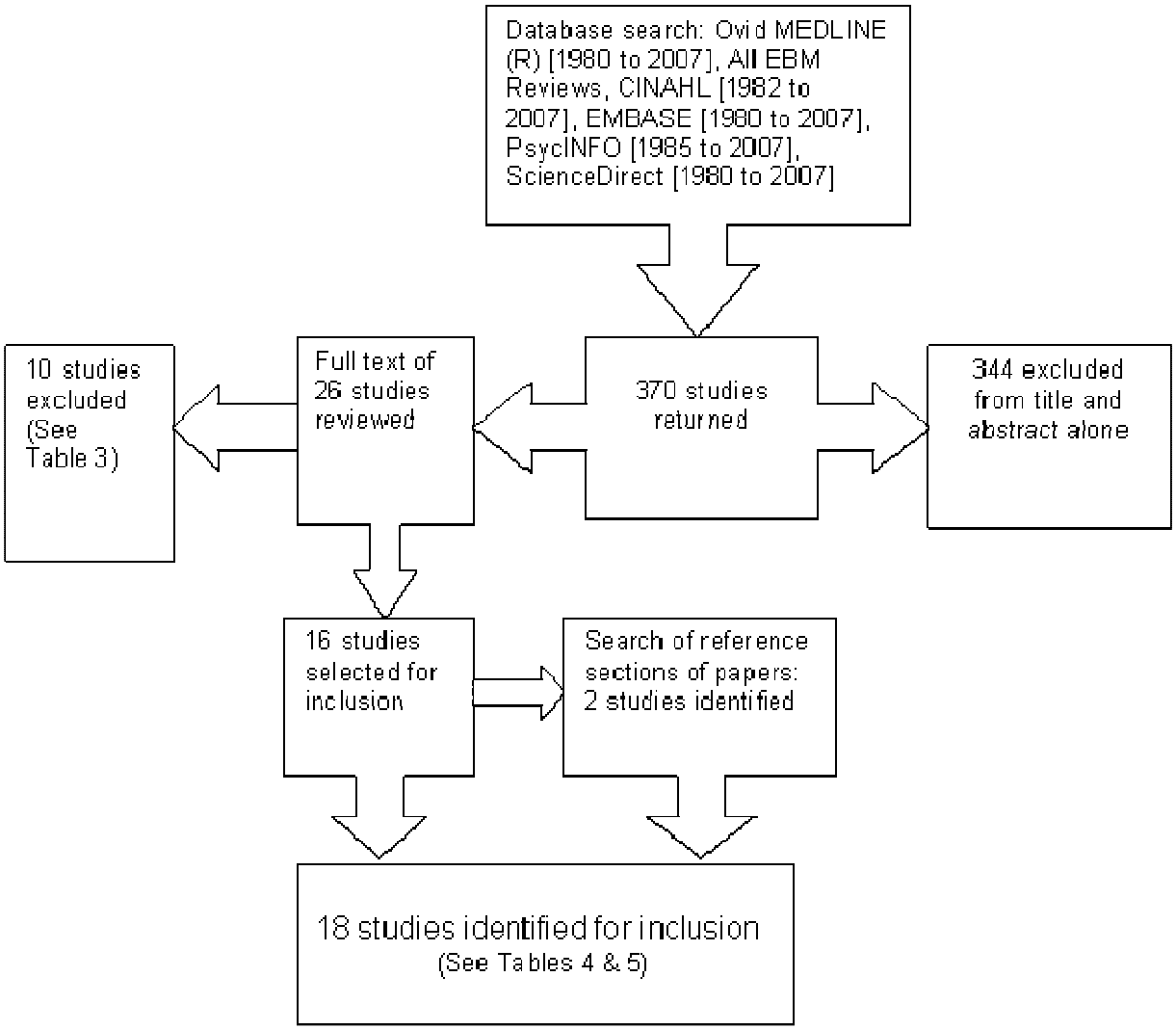
Table 7 Clinical studies

Component (maximum points available):	Study								
	A	B	C	D	E	F	G	H	I
Study question (2)	2	2	2	2	0	2	2	2	2
Study population (14)	9	2	2	2	10	7	4	9	11
Demographic/confounding factors (4)	1	2	4	3	2	2	1	2	4
RLS Diagnosis (2)	1	1	0	2	2	2	2	1	0
RLS standard diagnostic criteria used (2)	2	2	2	2	0	2	2	0	0
Outcome measurement (2)	1	0	0	0	0	0	0	1	0
Valid assessment/screening tool used (e.g. BDI-II) (2)	0	0	2	2	2	2	2	2	2
Statistical analysis (10)	4	0	8	5	5	8	0	8	4
Funding or sponsorship (2)	2	2	2	2	2	2	2	2	2
Total (40)	22	11	22	20	23	27	15	27	25
Quality Score	**0.550**	**0.275**	**0.550**	**0.500**	**0.575**	**0.675**	**0.375**	**0.675**	**0.625**

A. Banno et al 2000*
B. Bassetti et al 2001
C. Cuellar et al 2007
D. Hornyak et al 2005
E. Mosko et al 1989
F. Saletu et al 2002*
G. Vandeputte et al 2003
H. Winkelmann et al 2005*
I. Winkelmann et al 2006

* Case-control studies

Figure 1: Flowchart illustrating the article identification process



Investigating the Link between Depression and Restless Legs Syndrome: A Controlled Comparison of Mood and Motor Restlessness in Restless Legs Syndrome, with Primary Insomnia and Good Sleeper Controls.

Running Title: Investigating the Link between Depression and Restless Legs Syndrome

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ABSTRACT

Background: Restless legs Syndrome is a sensorimotor disorder characterised by unpleasant sensations in the legs when at rest and only relieved by movement. RLS is associated with deterioration in quality of life and depression is a common comorbid problem.

Methods: The present study aimed to establish whether RLS is a risk factor for depressive symptoms by comparing 3 groups - RLS patients (RLS), a primary insomnia group (PI), and non-restless good sleeper controls (NRC). Fifteen participants were recruited to each group. To elucidate the mechanisms of the observed comorbidity between RLS and Depression, measures of mood/affect prior to, during and immediately following a Suggested Immobilization Test (SIT) were employed. The BDI-II measured depressive symptoms retrospectively over the previous two-week period. A mood visual analogue scale (VAS) was rated by participants during the SIT at 5-minute intervals. The Positive and Negative Affect Schedule (PANAS) retrospectively measured affect experienced by participants during the SIT. In addition, new actigraphy techniques were utilised to measure Periodic Leg Movements during Sleep (PLMS) over 3 nights at home – an objective measure of RLS severity.

Results: The groups did not differ on demographic data except for age which was added as a covariate to further analyses. The RLS group had higher levels of negative affect following the SIT than the PI and NRC groups (both $p<.05$). The RLS group also had higher levels of positive affect than the PI and NRC groups (both $p<.05$). The level of sensory discomfort felt in the legs during the SIT was strongly associated with negative affect in the RLS group ($r=.853$, $p<.001$). PLMS were not found to be associated with BDI-II scores.

Conclusions: It appears that sleep quality and depressive symptoms as measured by the BDI-II were similar in the RLS and PI groups. There were some limitations of the study but tentative conclusions were made. The role of emotional arousal in RLS, shown by the high correlation between sensory discomfort and negative affect, potentially demonstrates a qualitative difference in the restlessness experienced by this group and further studies are required.

1. Introduction

> *"As I pass a window I peer at the outer, unfriendly impenetrable darkness. I wonder how many miles I've walked since sundown. A 26 mile marathon? I feel like it. Whatever is plaguing me holds tightly and does not want to let me go. What have I done to cause this? What is stealing my sleep every night and why? Like a slow, dreamy sleep walker, I crawl into bed. Tears seep from the corners of eyes. Maybe I do have witches blood in my veins like Jack says."*
>
> (From Wilson; 1996; p35 [1])

The above excerpt offers valuable insight into the experience of a person with a condition known as Restless Legs Syndrome (RLS). This qualitative account conveys the impact of RLS on this individual's mood and reveals some of the negative cognitions surrounding locus of control and helplessness. Those who have RLS may well identify with this account and the burgeoning research in this area acknowledges RLS and its consequences as having a negative impact on psychological, as well as physical, well-being.

The first definite account of RLS came from Thomas Willis, an accomplished physician in the 17th Century, who described in his 1685 book a patient who would have met modern day criteria for RLS [2]. He noted the patient had difficulty sleeping due to discomfort in the limbs. In the 19th Century a German neurologist, Whittmaack, named the same set of clinical symptoms as "anxietas tibiarum" but it was not until 1945 that the all clinical features were defined and the phrase *restless legs syndrome* was coined by Karl Ekbom [3,4]. Ekbom emphasised the sensory element that accompanied the motor symptoms. Also around this time the characteristic involuntary jerking movements of the legs were recognised. In 1965 Coccagna and Lugaresi published the first polysomnographic findings showing involuntary leg movements during sleep in a patient with RLS [5]. Formal nosology of RLS began with the first edition of the International Classification of Sleep Disorders (ICSD; American Academy of Sleep Medicine)[6]. RLS was classified as a type of intrinsic dyssomnia in recognition of the syndrome's interference with sleep initiation or

maintenance and that these difficulties originated from factors within the body. The latest edition of the classification system (ICSD-2) categorises RLS as a sensorimotor disorder along with other sleep-related movement disorders [7]. The disorder is now internationally recognised and in 2003 the International Restless Legs Syndrome Study Group (IRLSSG) attended a National Institutes of Health workshop to devise an up-to-date version of the essential diagnostic criteria, plus supportive and associated features of the syndrome (see Table 1) [8].

INSERT TABLE 1 HERE

RLS is described by patients as creeping or tingling sensations mostly occurring deep within the legs, coupled with an inescapable desire to move the affected limbs. Movement brings only momentary relief and symptoms appear to get worse when at rest. Many people with RLS also complain of sleep disturbance related to the RLS symptoms occurring at night. It is usually the impact of the sleep disturbance that leads people to seek treatment.

At present there is no cure for this condition and the aetiology has not yet been established. There are two types of RLS: primary and secondary. Primary or idiopathic RLS can have a childhood onset and slowly progresses, worsening with age. Secondary RLS usually occurs late in life and is linked to medical conditions, such as, renal failure, iron deficiency and pregnancy, or side-effects of medication [9-11]. Current treatments include improving sleep hygiene, iron supplements, and drug therapy such as dopamine antagonists, anti-convulsants and benzodiazepines [12].

A prevalence rate of 10% has been estimated of *at least weekly RLS symptoms* amongst adults in a population sample in North America [13]. Similarly, a study of a large multi-national primary care population in Europe and the US estimated a prevalence of 9.6% of *weekly occurring RLS symptoms* [14]. Nevertheless RLS remains under diagnosed. Two of the largest epidemiological studies concluded that the low rates of diagnosis found in each of the samples was due to

physicians' low familiarity with the disorder and RLS not being recognised as a medically significant disorder [14,15]. However, there is growing research evidence demonstrating the negative impact of the condition on the person's mental health and quality of life.

As with many other physical conditions, including sleep disorders, the rate of depression is higher in people with RLS compared to control groups [16-22]. A recent study compared rates of depression between individuals with RLS and a community sample suffering from other somatic conditions and suggested that RLS patients are at increased risk of psychological distress [22]. This finding is important as it indicates that individuals with RLS could be more at risk of developing depressive symptomatology than individuals with other somatic conditions such as diabetes or cardiovascular disorders.

In a clinical and neurophysiological study, Saletu and colleagues [20] identified further links between RLS and depression. They looked at daytime brain function in RLS and Periodic Limb Movement Disorder (PLMD) compared to matched-controls and also investigated objective and subjective sleep and awakening quality in a subset of the sample versus controls. The EEG mapping revealed neurophysiological correlates of depression in RLS, which were verified by self-report data. The greatest differences between the groups occurred in the EEG measures that had been found to show the highest correlations to the Hamilton Rating Scale for Depression in a previous study investigating EEG patterns in depressed individuals. EEG mapping also revealed decreased sleep efficiency measured by polysomnography (PSG) in the RLS group compared to controls, but there was no increase in subjective daytime sleepiness suggesting that those with RLS compensate in some way for the reduced sleep.

A further study investigated the relationship between subjective RLS symptom severity, sleep disturbances, and depressive symptoms [23]. Hornyak and colleagues used questionnaire data from 100 individuals with idiopathic RLS who had attended a sleep clinic to compare self-reported sleep quality and depressive symptoms (measured by the PSQI and BDI respectively) with the International RLS Study Group Rating Scale (IRLS). They found that depressive symptoms in

patients with RLS seemed to be related to subjective impairment of sleep ($r = 0.281$, $p = 0.007$) rather than to subjective reports of RLS severity ($r = 0.119$, $p = 0.237$). However introducing a more objective measure of night-time RLS severity and consequently of sleep disturbance, would help to further explain the RLS-depression relationship. The use of a control group would also help to circumvent a confounding factor in the above study, of the overlapping sleep items on the BDI and IRLS.

The reason or reasons for the observed increased comorbidity of RLS and depression is currently unknown. A number of possibilities have been suggested.

Firstly, it could be that being depressed makes a person more sensitive to mild RLS symptoms and heightens the impact of RLS on the individual, but depression as a direct cause of RLS is questionable. More likely is that RLS is an independent risk factor for depression due to the consequences of disturbed sleep and in severe cases a restriction on lifestyle. This has been identified with other sleep disorders, such as primary insomnia and obstructive sleep apnoea [24,25].

Another possibility is a neurological deficit that simultaneously causes both symptoms of RLS and depression. Dopamine deficiency has been suggested to play a part in the aetiology of both RLS [26,27] and depression[28]. However, as yet it is unclear whether RLS and Depression comorbidity is a consequence of a common pathophysiological pathway.

Finally the increased comorbidity could be an artefact of differential diagnosis. The overlap in the symptoms of depression and RLS could lead to people being misdiagnosed. Of the nine symptoms of depression listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [29], four could be a consequence of RLS: insomnia/hypersomnia; fatigue; psychomotor agitation or retardation; and diminished ability to concentrate or indecisiveness. For a diagnosis of depression to be given only depressed mood or anhedonia would need to be present to meet criteria. Therefore individuals with RLS may reach the clinical cut off

score on standardised self-report measures of depression even in the absence of a major depressive episode.

Regardless of which mechanisms are responsible for the elevated rate of depression in RLS, a further problem is apparent in the clinical management of this group as antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), [30] can aggravate restless leg symptoms. There is conflicting research in the literature, as well as differences in expert opinion, about the effects of anti-depressant medication on RLS symptom severity and the use of dopamine agonists as antidepressants.

As discussed above there is uncertainty over the mechanisms for the increased comorbidity between RLS and depression and difficulties in treatment of this group. Increased understanding of the mechanisms may facilitate development of improved treatments. Hence this study explores the hypothesis that RLS is an independent risk factor for depression due to RLS-related sleep disturbance. In particular it considers two the specific aspects of sleep disturbance found in RLS outlined below as potential contributing factors to comorbid depression in RLS.

One of the proposed specific mechanisms by which RLS patients' sleep might be disturbed is the increasing sensory discomfort as they lie at rest in bed and the compelling urge to move their legs. This mechanism is analogous to the psychobiological inhibition model of insomnia which conceptualises insomnia as a problem with arousal down-regulation [31]. Selective attention for either external or internal stimuli that threaten sleep and efforts to control sleep are thought to inhibit the natural reduction of arousal. Whilst individuals with psychophysiological or primary insomnia also complain of hyperarousal interfering with sleep onset and/or maintenance [32] this differs from the unique sensorimotor symptoms of RLS experienced by people with RLS prior to sleep onset. However it is not yet known if the impact of this restlessness or hyperarousal differs between these two groups. A control group consisting of individuals with primary insomnia would be a useful comparison to decipher whether the impact of RLS on sleep, and consequently mood, is similar to that found in primary insomnia, or whether the motor restlessness compounds difficulties

for RLS patients. The present study will therefore recruit three distinct groups: individuals with RLS; individuals with primary insomnia; and normal good-sleeper controls.

To further our understanding of the influence of motor restlessness on psychological distress, the level of positive and negative feelings will be explored by comparing those with RLS to restless primary insomnia and non-restless good-sleeper controls during an experimental procedure designed to elicit symptoms. The Suggested Immobilization Test (SIT) is used as a diagnostic test for RLS [33]. Electromyogram (EMG) recordings are taken from both legs during a one hour period of voluntary immobility. RLS patients show three times more leg movements during the SIT than controls (76 ± 9.6 vs. 29.9 ± 16.6) [34]. In addition to being a useful assessment of the validity of our group allocation procedure, this test will be used to create the sensory experience of RLS in our participants in order to observe the direct impact on affect.

Another of the proposed mechanisms by which RLS disturbs sleep is that Periodic Leg Movements during Sleep (PLMS) may reduce the quality of sleep in RLS patients by causing micro-arousals which reduce the amount of deep sleep. PLMS are described as extensions of the big toe followed by dorsiflexions of the foot sometimes with flexion of the knees and hips and occur in 80% of people with RLS [35,36]. PLMS occur repetitively during sleep, last 0.5-5 seconds and have an intermovement interval (IMI) of between 4 and 90 seconds.

Millman and colleagues [37] found that obstructive sleep apnoea (OSA) can produce symptoms of depression and these appear to be related to the severity of the underlying apnoeas. This is an important potentially confounding factor, as many people with OSA have also been found to have elevated levels of depression and PLMS [25]. The focus of the present study is related to the influence of PLMS on levels of depression in RLS and therefore people suffering from OSA will be excluded.

By objectively measuring the PLMS in individuals with RLS we can explore what impact this has on subjective quality of sleep and level of depressive symptomatology. Hornyak et al [38]

investigated whether PLMS, measured by PSG, were associated with subjective quality of sleep in people with RLS, primary insomnia and secondary insomnia. They found a negative correlation between PLMS and subjective sleep quality in those with RLS (n=33) on the first night ($r = -.464$, $p < .01$). This correlation was not found on the second night and the authors concluded that the first night result may be due to more superficial sleep as a result of being in the laboratory environment. However the night-to-night variability of the PLMS index has been well-documented [36]. Monitoring PLMS over more than 2 nights and within the person's home environment may reveal whether an association exists between subjective sleep quality and PLMS.

The present study measured participants' PLMS at home over three nights using actigraphy. This is now possible due to new actigraph technology which allows PLMS to be measured in a person's home environment. A new technique has been developed by Cambridge Neurotechnology Ltd that measures Periodic Limb Movements (PLM) in both legs simultaneously by an Actiwatch™ device on each foot, which is then combined to give an index of PLM (PLM per hour). This gives a direct objective measurement of movement in the lower limbs. Using actigraphy as apposed to PSG and EMG means that measurements can be obtained over a longer period of time, allowing for the assessment of the night-to-night variability of PLMS, without the need for lengthy inpatient investigation.

In summary, in order to elucidate further the link between RLS and depressive symptoms this study will investigate the levels of positive and negative affect experienced during a Suggested Immobilization Test (SIT) and how this differs between the groups. Assuming that sleep disturbance does mediate the level of depression in people with RLS, this study will also consider the hypothesis that PLMS are responsible for sleep disruption in RLS patients and are therefore associated with a reduction in self-reported sleep quality and an increase in depressive symptoms.

1.1 Aims and Hypotheses

The aim of the present study was to compare levels of depressive symptoms, and positive and negative affect in three groups: a *RLS group* (RLS), a *restless primary insomnia group* (PI) and a

non-restless control group (NRC) to establish whether RLS is an independent risk factor for depression, taking into account PLMS, which may influence the level of sleep disturbance. The main hypothesis postulated that the groups would differ in levels of positive and negative affect following a SIT. The RLS group was expected to have higher levels of negative affect than the PI and NRC groups. The NRC group was predicted to have higher levels of positive affect than the RLS and PI groups. There were a number of secondary hypotheses: a) higher PLMS index scores would be positively related to the level of depression reported on the BDI-II in the RLS group; b) the mean level of sensory discomfort score (MDS) during the SIT would be highest in the RLS group and lowest in the NRC group and positively correlated with the level of negative affect in the RLS group; c) participants with RLS would have the greatest SIT PLM and PLMS index followed by the PIs and then NRCs; and d) the PLMS index would be negatively correlated with subjective reports of sleep quality in the RLS group.

2. Methods

2.1 Design

The study employed a between-groups design comparing three groups: a RLS group (RLS), a primary insomnia group as a clinical control (PI) and a non-restless, good-sleeper, control group (NRC). The independent variables were the presence or absence (depending on the group) of: (1) sleep disturbance, (2) “Restlessness”, (3) motor disorder, and (4) depressive symptoms. There were three dependent variables, namely, three different measures of psychological distress over different time periods: a retrospective measure, the Beck Depression Inventory, Second Edition (BDI-II)[39], was used as a standard measure of depressive symptomatology over the previous two weeks; a concurrent measure of mood, a visual analogue scale, taken throughout the SIT; and an attributional measure, the Positive and Negative Affectivity Scale (PANAS)[40], assessed the emotional reaction to the SIT as a whole. Of these measures the PANAS was the primary dependent variable.

2.2 Participants

Participants were recruited from the general population by advertisements in newspapers, radio and GP surgery waiting rooms (press cuttings and poster are presented in Appendix 2.2). Seventy-four potential participants were screened (see below for details of screening procedure). A number of participants were excluded from the study at this stage based on the following exclusion criteria age, <18years old or >80years old (n=2); diagnosis of major depression or bipolar disorder; prescribed medication to aid sleep; sleep apnoea (n=2), kidney disease(n=1); and pregnancy(n=2). A further 18 participants who were screened for the study declined to take part. Forty-nine volunteers who provided written informed consent entered the study and were allocated to one of the three groups based on the outcome of the face-to-face interview and their responses to the screening questionnaires. Four individuals where excluded at this stage due to presence of PLMD without RLS (n=1); cardiovascular problems (n=1); and a diagnosis of Major Depression (n=2). Those in the PI group complained of restlessness that affected the quality of their sleep but did not fulfil criteria for RLS (verified by a high score on the Pre-Sleep Arousal Scale, PSAS, [41]). The NRC group have no sleep-related motor problems or movement disorder or clinically significant insomnia as indicated by a score < 8 on the Insomnia Severity Index (ISI) [42]. A subset of the sample was randomly selected by a computer programme for review by the Director of the University of Glasgow Sleep Research Centre to ensure that the grouping allocation was reliable. Findings from the interview, screening questionnaires and results of the SIT and actigraphy assisted clinical decision making. In addition, in order to resolve any diagnostic uncertainties, participants were discussed with the Director of the Sleep Centre to confirm whether they had been correctly classified.

2.2.1 Sample Size Estimation

Given that the relationship between SIT-PLM (as a measure of RLS severity) and psychological distress has not been directly compared in previous studies an expected effect size was not readily identifiable. The power of the present study was increased by strict adherence to the grouping protocol in order to reduce within-group variability. Using data from the study by Saletu et al [20],

a large effect size was found (f = 0.60[2]) for the difference between RLS, PLMD and controls on a self-report measure of depression (See Appendix 2.3 for calculation). *A priori* sample size calculations for a one-way ANOVA design, using an effect size of 0.6, significance level set at 0.05 and standard power of 0.8, suggested a sample size of 10 per group. These numbers were similar to another study which recruited 16 individuals with RLS with 16 age-matched controls, and detected a significant difference in SIT PLM (28.4 vs. 5.0; p< 0.01) and PLMS index (76.1 vs. 26.9; p <0.001) [34]. Therefore it was proposed that at least 15 participants should be recruited to each of the three groups.

2.3 Measures

2.3.1 Demographic, screening and clinical measures

Participants were screened via telephone interviews prior to being invited to the Sleep Centre. Information gathered included: age; weekly alcohol intake; current smoking status; medical history; psychiatric history; medication use; and Body Mass Index (BMI).

The essential diagnostic criteria for RLS as defined by the IRLSSG were incorporated into telephone screening questions. These questions were based on the recommendations from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health [8] and are listed in Table 2. Screening questions based on the IRLSSG criteria have been shown to have between 87.5%-100% sensitivity and 96% specificity for RLS diagnosis [8,43].

INSERT TABLE 2 HERE

Subjective RLS symptom severity was assessed by the International Restless Legs Syndrome Study Group Rating Scale (IRLS) [44]. This measure is a reliable 10-item self-report questionnaire which has high levels of internal consistency (Cronbach's α = 0.95) and good test-retest reliability

[2] Cohen's [ref] conventional value for an operationally defined large effect size for the one-way ANOVA is f =0.4.

(r = 0.87). This measure was used to ensure adequate severity of the RLS symptoms in those meeting the diagnostic criteria and a cut-off value of above 10 indicated the presence of RLS symptoms.

The Pre-Sleep Arousal Scale (PSAS) [41] was employed and is a reliable self-report instrument, commonly used in insomnia research studies, which describes the intensity of cognitive and somatic symptoms of arousal just as the individual is falling asleep. There are two subscales, Cognitive and Somatic, each with 8 items. Internal consistency of both the Cognitive and Somatic subscales are satisfactory (Cronbach's $\alpha = 0.88$ and 0.79 respectively).

The Insomnia Severity Index (ISI) [42] was also used which is a brief 7-item self-report measure which targets subjective symptoms and perceived consequences of insomnia and level of distress caused by those difficulties. Investigations of the ISI's psychometric properties indicate adequate internal consistency (Cronbach's $\alpha = 0.74$). There is also preliminary evidence of its concurrent, predictive, convergent and content validity [45].

Further questions based on a suggested outline of a Sleep History Assessment [32] were asked during interview to rule out other sleep-related problems such as sleep apnoea and to facilitate categorisation of the volunteers into appropriate groups. The Epworth Sleepiness scale (ESS) [46] was also administered as a self-report measure of daytime sleepiness. It provides a useful indicator of the presence of various sleep related disorders such as sleep apnoea, narcolepsy and idiopathic hypersomnia. The ESS has demonstrated good internal consistency and test-retest reliability (Cronbach's $\alpha = 0.88$ and $r = 0.82$) [47].

Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) [48]. The PSQI was developed to provide a reliable, standardised measure of sleep quality and to discriminate between good and poor sleepers. There are 7 component scores targeting a variety of areas of sleep quality and these combine to give a global score ranging from 0-21. A PSQI global score >5 was shown to have 89.6% sensitivity and 86.5% specificity for distinguishing good and

poor sleepers. In addition a score >5 indicates that an individual is having severe difficulty in at least two areas, or moderate difficulty in more than three areas. A score greater than 5 on the PSQI confirmed the presence of a sleep disturbance in the RLS and PI groups.

Participants were required to fill out a sleep diary, adapted from Morin & Espie [32], in conjunction with the actigraphy. A copy of the sleep diary is shown in Appendix 2.4. The sleep diary has been established as a useful and reliable measure of sleep latency, wakefulness, sleep time and sleep efficiency and is commonly used in sleep research and clinical practice [32].

Quality of life was also measured using the Short-Form 36 Health Survey (Version 2.0) (SF-36v2) [49]. There are eight components: Physical Function; Role limitations due to physical health; Bodily Pain; General Health; Mental Health; Role limitations due to mental health; Vitality; and Social Functioning. A physical health component summary score (PCS) is derived from the first four scales and a mental health component summary score (MCS) derived from the latter four scales. The components have been found to have good internal consistency in a UK sample (Cronbach's α = 0.80-0.95)[50].

The Beck Depression Inventory Second Edition (BDI-II) [39] is a 21-item self-report questionnaire which gives a total score (range 0-63) relating to the level of depressive symptoms. Internal consistency is high in both psychiatric and non-psychiatric populations (Cronbach's α = 0.92 and 0.93 respectively) [39]. Test retest reliability is also high at r = 0.93. The BDI-II has demonstrated good construct, convergent and discriminant validity [39]. Although the BDI has a strong somatic component, it has been commonly used in studies of chronic and acute health conditions. For the present study it was employed as a secondary measure, with the PANAS being the primary measure.

2.3.2. Prospective experimental measures

2.3.2.1. Suggested Immobilisation Test

Participants were asked to complete a daytime Suggested Immobilization test (SIT) in which they were instructed to sit on a bed at a 45º angle and not to voluntarily move their legs for a period of one hour. Periodic Leg Movements (PLM) were measured using electromyogram channels attached to the anterior tibialis muscles of both legs. The SIT PLM index was calculated in accordance with recent criteria defined by Michaud et al [35]. Criteria for scoring PLMS are appropriate for the SIT except for leg movement duration which has been increased from 0.5-5s to 0.5-10s. A cut-off score for SIT PLM of 12 was found to have a sensitivity of 62% and a specificity of 84% and is recommend when testing individuals with varying levels of symptom severity[51].

Two Visual Analogue Scales (VAS) measured perception of sensory discomfort in the participants' legs during the SIT and their mood throughout the test at 5 minute intervals. The sensory discomfort scale was constructed with a 100mm horizontal line with the descriptors "no discomfort" on the left to "extreme discomfort" on the right taken from an established VAS, developed as an addition to the SIT procedure [33]. The 12 discomfort scores were then averaged to give a mean discomfort score (MDS). An MDS >11 has been found to correctly classify 82.7% of all subjects in a RLS group and a control group with sensitivity of 82% and a specificity of 84% [51] and was adopted for this study. The mood VAS, similarly a 100mm horizontal line, had the descriptors "worst ever" on the left to "best ever" on the right. A mean mood score was derived from the 12 scores.

2.3.2.2. PANAS

The level of positive and negative affect experienced during the SIT was measured using the Positive and Negative Affectivity Schedule (PANAS) [40]. The internal consistency reliabilities are high for both positive and negative affect scales (Cronbach's $\alpha = 0.89$ and 0.85 respectively for moment timescale instructions). Both scales have a range of 10 - 50. The test-retest reliability of the positive and negative scales are $r = 0.54$ and 0.45 respectively at the "moment" timescale which is explained by the measure tapping into state rather than trait affect.

2.3.2.3. Actigraphy

The participants' periodic leg movements during sleep (PLMS) were measured at home using Actiwatches, produced by Cambridge Neurotechnology, which were taped to each foot at the base of the big toe. The analysis software allows movements that occur in both legs to be scored simultaneously. The adaptations made by Moorish and colleagues [52] to the American Sleep Disorders Association (ASDA) criteria for scoring PLMS, normally measured by EMG during PSG, were used in the present study in order to reduce the chance of artificially inflating the number of PLMS due to the lowest epoch being two seconds. Participants were given instructions to wear the Actiwatch™ devices on both feet for three nights and to fill out a sleep diary each morning. A PLMS index > 5 was adopted as this indicates the presence of Periodic Limb Movement Disorder (PLMD) according to the International Classification of Sleep Disorders – Revised (ICSD) [6], however whilst this is found in around 80%-90% of people with RLS its presence is not essential [8].

2.4 Procedure

Following screening, potential participants who did not meet any of the exclusion criteria were sent participant information sheets and invited to attend the University of Glasgow Sleep Centre. Participants provided informed written consent before proceeding to the next stage - a face-to-face interview with the researcher and completion the self-report measures. Participants in all three groups were required to complete the SIT. The researcher set up the EMG equipment and carried out the necessary biocalibration procedure before beginning the SIT (See Appendix 2.5 for biocalibration). The researcher had received prior training from the Sleep Centre's Clinical Physiologist. Participants rated their sensory discomfort and mood on a visual analogue scale every 5 minutes throughout the 1-hour duration of the test. After the test they were asked to rate their affect during the SIT using the PANAS [40]. If data from the self-report questionnaires indicated that the participant did not meet criteria for their allocated group, they were reallocated or excluded from the study. Following the SIT, participants were given both verbal and written instructions regarding the use of the Actiwatches (See appendix 2.6 for the written instructions). Once the 3-nights of actigraphy recording had been completed, participants posted their Actiwatches and sleep

diary to the Sleep Centre. The Actiwatch data was electronically summed using specialist software. The average PLM index for each participant was calculated from all three nights' data. Participants were then sent a report of the results of testing.

2.5. Equipment

The equipment required for the SIT procedure was as follows. Two self-adhesive electrodes (Ambu® Neuroline 720 EMG electrodes manufactured by Ambu) were positioned on each leg above the anterior tibialis muscle, and two electrodes (also Ambu® Neuroline 720) for the baseline, were placed on the forehead (see Figure 1). The electrodes were attached to a Trackit 24 device (manufactured by Lifelines Ltd) and signals relayed via a Bluetooth module back to the control room where the researcher watched the signals live on a PC monitor. The data was stored on a flash memory card and downloaded and analysed using Stellate Harmonie Version 6 software (manufactured by Stellate Systems Incorporated). The traces from each SIT procedure were then scored manually (see Figure 2 for a sample of an EMG trace).

INSERT FIGURE 1 & 2 HERE

The actigraphy utilised two AW4 Actiwatches from Cambridge Neurotechnology Ltd (CNT) for each participant. The Actiwatches were taped to each foot using low allergy tape to avoid skin irritation. The exact positioning of the Actiwatch™ is illustrated in Figure 3. The Actiwatch data was downloaded using an Actiwatch reader, connected by serial port to the PC and analysed using the first version of PLMS Software®, also manufactured by CNT.

INSERT FIGURE 3 HERE

2.6 Data Analysis

Preliminary analysis was conducted on the demographic data to ensure that the groups were similar. Differences between the groups in demographic data were added as covariates in the main analysis. Confirmatory analyses were carried out on the screening measures to verify that groups differed appropriately on each of the variables. Prior to formal data analysis, data were inspected to ensure that assumptions for parametric tests were met. All of the data, except PANAS negative and PLMS index scores, were normally distributed as indicated by Kolmorogov-Smirnov tests. Where variances were heterogeneous, as indicated by Levene's Test for the Homogeneity of Variances, data were transformed using appropriate techniques [53] (See appendix 2.7). However, given the robustness of the F-test and post-hoc Tukey Tests and the equal sample sizes the untransformed data and analyses were reported [54,53]. The main hypotheses were tested by analysing the differences between the groups using one-way analysis of variance (ANOVA) for each of the dependent variables. The analysis was then repeated using analysis of covariance (ANCOVA) to investigate the impact of adding covariates (see appendix 2.8). However, non-normality and heterogeneous variances could not be rectified for PANAS Negative and PLMS index and therefore non-parametric tests were employed where appropriate. In addition, correlational analyses of the PLMS index and subjective sleep quality, RLS severity and depression were performed using Pearson's product moment correlation coefficient unless non-parametric tests were indicated, in which case Spearman's rank order correlation coefficient was utilised. All analyses were carried out using Statistical Package for Social Sciences Version 15. Significance tests were 2-tailed and a significance threshold of $p<.05$ implemented.

2.7. *Ethical approval*

Ethical approval for the project was granted from the Greater Glasgow & Clyde Primary Care Community & Mental Health Research Ethics Committee (See Appendix 3.2 for a copy of the approval letter).

3. Results

3.1. Participant Characteristics

The mean age across all participants was 34.7 years (SD = 10.8 years), with a total of 26 females and 19 males. The average BMI of participants was 24.3 (SD = 3.6) and 8 (17.8%) of the overall sample were smokers. The average units of alcohol consumed per week was 5.9 units (SD = 8.5 units). In total, 13 (28.9%) of the participants reported that they snored. Table 3 shows the demographic characteristics by group. With regards to group differences in demographic data, ANOVA and Tukey's post-hoc Test demonstrated that the RLS group was significantly older than the non-restless controls (NRC) (p= 0.014). Given this finding, each of the subsequent analyses of group differences were performed first without a covariate and then again with an analysis of covariance (ANCOVA), with age as a covariate.

INSERT TABLE 3 HERE

3.2. Screening and clinical measures

The mean scores and standard deviations for each of the screening and clinical measures are presented in Table 4. As expected on the measures relating to sleep, those in the NRC group scored significantly lower than the PI and RLS groups on the ISI, PSQI and the physical subscale of the PSAS, confirming that they were good sleepers. The PI group scored significantly higher on the cognitive subscale of the PSAS compared to the NRC but not the RLS group. The RLS group and the PI group did not significantly differ on any of the sleep related measures, confirming that both of these groups are characterized by the presence of a sleep disorder. No significant differences were found between any of the groups on the ESS. The IRLS scores were compared for the RLS and PI groups by Student t-test and the difference between the means was found to be significant ($t(28) = 7.6$; $p<.001$), confirming the presence of a motor disorder in addition to a sleep disorder in the RLS group. With regard to sleep diary data (see Table 4 for data), this confirmed that the NRC comprised good sleepers and had significantly higher Sleep Efficiency scores than the RLS group ($P<.001$) and PI group ($p =.003$). Similar to the sleep-related questionnaire measures, the sleep diary data also confirmed the presence of a sleep disorder in both the RLS and PI groups. The

groups differed in reported quality of life measured by the SF36v2, the RLS group reported poorer physical health than the PI and NRC groups. The quality of life mental health component score only significantly differed between the RLS group and the NRC group with the RLS group reporting poorer mental health. There was no significant difference between the RLS and PI group on the mental health component of the SF36v2. The RLS group scored significantly higher than the NRC group on the BDI-II but not the PI group. Further ANCOVAs of the questionnaire data with age as a covariate indicated that the differences between the groups remained significant (See Appendix 2.8).

INSERT TABLE 4 HERE

3.3. Experimental data

3.3.1. SIT

The SIT procedure generated a score of the number of periodic leg movements in one hour of voluntary immobilisation, a mean sensory discomfort score and a mean mood visual analogue score for each of the participants. One of the participant's experiment was cut short due to technical problems and the SIT index was calculated by dividing the number of PLM by the number of minutes of the test that were completed and multiplying by 60. It was predicted that the RLS group would have the highest SIT PLM index, followed by the PIs and then the controls. The data for each of the three groups is shown in Table 5. The results indicate that the RLS group had a mean SIT index approximately 2.5 times greater than both NRCs ($p = .022$) and PIs ($p= .021$) partially confirming the hypothesis. The results of the SIT procedure are illustrated in Figure 4 and the magnitude of the difference in SIT PLM index scores can be seen between the groups. Surprisingly the PIs and the NRCs did not differ on the level of PLM during the SIT and therefore this part of the hypothesis was not upheld. The PIs and NRCs did not differ in the level of movement and therefore suggests that the SIT PLM index is an indictor of motor disorder rather than restlessness

per se. Eighty-percent of the RLS group had a SIT PLM index >12. However, only 60% of controls were correctly identified using a cut-off of 12, questioning the specificity of this measure.

INSERT TABLE 5 HERE

3.3.2. Visual analogue scales: sensory discomfort and mood

It was hypothesized that the sensory discomfort experienced during the SIT would be highest in the RLS group and lowest in the NRC group. The results from the sensory discomfort analogue scale indicated that the RLS group had a significantly higher Mean Discomfort Score (MDS) than the NRC group (p=.003) but not the PI group (p=.262) (see Table 5 for data). However Figure 4 illustrates a trend towards the MDS being larger in the RLS group compared to the PI group. Applying the MDS cut-off of 11 to the MDS data revealed that 73.3% of the RLS group were correctly identified. However 80% of the PI group were also in the clinical range compared with just 53.3% of the NRC group which suggests that the MDS might be measuring the sensory aspect of restlessness rather than the discomfort tied to a specific motor disorder. No specific hypotheses were made about the Mean Mood Score from the visual analogue during the SIT and this scale did not in fact show any differences between the three groups.

INSERT FIGURE 4 HERE

3.3.3 PANAS

The PANAS was employed as a retrospective measure of affect and was completed by participants immediately following the SIT procedure. The instructions asked them to rate, on a 5-point Likert Scale, to what extent they had felt a range of positive and negative emotions during the previous hour. The overall mean scores for the PANAS Positive and Negative Scales were 20.4 (SD = 6.7;

Range = 10-41) and 12.0 (SD = 2.6; Range = 10-20) respectively. Internal consistency of the Positive Scale was high (Cronbach's α = 0.85; range: 0.82-0.86). However the Negative Scale was disappointing in terms of reliability (Cronbach's α = 0.42; range: 0.24 - 0.64). This was perhaps related to the small variance of the measure. Two of the variables had zero variance and were removed automatically (Ashamed; Afraid). Following analysis of alpha if item-deleted values, two further variables were removed (Nervous; Guilty), improving reliability considerably (Cronbach's α = 0.66; range: 0.50 - 0.68), although the coefficient remained below established minimum reliability criteria [55]. The two scales did correlate positively with each other, confirming that they are not measuring the opposite extremes of the same construct (r_s=.46, p=.002).

The main hypothesis predicted that the RLS group would have greater levels of negative affect and this prediction was upheld. Unadjusted PANAS data for each group can be seen in Table 5. In addition, it was predicted that the NRC would have the highest levels of positive affect. This was not upheld and in fact the RLS group had significantly higher levels of positive affect compared to the PI and NRC groups (see Table 5). Further analysis was carried out using ANCOVA (see Appendix 2.8 for data). In addition to age, level of pre-existing depressive symptoms were controlled for by adding the BDI-II mean score as a covariate. The results demonstrated that a significant difference remained between the groups on the Positive (F(2, 45) = 3.39, p = .044) and the Negative (F(2, 45) = 4.88, p =.013) scales of the PANAS when controlling for age and premorbid depressive symptoms.

3.3.4. Actigraphy

The sleep parameters obtained from the participants' sleep diaries were essential to analyse the Actigraphy data. All included participants returned their sleep diary along with the Actiwatches. The PLMS indices obtained for each of the groups can be seen in Table 5. It was hypothesised that the RLS group would have the largest PLMS index score and the results confirmed this prediction. Non-parametric testing revealed that the RLS group's PLMS index was significantly higher than both the PI (z=58.5; p=.025) and NRC groups (z=45; p=.005). It was also hypothesised that the PI

group would have a greater PLMS index than the NRCs. The results did not support this hypothesis – no significant difference was found between the PIs and NRCs (z=86.5; p=.280).

3.4. Association between periodic leg movements, mood and sleep quality.

The Spearman's rank order correlation coefficient was calculated between PLMS index and BDI-II total score to check for an underlying associated between depression and PLMS across all participants. Although a positive correlation was revealed, this did not reach significance (r_s= .182, p=.231). It was predicted, *a priori*, that higher PLM index scores as measured by actigraphy would be positively related to the level of depression reported on the BDI-II in the RLS group. The opposite was found using Spearman's Rho with a non-significant negative correlation between PLMS index and BDI-II scores in the RLS group (r_s= -.175, p=.532). This was also the case for the NRC group (r_s= -.385, p=.156), however, interestingly for the PI group PLMS index scores were strongly associated with depression scores on the BDI (r_s=.638, p=.01). This correlation was reduced and became non-significant when the analysis was repeated using the using the BDI-II score minus the sleep–related items (r_s=.457, p=.087).

It was predicted that PLMS would be positively associated with measures of sleep quality in the RLS group (a higher score on the PSQI indicates poorer sleep quality). There was a non-significant positive correlation between PLMS index and PSQI scores in the RLS group (r_s=.447, p=.094). Furthermore the RLS group's ratings on the IRLS correlated strongly with the PSQI (r=.573, p=.013) and ISI (r=.852, p<.001).

3.5. Association between sensory discomfort and affect

Possible underlying associations between affect and sensory discomfort during the SIT were investigated using Pearson's product-moment correlation coefficient except where parametric assumptions were not met (see data analysis section above). Overall a strong positive correlation was found between negative affect and sensory discomfort in the legs (r_s = .635, p<.001) and a moderate correlation between positive affect and sensory discomfort (r= .39, p = .008).

It was hypothesised, *a priori*, that the level of negative affect would be positively correlated to the level of sensory discomfort in the RLS group. Further analysis of the correlations in each group found, as predicted, that in the RLS group negative affect was strongly associated to sensory discomfort (r_s = .853, p<.001). This association was strengthened when the unreliable items of the PANAS Negative Scale were removed (r_s =.906, p<.001)(see Figure 5), indicating that over 80% of the variance in negative affect can be accounted for by sensory discomfort. In the PI (r_s=.160, p = .569) and NRC (r_s=.314, p= .255) groups, positive correlations were revealed between negative affect and sensory discomfort, although neither reached statistical significance.

INSERT FIGURE 5 HERE

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4. Discussion

This study investigated the previously reported relationship between RLS and depression, using a comparative design, comprising both clinical [primary insomnia (PI)] and good sleeper [non-restless (NRC)] control groups. The groups were compared on a number of subjective and objective measures. The main hypotheses predicted how the groups would differ in their levels of positive and negative affect following the SIT. There were a number of secondary hypotheses examining the level of depressive symptoms and the subjective measures of sleep quality, as well objective measures of involuntary movements during sleep - PLMS. When controlling for age as a covariate, all of the results held.

As predicted the RLS group had higher levels of negative affect following the SIT than the PI and NRC groups however they also had higher levels of positive affect compared to both the PI and NRC groups. The latter finding was unexpected. One explanation is that this was as a result of a rebound effect as the PANAS was completed immediately after the participants were allowed to move again. Another possibility is related to the positive emotions in the PANAS such as “interested” and “enthusiastic” which were more frequently endorsed by the RLS group. It could be

that the participant information sheet description (see Appendix 3.3) of the SIT as a diagnostic test for RLS was welcomed by these participants. Therefore the RLS group may have regarded the SIT as having particular relevance to them.

Notwithstanding these possibilities, it should be noted that the presence of positive and negative affect occurring simultaneously is not unusual in itself. Watson and Tellegren's model [56] of emotion proposes that positive and negative affect are orthogonal constructs, therefore high negative affect and high positive affect can occur at the same time. However in comparison to healthy undergraduate student norms, the levels of positive and negative affect in all the groups in the present study were below typical values [57]. Inspection of the mood terms according to Watson & Tellegrens' model used to define low positive and low negative affect, such as drowsy, dull, sleepy for positive affect, and calm, placid and relaxed for negative affect, demonstrates that the PANAS could well have captured how the participants felt during an hour of inactivity. This may also explain the lack of variance in the negative affect scale, particularly for the control groups. The lack of high negative affect in the RLS group could also be in part due to the timing of the SIT which may have meant, depending on severity of RLS, that the sensory symptoms were not evoked. This issue is discussed further below.

With regard to the secondary hypotheses, the predicted positive correlation between PLMS and level of depressive symptoms, as measured by the BDI-II, in the RLS group was not found. Hornyak and colleagues' study [23] found a small positive correlation, explaining four-percent of the variance, between depressive symptoms and PSQI rather than subjective self report of RLS severity. Using actigraphy as an objective measure of RLS severity (assuming increased PLMS leads to increased arousals) in the present study also failed to reveal an association with level of depressive symptoms as measured by the BDI. Therefore it appears that neither subjective nor objective measures of RLS severity are associated with a subjective measure of depression.

It was hypothesised that the association previously found between RLS and depression could be accounted for by the increased PLMS in people with RLS disturbing their sleep; and consequently

increasing their risk of depression. Results showed that whereas the RLS group had significantly higher PLMS index scores, they did not differ from the PI group on the sleep diary parameters or the subjective reports of sleep quality measured by the PSQI and ISI. Bearing in mind that people with a diagnosis of Major Depression were excluded, mild depressive symptoms were found in the two clinical groups. These findings then suggest that the PLMS per se were not a causal factor in the levels of sleep disturbance and depressive symptoms reported by the RLS group; however this is speculative as these variables would have to be entered into a regression analysis in order to draw that conclusion. A regression analysis could not be carried out on this occasion due to a number of assumptions not being met.

A possible explanation for the RLS group having similar levels of subjective sleep disturbance to the PI group despite higher PLMS is that people are not always consciously aware of PLMS and often have to be told by a partner about their leg movements and therefore these would not be reflected in their self-reported sleep quality. Alternatively, there may be another mechanism for the sleep disturbance in the RLS group such as the increasing sensory discomfort as they lie in bed and trying to resist the urge to move their legs, which would be similar to the effects of sleep effort in people with primary insomnia [31].

The mean level of sensory discomfort (MDS) during the SIT was higher in the RLS group compared to the NRC group as predicted. However there was no significant difference between the RLS and PI groups. Figure 3 demonstrated a trend in the direction predicted between the RLS group and the PI group with higher MDS in the RLS group. *Post-hoc* power calculations suggest that 48 participants in each group would have been required for the difference in MDS between RLS and PI groups to reach statistical significance. As RLS patients have not previously been compared to people with primary insomnia on this measure, a lack of statistical power could well be responsible for these findings. Another factor may be, as the diagnostic criteria of RLS emphasize, that movement in individuals with RLS group relieves sensory discomfort and the RLS group have the highest SIT PLM index. The greater movement in this group may lower the level of sensory discomfort. However further analysis using the SIT PLM index as a covariate to control for

the effects of movement did not find a significant difference between the RLS and PI group on MDS (See Appendix 2.8 for the supplementary analysis). So why might the PI group also find the SIT challenging? Poor stimulus control has been proposed as a 'setting condition' for primary insomnia and given the context of the experiment - a bedroom environment - this may have increased their sensory discomfort. They may try to remain motionless in bed at night in a bid to fall asleep and the SIT may trigger both automated conditioned arousal and the behavioural tendency to remain still. The net effect of this could be sensory discomfort. Nevertheless despite higher levels of sensory discomfort in the PI compared to the NRC group, this did not appear to create a high negative affective response.

As predicted, the level of negative affect in the RLS group was strongly associated with the level of sensory discomfort during the test, with the sensory discomfort explaining 80% of the variance in PANAS negative scores. This strong association was unique to the RLS group (sensory discomfort explained 2.5% of the variance in negative affect in the PI group) and could suggest that the experience of restlessness during the SIT differed between the groups. There was no significant difference in the RLS group and PI group on measures of sleep quality suggesting that people with RLS are similar to people with primary insomnia in terms of *level* of sleep disturbance. However, there was a trend towards the cognitive arousal measured by the PSAS to be greater in the PI group than the RLS group and *post-hoc* power calculations predicted that a further 11 people in each group would be required for this trend to become significant. Whilst the PI group had the typical high levels of cognitive arousal before sleep, the RLS group may be more affected by the psychological distress that accompanies the sensations in their legs and compelling urge to move prior to sleep onset. The presence of a motor disorder appears to be associated with qualitative difference in the experience of restlessness for the RLS group, although the outcome may be similar – problems with arousal and initiating sleep. The negative affect in the PI group appears to be less influenced by being asked to stay immobile and could be due to timing of the SIT or negative attributions regarding arousal being related to the controllability of sleep in primary insomnia rather than restlessness.

It is plausible with such a high correlation between sensory discomfort and negative affect in the RLS group that these measures tap into the same construct. It appears that the RLS patients with higher levels of sensory discomfort responded positively to the negative and positive PANAS items, possibly capturing their level of arousal. These individuals possibly found it difficult to separate the sensory experience from the emotional impact caused by the discomfort which may also explain the trend towards lower PSAS cognitive arousal scores. This issue creates a dilemma for future measurement of the immediate affective response to RLS symptoms. In the arena of Chronic Pain Management the age-old view of mind and body is being replaced by a much more holistic view whereby pain is recognised as having cognitive, affective and behavioural components and RLS could also be viewed in this way [58]. The pain literature suggests that unpredictable pain causes anxiety and heightened vigilance, leading to an increase in pain sensitivity [59]. Anecdotally, people with severe RLS often describe it as painful and therefore the sensory RLS symptoms or the anticipation of symptoms may elicit negative affect leading to increased perception of motor and sensory symptoms. This raises a further issue of controllability. There is evidence from pain research that the perception of control over pain can increase coping [58]. For those with the severest forms of RLS the ability to self-regulate emotion may be crucial to reduce distress caused by the RLS symptoms.

Finally, there was no correlation found between the objective measure of RLS severity (PLMS) and a subjective measure of sleep quality (PSQI) whereas the self-report measure of RLS severity (IRLS) correlated positively with the PSQI and the ISI. Insomnia research shows that people's subjective accounts of sleep do not always correlate with objective measures [60] and therefore RLS patients are perhaps no different in this respect. However there is also the possibility that not all PLMS measured by the actigraphy caused microarousals. Although PLMS and PLMS-arousal indices as measured by PSG have been found to be highly correlated with one another [51], being unable to verify whether PLMS were related to microarousals or wakefulness is a potential disadvantage to using actigraphy.

This study is the first to have investigated the levels of positive and negative affect in patients with RLS. The finding of a strong association between sensory discomfort and negative affect in the RLS group is an important one. The results shed some light on the possible mechanisms for the increased comorbidity between RLS and depression. Essentially the results indicate that the sensory discomfort felt by the RLS group prior to sleep onset could be associated with an increase in negative affect and this emotional as well as physical arousal delays sleep onset. The sleep disturbance caused by these experiences results in an increased risk of depression similar to the insomnia population as a whole [24] and may be compounded further by the increased exposure to negative affect.

There are a number of important limitations to the present study that must be considered. Firstly, despite no effect of age, future studies should use age and gender matched controls. This was not possible in the present study due to the methods of recruitment and the people responding positively to the RLS advertisement tended to be older than those with sleep complaints or normal sleeper controls.

Secondly, due to practical constraints, the SIT procedure was carried out during the day. Hening et al [61] found that an independent circadian factor modulates the intensity of RLS symptoms, hence the standard diagnostic criteria relating to the RLS symptoms occurring mostly at night. They measured sensory discomfort and periodic leg movements and found that both of these increased throughout the day and peaked in the hours after midnight in a group of people with severe RLS. Therefore carrying out the SIT during the day may mean there is actually a reduction in the PLM index and sensory discomfort for the less severely affected individuals. Nevertheless the RLS group did have significantly higher SIT PLM scores than the two control groups. However future studies, testing at night, prior to sleep onset, may produce a greater difference in levels of sensory discomfort, with the RLS group experiencing much more discomfort.

Another potential criticism of the present study is that the SIT traces were not also scored by an independent rater. The main author scored all of the SIT data for every participant. Whilst this

ensured consistency of the scoring, no evidence of inter-rater reliability could be provided for the present study.

Finally, the reliability of the PANAS negative subscale is disappointing, calling the results into question. The low internal consistency of this scale means that the items do not correlate highly with one another and therefore the validity of the measure is uncertain. This also reduces the likelihood that the findings of this study are replicable. The PANAS was chosen because of good face validity but on reflection this may not have been the best measure as we cannot be sure that it is not just tapping into the sensory discomfort. Perhaps a better approach would be to look at the items on the PANAS individually. Some of the items, for example "jittery" are more likely to be tapping into the motor and sensory symptoms than others. Another approach might be to measure facial EMG as an alternative measure of emotion, which would also circumvent the problem of the measurement of affect being retrospective. The facial EMG and leg EMG could be analysed in parallel showing the impact of leg movements and periods of inactivity on mood.

If we consider the findings of the present study a true reflection of the impact of sensory discomfort on mood in those with RLS, there are obvious implications for clinical practice and future research. Currently RLS patients, if properly diagnosed, are treated by their GP using various medications or referred to Neurologists for investigation. The Neurologist will attempt to treat the motor disorder and may be unaware of the problems of emotional and physiological arousal when trying to remain at rest. Whilst medication may help to relieve or dull down the sensory discomfort, this does not work for all patients and in other cases certain medications can lead to an augmentation of symptoms [26]. These results provide some initial evidence that the distress caused by RLS symptoms may have a psychophysiological basis and so be amenable to psychological treatment. Cognitive behavioural techniques that have been shown to be effective for treating insomnia [62] could also be useful for reducing the impact of RLS. Provision of information regarding RLS may help to alleviate the sense of being helpless. Cognitive restructuring to help tackle unhelpful beliefs that elicit negative affect and avoidance of situations such as going to the cinema may also prove beneficial. Cognitive coping strategies that have been shown to be effective in increasing pain

tolerance may also be useful, such as pleasant imagery or distraction techniques [58]. New acceptance-based approaches and mindfulness techniques which have been applied successfully to chronic pain may also be helpful. A recently published preliminary study evaluating an acceptance and mindfulness based group therapy has demonstrated promising results [63] and should be explored in future research. However prior to this, a number of issues need to be resolved. Further research comparing RLS patients with PI groups is required, using the standard SIT procedure just prior to sleep onset. Sleep onset should be calculated according to the individual's circadian rhythm, using for example core body temperature. It would be interesting to discover whether the levels of positive and negative affect would be different to those found in the present study. Another important suggestion would be to measure subjective and objective sleep quality, affect and RLS severity prospectively over the same time period which would enable analyses of which factor or factors predicted the level of depressive symptoms.

5. Conclusion

This study was the first to investigate levels of positive and negative affect in RLS and to use PI as a clinical control group. Use of the PI group enabled exploration of what relationships may be specific to the RLS syndrome and which may be accounted for by having a sleep disorder of some type. Perhaps the most striking result is the high correlation between negative affect and sensory discomfort in the RLS group, however, the difficulties with the reliability of the scale in this case and the likelihood of affect and sensory discomfort being orthogonal constructs must be considered. Further studies are needed to establish the validity of the use of the PANAS on a sleep disorder population. Despite the practical limitations of the study, significant differences were found between the RLS group and the control groups on the objective measures of the SIT and actigraphy with relatively small sample sizes. This study supports the view that the increased comorbidity between RLS and depression is due mainly to the level of sleep disturbance and this sleep disturbance is not directly related to the number of PLMS. This study also underlines sensory discomfort experienced by RLS patients as they are trying to fall asleep and points to the resultant emotional arousal as having a potential role in the sleep disturbance and increased level of depressive symptoms. Taking into account the limitations of the study, any conclusions drawn from the present study must be approached with some caution. The results of this study have important implications for future research and clinical practice. It is important that the RLS patients' experience is recognised and understood, as the excerpt at the beginning of this paper demonstrates, RLS can leave those with the condition with intolerable anguish and distress.

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Table 1. Clinical Features of Restless Legs Syndrome

Essential diagnostic criteria for restless legs syndrome
1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)
Supportive clinical features for restless legs syndrome
Family history
Response to dopamingeric therapy
Periodic limb movements (during wakefulness or sleep)
Associated features of restless legs syndrome
Natural clinical course, typically chronic and progressive
Physical examination normal in primary RLS
Sleep disturbance common in severely affected patients

Diagnostic criteria are mandatory for a positive diagnosis of RLS. Supportive clinical features although not essential may help resolve diagnostic uncertainty. Associated features are typical but do not contribute to the diagnosis. Adapted from ref [20].

Table 2. Telephone screening questions utilised in the study.

Telephone Screening Questions
1. Do you have, or have you sometimes experienced, a recurrent need or urge to move your legs while sitting or lying down?
2. When present, do these uncomfortable feelings or this urge to move become worse when you are resting (either sitting or lying down), and relieved by movement?
3. Are these uncomfortable feelings, or this urge to move, worse in the evening or at night, compared with the morning?
4. During the last 12 months, have these uncomfortable feelings or sensations in your legs, or the need to move your legs while sitting or lying down, happened to you on average for one or more nights/days per week?

A positive diagnosis requires that the respondent answer YES to the first 3 questions.

Table 3. Participant demographics within the RLS, PI and NRC groups (means with standard deviations in parentheses).

Demographic	RLS (n=15)	PI (n=15)	NRC (n=15)	$F(2, 45)/\chi^2(2)$	p
Age (years)	39.8 (13.7)	35.4 (9.8)	28.9 (4.2)	4.43 ‡	.018
Gender (male/female)	6/9	5/10	8/7	1.28	.529
BMI	25.8 (4.4)	23.6 (2.3)	23.5 (3.6)	1.98	.151
Smoker (n)	3	3	2	.30	.859
Alcohol	3.6 (5.4)	7.1 (9.8)	6.9 (9.7)	.740	.483
Snorer (n)	4	4	5	.213	.897

*: indicates significant (P<.05) difference between RLS and PI with Tukey *post-hoc* Test
‡: indicates significant (P<.05) difference between RLS and NRC with Tukey *post-hoc* Test
†: indicates significant (P<.05) difference between PI and NRC with Tukey *post-hoc* Test

Table 4. Screening, clinical and sleep diary measures for the RLS, PI, and NRC groups (means with standard deviations in parentheses).

Measure	Overall	RLS (n=15)	PI (n=15)	NRC (n=15)	F(2, 45)	p
ISI	9.5 (6.8)	14.1 (5.9)	11.9 (5.2)	2.6 (1.8)	26.05‡†	<.001
PSAS COG	19.5 (7.2)	19.9 (6.1)	24.0 (8.1)	14.5 (3.3)	8.89†	.001
PSAS PHY	11.3 (4.1)	13.7 (4.1)	12.1 (4.3)	8.2 (0.6)	10.27‡†	<.001
PSQI	7.7 (4.4)	9.9 (4.2)	9.7 (3.3)	3.3 (1.4)	20.59‡†	<.001
EPWORTH	6.7 (4.4)	7.9 (4.8)	6.0 (4.1)	5.7 (4.3)	1.12	.337
IRLS [§]	8.3 (10.8)	21.5 (7.5)	3.5 (5.3)	N/A	7.61*‡	<.001
SOL[¶]	23.7 (14.6)	26.9 (17.1)	29.5 (12.4)	14.1 (10.0)	4.94†	.013
WAKE	2.0 (1.7)	2.4 (1.5)	2.7 (2.0)	1.0 (0.8)	5.04‡†	.011
WASO[¶]	17.9 (23.0)	26.6 (23.2)	27.9 (27.0)	2.1 (1.8)	7.54‡†	.002
TST	6.7 (1.3)	6.1 (1.1)	6.3 (1.4)	7.5 (0.7)	7.24‡†	.002
TIB	7.9 (1.1)	8.1 (1.2)	7.8 (1.3)	7.9 (0.6)	0.18	.833
SE	84.4 (13.4)	76.3 (14.0)	81.0 (12.3)	95.2 (4.3)	11.85‡†	<.001
SF36PH	81.5 (17.6)	67.3 (20.4)	85.0 (12.7)	92.0 (6.9)	11.67*‡	<.001
SF36MH	74.9 (15.9)	64.8 (16.2)	75.0 (16.0)	84.9 (7.6)	7.90‡	.001
BDI	7.5 (6.8)	10.6 (8.8)	7.9 (5.3)	4.1 (4.2)	3.94‡	.027

[§] Independent samples t-test replaced the ANOVA as the IRLS was not relevant for the NRC group.

[¶] Outliers removed from each group

ISI: Insomnia Severity Scale; PSAS Cog: Pre-Sleep Arousal Scale Cognitive subscale; PSAS PHY: Pre-Sleep Arousal Scale Physical Subscale; PSQI: Pittsburgh Sleep Quality Index; IRLS: International Restless Legs Syndrome Study Group RLS Severity Scale; EPWORTH: Epworth Sleepiness Scale; SOL: Sleep Onset; WAKE: Number of wakenings; WASO: Wake time after sleep onset; TST: Total Sleep Time; TIB: Total Time in Bed; SE: Sleep Efficiency {TST/TIB × 100}; SF36PH: Short Form 36 Version 2 Physical Health Subtotal; SF36MH: Short Form 36 Version 2 Mental Health Subtotal; BDI: Beck Depression Inventory (2^{nd} Eds).

*: indicates significant (P<.05) difference between RLS and PI with Tukey *post-hoc* Test
‡: indicates significant (P<.05) difference between RLS and NRC with Tukey *post-hoc* Test
†: indicates significant (P<.05) difference between PI and NRC with Tukey *post-hoc* Test

Table 5. SIT, Actigraphy and PANAS measures in RLS, PI and NRC groups (means with standard deviations in parentheses).

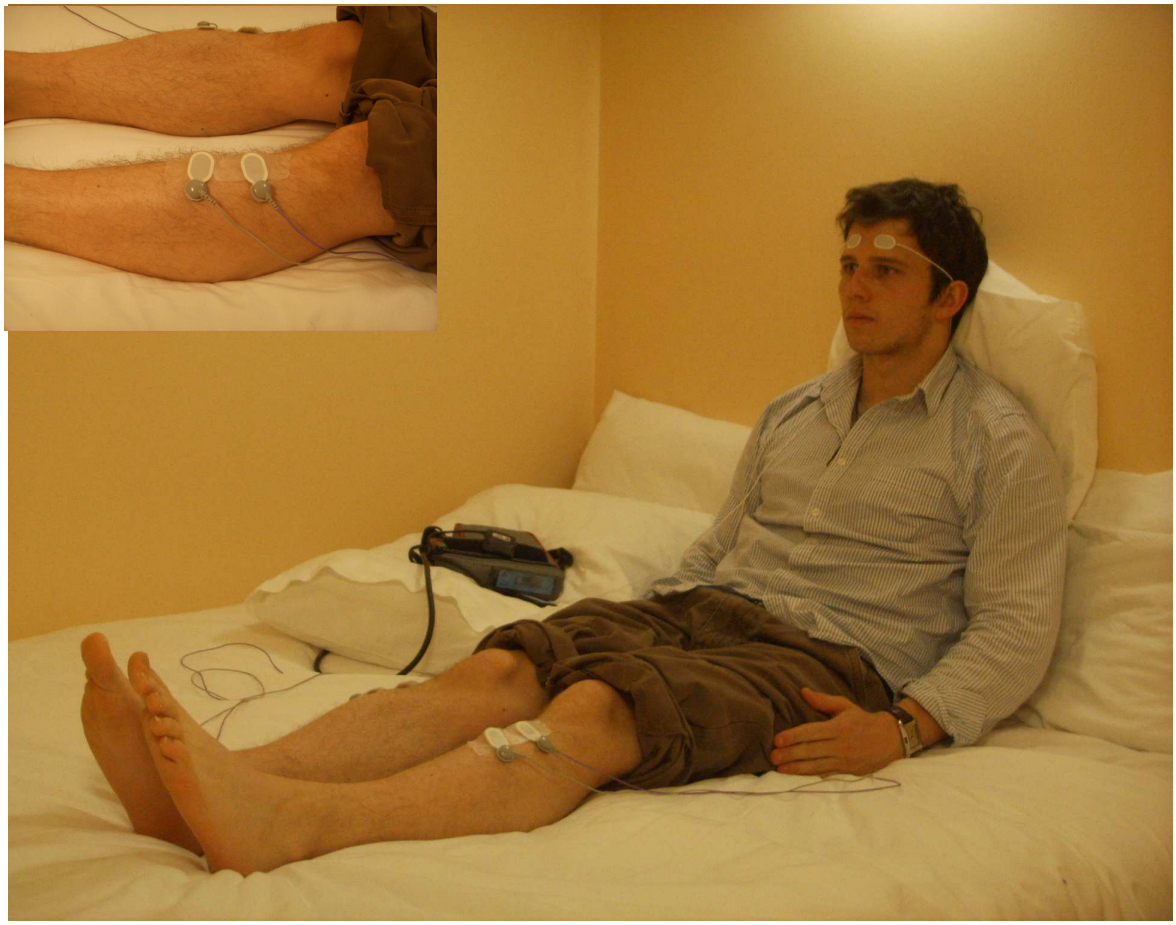
Variable	RLS (n=15)	PI (n=15)	NRC (n=15)	F(2, 45)/ $\chi^2(2)$	p
SIT index	51.5 (42.3)	19.7 (20.7)	19.9 (26.5)	5.15*‡	.010
MDS	32.0 (23.6)	21.8 (15.4)	10.4 (5.0)	6.08‡	.005
MMS	64.0 (18.8)	65.9 (18.1)	77.0 (15.9)	2.37	.106
PLMS index[§]	15.0 (14.8)	4.5 (4.9)	3.4 (3.8)	9.40*‡	.009
PANAS pos	24.3 (7.6)	18.6 (5.6)	18.3 (5.1)	4.54*‡	.016
PANAS neg[§]	13.9 (3.5)	11.5 (1.6)	10.7 (1.1)	9.59*‡	.008
PANAS neg 6-item	9.6 (3.5)	7.2 (1.3)	6.6 (0.7)	7.58*‡	.023

[§] Kruskal Wallis Test and Mann-Whitney Tests for *post-hoc* pairwise comparisons

SIT index: The number of PLMs during the Suggested Immobilisation Test; MDS: Mean discomfort Score; MMS: Mean Mood Score; PLMS index: The PLMS index for both legs combined averaged over 3 nights; PLMS time: The average time in minutes of PLMS in combined legs for all three nights; PANAS pos: Positive and Negative Affectivity Scale Positive Scale; PANAS neg: Positive and Negative Affectivity Scale Negative Scale.

*: indicates significant (P<.05) difference between RLS and PI with Tukey *post-hoc* Test
‡: indicates significant (P<.05) difference between RLS and NRC with Tukey *post-hoc* Test
†: indicates significant (P<.05) difference between PI and NRC with Tukey *post-hoc* Test

Figure 1. Photograph of Suggested Immobilisation Test set up.



Main photograph shows the context of the Suggested Immobilisation Test (SIT) and participant position, with two electrodes attached to the forehead and two electrodes attached to each leg. The photograph inset illustrates the positioning of the electrodes above the anterior tibialis muscles approximately 3cm apart.

Figure 2. Example from Stellate Harmonie Version 6 Software of Periodic Leg Movements.

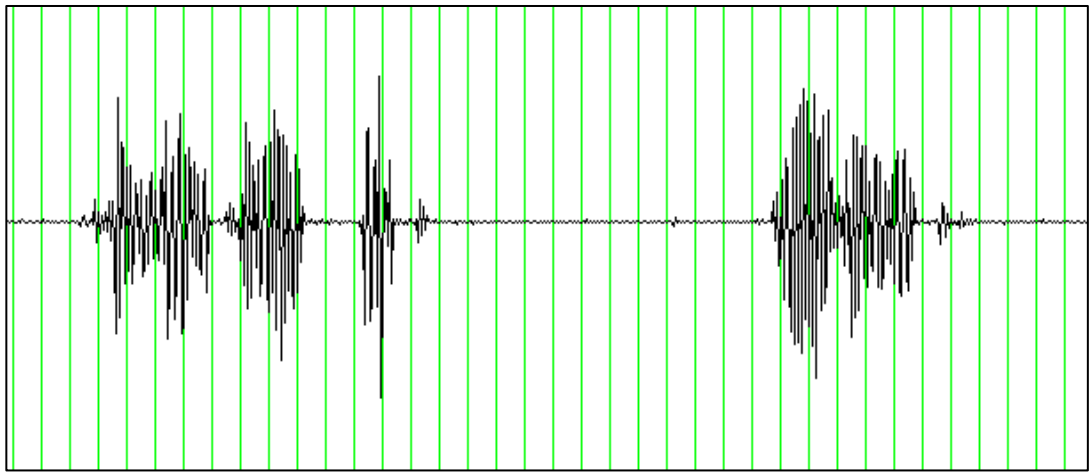


Figure shows periodic leg movements detected by the surface electrodes above the right anterior tibialis muscle in a participant with RLS. Each green line represents 1 second.

Figure 3. Positioning of AW4 Actiwatch (Cambridge Neurotechnology) on the foot.

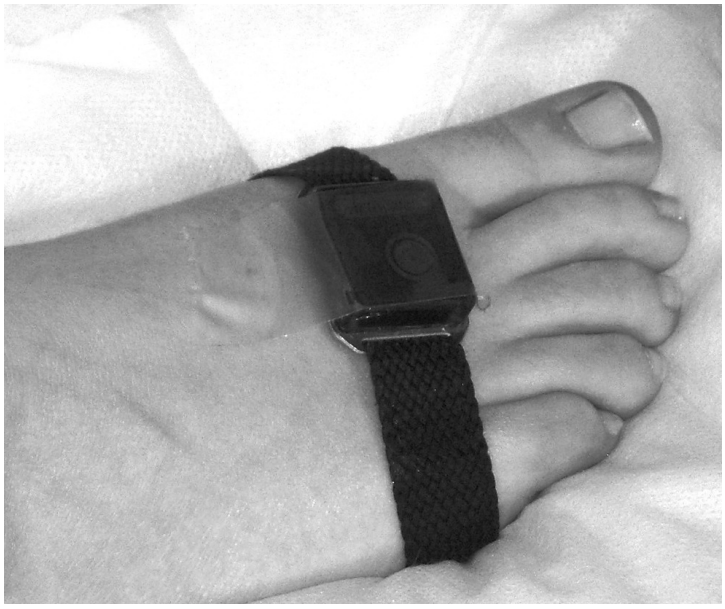
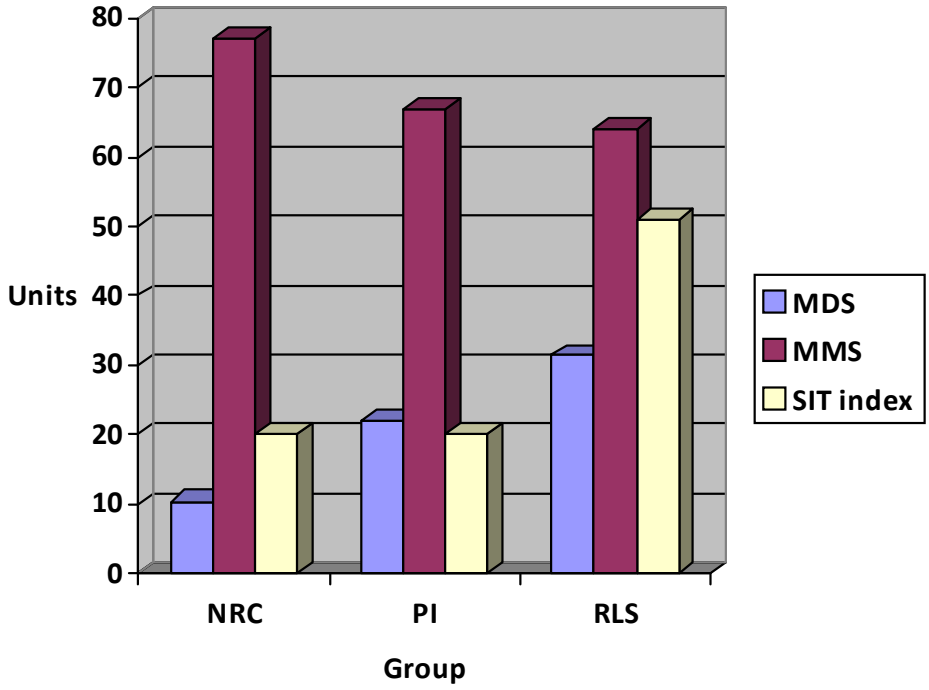
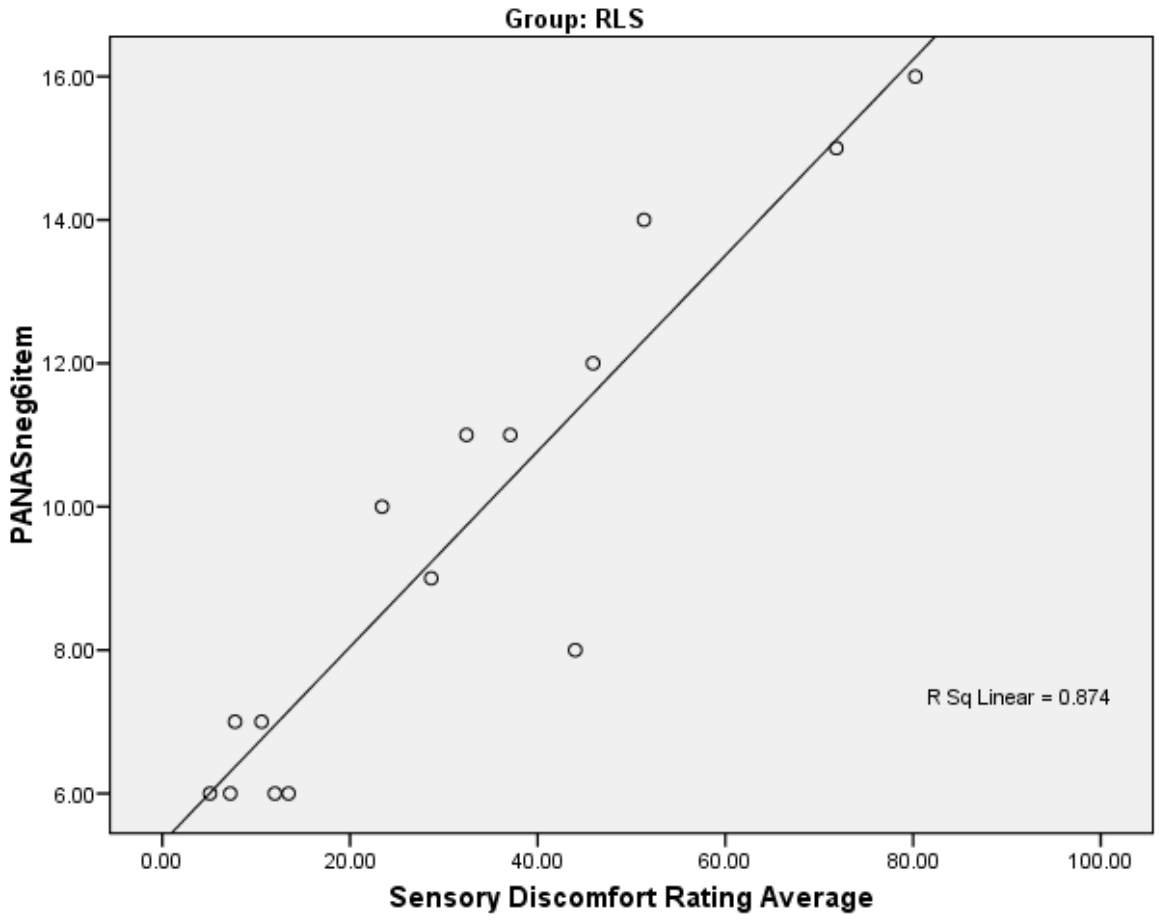


Figure 4. Bar chart illustrating the results from the SIT for all three groups; RLS, PI and NRC.



SIT index: The number of PLMs during the Suggested Immobilisation Test;
MDS: Mean discomfort Score; MMS: Mean Mood Score.

Figure 5. Scatterplot illustrating the association between negative affect and sensory discomfort in the RLS group.



CHAPTER THREE:
ADVANCED CLINICAL PRACTICE I REFLECTIVE CRITICAL ACCOUNT

Reflecting on the never-ending journey from incompetence to competence

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ABSTRACT

The aim of this reflective account is to chart my own professional development throughout training. I use excerpts from a reflection written at the beginning of my current placement to illustrate how my understanding of the role has grown. I discuss the usefulness of reflecting on learning experiences, using structured reflective models to facilitate reflection and how this contributes to my practice. By becoming a more reflective practitioner, I hope to always be aware of my internal influences that I bring to each session and therefore be a more competent therapist. Reflection or self-discovery can also show us the gaps in our knowledge and provide us with the impetus to continue life-long learning.

CHAPTER FOUR:
ADVANCED CLINICAL PRACTICE II REFLECTIVE CRITICAL ACCOUNT

The Psychologist & Consultant
A Trainee's Perspective of the Further Development of Professional Roles

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ABSTRACT

Being on my last placement of my training has brought up a range of emotions – excitement, trepidation, and satisfaction. This account focuses on the Intended Learning Outcomes for this final placement; namely the ILOs concerned with working with an inter-professional and multi-agency approach and consultancy. A meeting with the manager of the CMHT were I am based stimulated my thoughts on working in partnership with Social Care. There was a clear sense that the psychologists in the team had been a real asset in creating a well-functioning team as is envisioned by the BPS document "Working Psychologically in Teams". I then reflect on my own personal experiences of working in consultation with members of the CMHT, in particular a piece of work I carried out with a Community Psychiatric Nurse. My reflection has aided my future plans in terms of how I would want to improve this skill especially in view of my transition from trainee to qualified Clinical Psychologist approaching.

APPENDICES

AUTHOR GUIDELINES FOR SUBMISSION TO *MOVEMENT DISORDERS*

Movement Disorders Manuscript instructions

Scope

Movement Disorders publishes Reviews, Full-length Articles, Brief Reports, Clinical or Scientific Notes, and Letters. Case reports in which interesting diagnostic difficulties arose in which a definitive pathological or genetic diagnosis was ultimately made can be submitted for the Clinico-Pathological Grand Round section of the journal. The case history and the pathological findings should be submitted to the editors. If the editor determines that the report is appropriate for the Grand Round format two referees can be solicited to discuss the case and become co-authors of the report. All articles in *Movement* Disorders can be accompanied by a video when appropriate.

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Letters allow publication of views and discussion of previously published material in the Journal or interesting observations (up to 800 words total). This section is also the appropriate venue for single case histories without video.

Clinical Trial Reports must be written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher D et al., JAMA 2001;285:1987–1991; see also Moher D et al., Lancet 2001;357:1191–1194.) Authors should ensure that information on all of the critical design features listed in the CONSORT checklist is reported in the manuscript. (Reviewers are provided with the checklist to assess the manuscript for the relevant content.) The CONSORT flow diagram (figure) should be included with the manuscript, clearly outlining the flow of patients through the trial. In addition, a statement is required in the cover letter specifically confirming that there has been no ghost writing by anyone not named on the author list (see Editorial in *Movement* Disorders 2005;20:1536). The precise financial relationship between a clinical trial sponsor and the authors must be delineated in the manuscript.

Form of Manuscripts.

The text of the manuscript should be in the following sequence: (1) Title page, (2) Abstract, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgment, (8) References, (9) Video Legend, (10 Figures, and (11) Tables. Pages should be numbered in succession, the title page being one.

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Drug Names : Use generic names only in referring to drugs, followed in parentheses after first mention by any commonly used generic variant.

Abbreviations : Follow the list of abbreviations given in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (see section on References). For additional abbreviations, consult the CBE Style Manual (available from the Council of Biology Editors, 9650 Rockville Pike, Bethesda, Maryland 20814, USA) or other standard sources.
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References are to be cited in the text by number, and in the list of References they are to be numbered in the order in which they are cited. The reference section should be double-spaced at the end of the text, following the sample formats given below. Provide all authors' names when fewer than seven; when seven or more, list the first three and add et al. Provide article titles and inclusive pages. Accuracy of reference data is the responsibility of the author. For abbreviations of journal names, refer to List of Journals Indexed in Index Medicus (available from the Superintendent of Documents, U.S. Government Printing Office, Washington DC 20402, USA, DHEW Publication No. (NIH) 83-267; ISSN 0093-3821).

Sample References

Journal article:
1. Horgan JH, O'Callaghan WG, Teo KK. Therapy of angina pectoris with low-dose perhexiline. J Cardiovasc Pharmacol 1981;3:566–572.
Book:
2. Vanhoutte PM, Leusen I, editors. Vasodilatation. New York: Raven Press; 1981. 96 p.
Chapter in a book:
3. Patrono C, Ciabattoni G, Pugliese F, et al. Effect of dietary variation in linoleic acid content on platelet aggregation and the major urinary metabolites of the E prostaglandins and (PGE-M) in infants. In: Hegyeli RJ, editor. Prostaglandins and cardiovascular disease. New York: Raven Press; 1981. p 111–122. (Atherosclerosis reviews; vol. 8).

AUTHOR GUIDELINES FOR SUBMISSION TO *SLEEP MEDICINE*

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Title Page
Authors' full names, academic or professional affiliations, and complete addresses must be included on the title page. The corresponding author must be indicated by an asterisk, and his/her full contact details must be included (telephone and fax numbers and e-mail address).

Abstract
A structured abstract of approximately 200 words is mandatory at the beginning of each article. The abstract should be organized by: **Objective or Background, Methods, Results, and Conclusions**. Review articles and case reports do not need a structured abstract.

Keywords
6-8 items must be included on the title page. Authors are encouraged to choose their own key words, but Medical Subject Headings (issued with the January Index Medicus, latest edition) may be used as a guideline.

References
References to literature must be indicated by Arabic numerals which run consecutively through the paper. Where a reference is cited more than once in the text the same number should be used each time. Reference style should follow the "Vancouver" style described in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (published in N Engl J Med 1997;336:309-315). The titles of journals should be abbreviated in conformity with Index Medicus. The following are sample styles:
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[2] Wechsler D. Wechsler Adult Intelligence Scale. New York: Grune & Stratton, 1976.
[3] Hirst W, Volpe B. Automatic and effortful encoding in amnesia. In: Gazzaniga M, editor. Handbook of cognitive neuroscience. New York: Plenum Press, 1984; p. 369-386.
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Legends should be typed double spaced on a separate page and numbered with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers or letters are used to identify parts of the illustrations, each should be explained clearly in the legend. The legends should permit the figures to be understood with reference to the text. If the figure has been published previously a credit line should be included.

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Manuscripts reporting the results of Phase III trials must follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines. For more information on these guidelines, please refer to:
Begg, C, Cho, M. Eastwood, S, et al. Improving the quality of randomized controlled trials: the CONSORT statement. JAMA 1996; 276:637-639.
Schulz, KF. The quest for unbiased research: Randomized clinical trials and the CONSORT reporting guidelines. Ann Neurol 1997; 41:569-573.

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PRESS CUTTINGS AND POSTER

Sunday Herald (30/03/08)

HEALTH: RESEARCH

Scientists wake up to restless legs

By **Judith Duffy**
Health Correspondent

RESEARCHERS are to investigate the leading cause of insomnia, thought to affect up to one in 10 people.

Restless legs syndrome (RLS) causes creeping or tingling sensations in the legs, which urge sufferers to move the affected limbs during periods of inactivity or sleep. There is no known cure and current treatments, which include drug therapy and iron supplements, are not always effective.

Researchers at Glasgow University are seeking RLS sufferers to participate in a study to measure the impact and severity of the disorder.

Lead researcher Lisa Galloway said the condition was largely unrecognised and undiagnosed. "People describe it as wanting to take their skin off and scratch under their legs as other than moving about, you can't get the sensation to go away," she said.

The exact causes of RLS are unknown, but it can be inherited or appear as a complication of another condition. Women and people over the age of 40 are more likely to be affected.

While pharmaceutical companies have been accused of exaggerating the prevalence of RLS to sell drugs to those with mild symptoms, Galloway said an aim of the research was to investigate alternative treatments.

"We are interested in the impact from a psychological point of view and if there is something we can do to reduce the impact on people," she said.

Email *restlesslegssyndrome@googlemail.com* for details of the study.

University of Glasgow News (28/03/08)

UNIVERSITY of GLASGOW

New hope for sufferers of restless legs

Issued: Fri, 28 Mar 2008 10:17:00 GMT

An often undiagnosed condition that is thought to affect up to 10% of the population is the subject of new research.

Restless Legs Syndrome (RLS) causes a creeping or tingling sensation deep within the leg and is coupled with an inescapable desire to move the affected limbs. Often leading to insomnia, there is no current cure for the condition which can be devastating for sufferers.

Lead researcher at the University of Glasgow Lisa Galloway said: "The symptoms can be very distressing for sufferers of RLS. Not only is the creeping sensation very uncomfortable but the symptoms are worse when resting meaning sufferers need to walk around to find relief. Sleep disturbance and insomnia are regular side effects of RLS and this can be devastating.

"Despite the high prevalence of the condition it is largely unrecognised and under diagnosed. We hope that by studying how RLS affects sufferers we will move closer to finding a cure."

Current treatments include diet, exercise, iron supplements and drug therapy but these are not always effective.

Lisa Galloway added: "People who present to their GP with RLS are typically prescribed Benzodiazepines and whilst these drugs may alleviate symptoms in the short-term, they are not a helpful long-term solution."

Researchers at the University of Glasgow Sleep Centre are looking for volunteers to take part in the study which will concentrate on sleep, mood and severity of symptoms. Individuals living in the Greater Glasgow area who believe they may be suffering from Restless Leg Syndrome and would like to volunteer for the study should contact Lisa Galloway on 07514 404 516 or email restlesslegssyndrome@googlemail.com

News summaries...

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email: Media Relations Office

NHS Greater Glasgow and Clyde

UNIVERSITY of GLASGOW

Can't sit still?
Uncomfortable sensations in your legs?
Does moving your legs help?

You may be suffering from

Restless Legs Syndrome (RLS)

Do you find yourself walking or pacing, moving your legs and feet or tossing and turning in bed to stop the RLS?

We are looking at the impact of a condition called RLS and require volunteers to take part.

Although research shows that many people suffer with this difficult condition, it is often under recognised. We need to know more about the impact this condition has on people, for example, their sleep and mood.

If you have answered yes to the above questions, or just consider that you are restless and that this can affect your sleep we are interested in hearing from you.

If you would like more information about what is involved in participation in this research study, please contact:

Lisa Galloway
Mobile: 07514 404516
Email: restlesslegssyndrome@googlemail.com

SALETU ET AL EFFECT SIZE CALCULATION

$$f = \varphi'$$

$$\varphi' = \sqrt{\frac{\sum (\mu_j - \mu)^2/k}{\sigma^2_e}}$$

$$\varphi' = \sqrt{\frac{(29.6 - 34.9)^2 + (39.9 - 34.9)^2 + (35.1-34.9)^2/ 3}{4.6^2 + 8.5^2 + 7.3^2 /3}}$$

$$\varphi' = \sqrt{\frac{17.71}{48.9}}$$

$$\varphi' = 0.602$$

SLEEP DIARY

The RLS Project

Sleep Diary

Name _____ ID#_____

This diary helps both us and yourself to find out your sleep pattern and how you feel about your sleep. In order to get a precise picture of your night-by-night sleep and your feelings about it, it is essential that you fill in the diary every morning. Please remember that there is not a right or wrong answer but just the way you slept each night.

Date started:	Night 1	Night 2	Night 3
1. What time did you rise from your bed this morning?			
2. At what time did you go to bed last night?			
3. How long did it take you to fall asleep?			
4. How many times did you awake during the night?			
5. How long were you awake during the night (in total)?			
6. About how long did you sleep altogether (hours/mins)?			
7. How many units of alcohol did you take last night?			
8. Did you take any sleeping tablets? (Y/N)			

Measuring the Quality of your sleep

1. How was your sleep? 0 1 2 3 4 very bad so so good very bad good			
2. How rested do you feel this morning? 0 1 2 3 4 not little so so quite very at all good			

BIOCALIBRATION

Movement	Time
Left foot toes back	: : .
Right foot toes back	: : .
Left foot toes forward	: : .
Right foot toes forward	: : .
Both feet toes back	: : .
Both feet toes forward	: : .
Lift left leg just off the bed	: : .
Lift right leg just off the bed	: : .
Both legs just off the bed	: : .
PEN	: : .

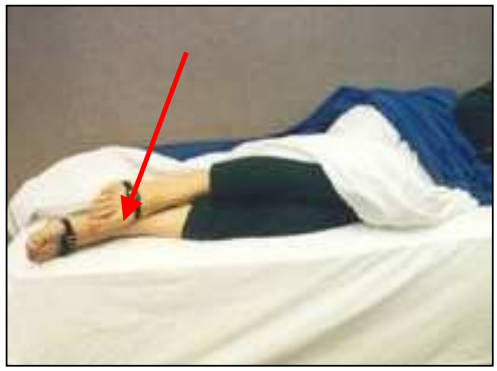
Restless Legs Syndrome Project
Actiwatch Instructions

Thank you for agreeing to take part in this study. Your participation is essential for future understanding of Restless Legs Syndrome.

What to do:

Each night:

1. Each night just **before** you go to bed strap each actiwatch to each foot, with the monitor just below the big toe. Each watch is labelled on the back, either left or right. Please ensure you have put the watch on the correct leg.



2. Make sure that the monitor is secure and will not slip from its position. You can use the tape provided to secure the actiwatch.

3. Keep the actiwatches on throughout the night.

4. When you get up in the morning **remove** the Actiwatches.

Each morning:

1. Please remember to fill in your sleep diary as soon as you get up when it is fresh in your mind.
2. This should only take 5 minutes or so.

After the 3 nights please return the *equipment* and *diary* to the Sleep Research Centre, or we can arrange collection from your work or home.

THANK YOU VERY MUCH FOR YOUR ASSISTANCE!!!

ANOVAS WITH TRANSFORMED DATA

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
TRANSBDI	Controls	15	.5473	.40341	.10416	.3239	.7707	.00	1.11
	Restless controls	15	.8462	.35581	.09187	.6492	1.0432	.00	1.26
	RLS	15	.9175	.41314	.10667	.6887	1.1463	.00	1.49
	Total	45	.7703	.41556	.06195	.6455	.8952	.00	1.49
TRANSPSQI	Controls	15	.6141	.14717	.03800	.5326	.6956	.30	.85
	Restless controls	15	1.0127	.12851	.03318	.9415	1.0839	.85	1.23
	RLS	15	1.0022	.19789	.05109	.8926	1.1118	.48	1.30
	Total	45	.8763	.24453	.03645	.8029	.9498	.30	1.30
TRANSISI	Controls	15	.5107	.20079	.05184	.3995	.6219	.30	.85
	Restless controls	15	1.0702	.20265	.05232	.9580	1.1825	.60	1.34
	RLS	15	1.1284	.26247	.06777	.9830	1.2737	.30	1.41
	Total	45	.9031	.35656	.05315	.7960	1.0102	.30	1.41
TSF36PHY	Controls	15	1.9627	.03478	.00898	1.9435	1.9820	1.86	2.00
	Restless controls	15	1.9245	.07036	.01817	1.8855	1.9634	1.77	2.00
	RLS	15	1.8071	.14581	.03765	1.7263	1.8878	1.52	1.99
	Total	45	1.8981	.11493	.01713	1.8636	1.9326	1.52	2.00
TPSASphy	Controls	15	.9130	.02745	.00709	.8978	.9282	.90	1.00
	Restless controls	15	1.0582	.14409	.03720	.9784	1.1380	.90	1.30
	RLS	15	1.1202	.12767	.03297	1.0495	1.1909	.95	1.34
	Total	45	1.0305	.14053	.02095	.9882	1.0727	.90	1.34
TIRLS1	Controls	15	.0000	.00000	.00000	.0000	.0000	.00	.00
	Restless controls	15	.3490	.51391	.13269	.0644	.6336	.00	1.18
	RLS	15	1.3268	.15642	.04039	1.2402	1.4134	1.04	1.56
	Total	45	.5586	.64371	.09596	.3652	.7520	.00	1.56
TSITPLM1	Controls	15	.9025	.69282	.17889	.5188	1.2862	.00	1.92
	Restless controls	15	1.0835	.53547	.13826	.7870	1.3800	.00	1.86
	RLS	15	1.5247	.48571	.12541	1.2557	1.7937	.70	2.14
	Total	45	1.1702	.62358	.09296	.9829	1.3576	.00	2.14
TMDS1	Controls	15	.9986	.25577	.06604	.8569	1.1402	.40	1.26
	Restless controls	15	1.1881	.51893	.13399	.9007	1.4754	.00	1.79
	RLS	15	1.3840	.36233	.09355	1.1834	1.5847	.78	1.91
	Total	45	1.1902	.41665	.06211	1.0650	1.3154	.00	1.91

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
TRANSBDI	Between Groups	1.158	2	.579	3.775	.031
	Within Groups	6.440	42	.153		
	Total	7.598	44			
TRANSPSQI	Between Groups	1.548	2	.774	30.034	.000
	Within Groups	1.083	42	.026		
	Total	2.631	44			
TRANSISI	Between Groups	3.490	2	1.745	34.839	.000
	Within Groups	2.104	42	.050		
	Total	5.594	44			
TSF36PHY	Between Groups	.197	2	.099	10.794	.000
	Within Groups	.384	42	.009		
	Total	.581	44			
TPSASphy	Between Groups	.339	2	.170	13.465	.000
	Within Groups	.529	42	.013		
	Total	.869	44			
TIRLS1	Between Groups	14.192	2	7.096	73.770	.000
	Within Groups	4.040	42	.096		
	Total	18.232	44			
TSITPLM1	Between Groups	3.073	2	1.536	4.597	.016
	Within Groups	14.037	42	.334		
	Total	17.110	44			
TMDS1	Between Groups	1.114	2	.557	3.587	.036
	Within Groups	6.524	42	.155		
	Total	7.638	44			

Post Hoc Tests

Multiple Comparisons

Tukey HSD

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
TRANSBDI	Controls	Restless controls	-.29895	.14299	.104	-.6463	.0484
		RLS	-.37027*	.14299	.034	-.7177	-.0229
	Restless controls	Controls	.29895	.14299	.104	-.0484	.6463
		RLS	-.07133	.14299	.872	-.4187	.2761
	RLS	Controls	.37027*	.14299	.034	.0229	.7177
		Restless controls	.07133	.14299	.872	-.2761	.4187
TRANSPSQI	Controls	Restless controls	-.39864*	.05863	.000	-.5411	-.2562
		RLS	-.38815*	.05863	.000	-.5306	-.2457
	Restless controls	Controls	.39864*	.05863	.000	.2562	.5411
		RLS	.01049	.05863	.983	-.1319	.1529
	RLS	Controls	.38815*	.05863	.000	.2457	.5306
		Restless controls	-.01049	.05863	.983	-.1529	.1319
TRANSISI	Controls	Restless controls	-.55956*	.08172	.000	-.7581	-.3610
		RLS	-.61770*	.08172	.000	-.8162	-.4192
	Restless controls	Controls	.55956*	.08172	.000	.3610	.7581
		RLS	-.05814	.08172	.758	-.2567	.1404
	RLS	Controls	.61770*	.08172	.000	.4192	.8162
		Restless controls	.05814	.08172	.758	-.1404	.2567
TSF36PHY	Controls	Restless controls	.03825	.03491	.522	-.0466	.1231
		RLS	.15563*	.03491	.000	.0708	.2404
	Restless controls	Controls	-.03825	.03491	.522	-.1231	.0466
		RLS	.11738*	.03491	.005	.0326	.2022
	RLS	Controls	-.15563*	.03491	.000	-.2404	-.0708
		Restless controls	-.11738*	.03491	.005	-.2022	-.0326
TPSASphy	Controls	Restless controls	-.14526*	.04100	.003	-.2449	-.0457
		RLS	-.20725*	.04100	.000	-.3068	-.1076
	Restless controls	Controls	.14526*	.04100	.003	.0457	.2449
		RLS	-.06198	.04100	.296	-.1616	.0376
	RLS	Controls	.20725*	.04100	.000	.1076	.3068
		Restless controls	.06198	.04100	.296	-.0376	.1616
TIRLS1	Controls	Restless controls	-.34897*	.11325	.010	-.6241	-.0738
		RLS	-1.32681*	.11325	.000	-1.6019	-1.0517
	Restless controls	Controls	.34897*	.11325	.010	.0738	.6241
		RLS	-.97784*	.11325	.000	-1.2530	-.7027
	RLS	Controls	1.32681*	.11325	.000	1.0517	1.6019
		Restless controls	.97784*	.11325	.000	.7027	1.2530
TSITPLM1	Controls	Restless controls	-.18101	.21110	.670	-.6939	.3319
		RLS	-.62220*	.21110	.014	-1.1351	-.1093
	Restless controls	Controls	.18101	.21110	.670	-.3319	.6939
		RLS	-.44119	.21110	.104	-.9540	.0717
	RLS	Controls	.62220*	.21110	.014	.1093	1.1351
		Restless controls	.44119	.21110	.104	-.0717	.9540
TMDS1	Controls	Restless controls	-.18951	.14391	.394	-.5391	.1601
		RLS	-.38545*	.14391	.028	-.7351	-.0358
	Restless controls	Controls	.18951	.14391	.394	-.1601	.5391
		RLS	-.19595	.14391	.370	-.5456	.1537
	RLS	Controls	.38545*	.14391	.028	.0358	.7351
		Restless controls	.19595	.14391	.370	-.1537	.5456

*. The mean difference is significant at the .05 level.

SUPPLEMENTARY ANALYSES

Questionnaire Data Analysis with Age as a Covariate

Tests of Between-Subjects Effects

Dependent Variable: SF36PHtotal

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	4887.315(a)	3	1629.105	7.666	.000
Intercept	23258.069	1	23258.069	109.442	.000
Age	29.706	1	29.706	.140	.710
Group	3846.953	2	1923.476	9.051	.001
Error	8713.107	41	212.515		
Total	312254.777	45			
Corrected Total	13600.421	44			

a R Squared = .359 (Adjusted R Squared = .312)

Tests of Between-Subjects Effects

Dependent Variable: SF36MHtotal

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3659.701(a)	3	1219.900	6.746	.001
Intercept	12368.292	1	12368.292	68.395	.000
Age	631.311	1	631.311	3.491	.069
Group	3659.701	2	1829.850	10.119	.000
Error	7414.326	41	180.837		
Total	263603.877	45			
Corrected Total	11074.027	44			

a R Squared = .330 (Adjusted R Squared = .281)

Tests of Between-Subjects Effects

Dependent Variable: Insomnia Severity Index Total Score

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1120.295(a)	3	373.432	16.957	.000
Intercept	310.449	1	310.449	14.097	.001
Age	.162	1	.162	.007	.932
Group	944.779	2	472.389	21.451	.000
Error	902.905	41	22.022		
Total	6113.000	45			
Corrected Total	2023.200	44			

a R Squared = .554 (Adjusted R Squared = .521)

Tests of Between-Subjects Effects

Dependent Variable: Pittsburgh Sleep Quality Questionnaire Global score

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	445.254(a)	3	148.418	14.887	.000
Intercept	86.394	1	86.394	8.666	.005
Age	22.454	1	22.454	2.252	.141
Group	295.085	2	147.543	14.800	.000
Error	408.746	41	9.969		
Total	3499.000	45			
Corrected Total	854.000	44			

a R Squared = .521 (Adjusted R Squared = .486)

Tests of Between-Subjects Effects

Dependent Variable: Pre-sleep Arousal Scale Cognitive total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	690.677(a)	3	230.226	5.972	.002
Intercept	1514.021	1	1514.021	39.275	.000
Age	14.944	1	14.944	.388	.537
Group	678.221	2	339.110	8.797	.001
Error	1580.523	41	38.549		
Total	19324.000	45			
Corrected Total	2271.200	44			

a R Squared = .304 (Adjusted R Squared = .253)

Tests of Between-Subjects Effects

Dependent Variable: Pre-sleep Arousal Scale Physical Total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	242.074(a)	3	80.691	6.698	.001
Intercept	396.977	1	396.977	32.952	.000
Age	.340	1	.340	.028	.867
Group	193.382	2	96.691	8.026	.001
Error	493.926	41	12.047		
Total	6516.000	45			
Corrected Total	736.000	44			

a R Squared = .329 (Adjusted R Squared = .280)

Tests of Between-Subjects Effects

Dependent Variable: EPWORTH test Total Score

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	43.308(a)	3	14.436	.727	.542
Intercept	146.243	1	146.243	7.368	.010
Age	.064	1	.064	.003	.955
Group	38.682	2	19.341	.974	.386
Error	813.803	41	19.849		
Total	2791.000	45			
Corrected Total	857.111	44			

a R Squared = .051 (Adjusted R Squared = -.019)

Tests of Between-Subjects Effects

Dependent Variable: RLS Rating Scale for Severity Total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2437.530(a)	2	1218.765	28.175	.000
Intercept	303.704	1	303.704	7.021	.013
Age	7.530	1	7.530	.174	.680
Group	2295.456	1	2295.456	53.066	.000
Error	1167.936	27	43.257		
Total	8268.000	30			
Corrected Total	3605.467	29			

a R Squared = .676 (Adjusted R Squared = .652)

Tests of Between-Subjects Effects

Dependent Variable: Pre-sleep Arousal Scale Physical Total

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	21.291(a)	2	10.646	.587	.563
Intercept	404.031	1	404.031	22.290	.000
Age	.458	1	.458	.025	.875
Group	18.985	1	18.985	1.047	.315
Error	489.409	27	18.126		
Total	5503.000	30			
Corrected Total	510.700	29			

a R Squared = .042 (Adjusted R Squared = -.029)

Tests of Between-Subjects Effects

Dependent Variable: Beck Depression Inventory v.2 Total Score

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	493.829(a)	3	164.610	4.334	.010
Intercept	685.226	1	685.226	18.040	.000
Age	170.096	1	170.096	4.478	.040
Group	475.009	2	237.504	6.253	.004
Error	1557.371	41	37.985		
Total	4605.000	45			
Corrected Total	2051.200	44			

a R Squared = .241 (Adjusted R Squared = .185)

Tests of Between-Subjects Effects

Dependent Variable: PANAS Positive Affect

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	559.241(a)	4	139.810	3.979	.008
Intercept	622.039	1	622.039	17.702	.000
Age	88.525	1	88.525	2.519	.120
BDItotal	56.636	1	56.636	1.612	.212
Group	238.475	2	119.237	3.393	.044
Error	1405.559	40	35.139		
Total	20692.000	45			
Corrected Total	1964.800	44			

a R Squared = .285 (Adjusted R Squared = .213)

Tests of Between-Subjects Effects

Dependent Variable: PANAS Negative Affect

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	83.795(a)	4	20.949	3.755	.011
Intercept	336.402	1	336.402	60.292	.000
Age	.335	1	.335	.060	.808
BDItotal	.799	1	.799	.143	.707
Group	54.501	2	27.250	4.884	.013
Error	223.183	40	5.580		
Total	6811.000	45			
Corrected Total	306.978	44			

a R Squared = .273 (Adjusted R Squared = .200)

Tests of Between-Subjects Effects

Dependent Variable: PANASneg6item

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	78.076(a)	4	19.519	3.961	.008
Intercept	161.116	1	161.116	32.693	.000
Age	1.631	1	1.631	.331	.568
BDItotal	.223	1	.223	.045	.833
Group	56.992	2	28.496	5.782	.006
Error	197.124	40	4.928		
Total	3013.000	45			
Corrected Total	275.200	44			

a R Squared = .284 (Adjusted R Squared = .212)

Tests of Between-Subjects Effects

Dependent Variable: PANASneg6item

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	77.923(a)	4	19.481	3.950	.009	.283
Intercept	173.644	1	173.644	35.208	.000	.468
Age	1.827	1	1.827	.370	.546	.009
BDIminusSleep	.070	1	.070	.014	.906	.000
Group	59.216	2	29.608	6.003	.005	.231
Error	197.277	40	4.932			
Total	3013.000	45				
Corrected Total	275.200	44				

a R Squared = .283 (Adjusted R Squared = .211)

Pairwise Comparisons

Dependent Variable: PANASneg6item

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference(a)	
					Upper Bound	Lower Bound
Controls	Restless controls	-.719	.878	1.000	-2.913	1.476
	RLS	-3.196*	1.003	.008	-5.702	-.689
Restless controls	Controls	.719	.878	1.000	-1.476	2.913
	RLS	-2.477*	.850	.017	-4.600	-.354
RLS	Controls	3.196*	1.003	.008	.689	5.702
	Restless controls	2.477*	.850	.017	.354	4.600

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Bonferroni.

Differences between groups on Mean Sensory Discomfort with SIT PLM index as a covariate.

Tests of Between-Subjects Effects

Dependent Variable: Sensory Discomfort Rating Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	3650.666[a]	3	1216.889	4.458	.008	.246
Intercept	7650.484	1	7650.484	28.027	.000	.406
SITPLMindex	319.793	1	319.793	1.172	.285	.028
Group	2250.071	2	1125.036	4.122	.023	.167
Error	11191.568	41	272.965			
Total	35035.924	45				
Corrected Total	14842.234	44				

a. R Squared = .246 (Adjusted R Squared = .191)

Estimated Marginal Means
Group

Estimates

Dependent Variable: Sensory Discomfort Rating Average

Group	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Controls	11.275[a]	4.350	2.490	20.060
Restless controls	22.742[a]	4.354	13.948	31.536
RLS	29.534[a]	4.601	20.242	38.827

a. Covariates appearing in the model are evaluated at the following values: SITPLMindex = 30.3556.

Pairwise Comparisons

Dependent Variable: Sensory Discomfort Rating Average

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Controls	Restless controls	-11.467	6.033	.193	-26.527	3.592
	RLS	-18.260*	6.560	.024	-34.634	-1.886
Restless controls	Controls	11.467	6.033	.193	-3.592	26.527
	RLS	-6.792	6.568	.921	-23.188	9.603
RLS	Controls	18.260*	6.560	.024	1.886	34.634
	Restless controls	6.792	6.568	.921	-9.603	23.188

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

MAJOR RESEARCH PROJECT PROPOSAL

Investigating the Link between Depression and Restless Legs Syndrome: A Controlled Comparison of Mood and Motor Restlessness in Restless Legs Syndrome, with Restless and Normal Controls.

Lisa Galloway
Intake 2005

Supervised by
Prof. Colin Espie

July 2007

SUMMARY

Restless legs Syndrome is a sensorimotor disorder characterised by unpleasant sensations in the legs when at rest that are only relieved by movement. RLS is associated with deterioration in quality of life. Depression is a common comorbid affective disorder found in those with RLS. Possible mechanisms for this association are described, including the impact of periodic leg movements during sleep (PLMS). The present study aims to establish whether RLS is an independent risk factor for depressive symptoms by comparing 3 groups of RLS suffers, restless controls (a primary insomnia group), and normal controls. There will be 10-15 participants recruited to each group. There are 3 primary dependent measures of mood with differing time periods. The Beck Depression Inventory (BDI-II), Positive and Negative Affect Schedule (PANAS), and a visual analogue scale (VAS). The PANAS will relate to affect during a suggested immobilization test (SIT) which will be used to provoke and measure RLS symptoms. The VAS will be concurrent with the SIT ad the BDI-II will measure depressive symptoms over a two week period. New actigraphy techniques will be used to measure PLMS over 4 nights at home. Between group differences will be analysed using ANOVAs for each of the 3 dependent variables. Initial analyses will reveal whether there are any covariates, whereby an ACOVA will be necessary. Bonferroni correction for multiple comparisons will be applied.

MRP Proposal

Investigating the Link between Depression and Restless Legs Syndrome: A Controlled Comparison of Mood and Motor Restlessness in Restless Legs Syndrome, with Restless and Normal Controls

Restless legs syndrome (RLS) is described by sufferers as creeping or tingling sensations mostly occurring deep within the legs, coupled with an inescapable desire to move the affected limbs. Movement brings only momentary relief and symptoms appear to get worse when at rest. Many people with RLS also complain of sleep disturbance related to the RLS symptoms occurring at night. It is usually the impact of the insomnia that leads people to seek treatment.

However, at present there is no cure for this condition and the aetiology has not yet been established. Current treatments include diet, exercise, iron supplement, and drug therapy such as dopamine antagonists and benzodiazepines. There are two kinds of RLS: primary and secondary. Primary or idiopathic RLS can have a childhood onset and slowly progresses, worsening with age. Secondary RLS usually occurs late in life and linked to medical conditions or side-effects of medication.

Phillips et al (2000) found a 10% prevalence rate of at least weekly RLS symptoms amongst adults in their population sample in North America. Hening et al (2004) estimated a prevalence of 9.6% of weekly occurring RLS symptoms in a large multi-national primary care population. Even so RLS remains under diagnosed and there is increasing research evidence demonstrating the negative impact of the condition on the sufferer's quality of life.

RLS can cause insomnia in sufferers of the condition. However this differs from primary insomnia or classic insomnia which is a psychophysiological disorder. With primary insomnia, people have mainly been conditioned not to sleep by sleep-preventing habits and this is then maintained by excessive worry about sleep (Morin & Espie, 2003). The proposed mechanism by which RLS sufferers have disturbed sleep is the increasing sensory discomfort as they lie at rest in bed and the compelling need to move their legs. Whilst those with primary insomnia may complain of

restlessness and hyper-arousal whilst trying to get to sleep this is quite separate from the specific symptoms of RLS which is a sensorimotor disorder. However is not yet known if the experience of restlessness in these two groups differs. A control group consisting of people with primary insomnia who complain of restlessness is therefore a useful comparison to decipher whether the impact of RLS on sleep, and consequently mood, is similar to that found in primary insomnia, or whether the motor restlessness compounds the difficulties common to RLS. The present study will therefore recruit three distinct groups: people with RLS; people with primary insomnia; and normal good-sleeper matched controls.

It is also thought that periodic leg movements during sleep (PLMS) may reduce the quality of sleep in RLS sufferers even if they are not occurring when the person is awake. PLMS are described as extensions of the big toe followed by dorsiflexions of the foot sometimes with flexion of the knees and hips (Michaud et al, 2001) and occur in 80% of RLS sufferers (Montplaisir et al, 1997). These movements can also be observed whilst awake during periods of inactivity. PLMS and periodic legs movements during wakefulness (PLMW) are usually measured by surface electromyogram (EMG) channels placed on the right and left anterior tibialis muscle. According to the scoring method, these movements last 0.5-10 seconds and are separated by intervals ranging from 4 to 90 seconds.

As with many other conditions, including sleep disorders, the rate of depression is higher in people with RLS compared to control groups (Sevim et al, 2004). Winkelmann et al (2005) compared rates of depression between people with RLS and a community sample of people suffering from other somatic conditions. The results suggested that RLS sufferers are at increased risk of psychological distress. This finding is important as it demonstrates that people with RLS could be more at risk of developing depressive symptomatology than people with other somatic conditions such as diabetes or cardiovascular disorders. The elevated rate of depression in RLS creates a problem for the clinical management of this group as antidepressants can aggravate restless leg symptoms. There is conflicting research in the literature, as well as expert opinion, about the effects of anti-depressant medication on RLS symptom severity and the use of dopamine agonists as antidepressants.

Depression is the mood disorder predominantly associated with RLS and therefore the impact of RLS symptoms on mood and positive and negative affect will be explored.

A clinical and neurophysiological study by Saletu and Colleagues (2002) looked at daytime brain function in RLS and Periodic Limb Movement Disorder (PLMD) compared to matched-controls and also investigated objective and subjective sleep and awakening quality in a subset of the sample versus controls. The EEG mapping revealed neurophysiological correlates of depression in RLS which was verified by self-report data. The greatest differences between RLS patients and controls occurred in the EEG measures that in depression showed the highest correlation to the Hamilton Depression score (the centroid of the delta/theta and alpha power and the dominant frequency and relative alpha 1 and alpha 2 power). They also revealed decreased sleep efficiency in the RLS group compared to controls, but there was no increased daytime sleepiness.

Hornyak et al (2005) investigated the relationship between RLS symptom severity, sleep disturbances, and depressive symptoms. They used questionnaire data from 100 people with idiopathic RLS who had attended their sleep clinic in order to compare self-reported sleep quality and depressive symptoms (measured by the PSQI and BDI respectively) with the International RLS Study Group Rating Scale (IRLS). They found that depressive symptoms in patients with RLS seemed to be related to subjective impairment of sleep ($r = 0.281$, $p = 0.007$) rather than to subjective reports of RLS severity ($r = 0.119$, $p = 0.237$). However it would be interesting to investigate whether introducing a more objective measure of RLS severity during the night would further explain the RLS-depression pathway. Also the use of a control group would help circumvent the problem of the overlapping sleep items on the BDI and IRLS.

The reason or reasons for the observed increased comorbidity of RLS and Depression is currently unknown. There are a number of possibilities.

Firstly, the Overlap in the symptoms of depression and RLS could lead to people being misdiagnosed. Of the nine symptoms of depression listed in DSM-IV, four of them could be a

consequence of RLS: insomnia/hypersomnia; fatigue; psychomotor agitation or retardation; and diminished ability to concentrate or indecisiveness. Only the presence of five out of nine symptoms, including depressed mood or anhedonia, for over two weeks, are required for a diagnosis of depression.

Secondly it could be that being depressed makes a person more sensitive to mild RLS symptoms and heightens the impact of RLS on the individual, but depression as a direct cause of RLS is questionable. More likely is that RLS is an independent risk factor for depression just as other sleep disorders have been found to be, due to the consequences of disturbed sleep and in severe cases a restriction on their lifestyle.

Lastly, another possibility is a neurological deficit that causes both symptoms of RLS and depression to happen simultaneously. Dopamine deficiency has been suggested to play a part in the aetiology of RLS and selective serotonin uptake inhibitor (SSRI) anti-depressant medication has been shown to worsen RLS, whilst a low dose dopamingeric agonist has improved symptoms (Teiv, Quadros, Barros & Wernech; 2002). It is unclear whether RLS and Depression comorbidity is a consequence of a common pathophysiological pathway.

The present study approaches the area of RLS and depression from the viewpoint of RLS being potentially an independent risk factor for depression. Below is an excerpt from a comprehensive book on RLS which provides insight into a RLS sufferer's experience:

> *"As I pass a window I peer at the outer, unfriendly impenetrable darkness. I wonder how many miles I've walked since sundown. A 26 mile marathon? I feel like it. Whatever is plaguing me holds tightly and does not want to let me go. What have I done to cause this? What is stealing my sleep every night and why? Like a slow, dreamy sleep walker, I crawl into bed. Tears seep from the corners of eyes. Maybe I do have witches blood in my veins like Jack says."*
>
> (From Wilson; 1996; p35)

This qualitative account clearly demonstrates the impact of RLS on this individual's mood and indicates some of the negative cognitions surrounding locus of control and helplessness. In order to investigate the association of RLS with depression, one of the possible mechanisms, sleep disturbance will be investigated, specifically, the role of periodic limb movements during sleep (PLMS). To further our understanding of the influence of motor restlessness on psychological distress, the level of positive and negative feelings will be explored by comparing those with RLS to restless controls and non-restless controls during an experimental procedure designed to elicit symptoms. The Suggested Immobilization Test (SIT) is used as a diagnostic test for RLS. Electromyogram (EMG) recordings are taken from both legs during a one hour period of voluntary immobility. RLS sufferers show three times more leg movements during the SIT than controls (76 ± 9.6 vs. 29.9 ± 16.6) (Montplaisir et al, 1998). In addition to being a useful assessment of the validity of our group allocation procedure, this test will be used to create the sensory experience of RLS in our participants in order to observe the direct impact on affect.

Watson et al (1987) found a significant correlation between the severity of depression and the number of apnoeas/hypopnoeas per hour of sleep. This is an important potentially confounding factor, as many people with obstructive sleep apnoea (OSA) have also been found to have elevated levels of depression and PLMS (Schröder & O'Hara, 2005). The focus of the present study is related to the influence of PLMS on levels of depression in RLS and therefore people suffering from OSA will be excluded.

By measuring the periodic leg movements in individuals with RLS during sleep we can explore what impact this has on subjective quality of sleep and level of depressive symptomatology. Hornyak et al (2004) investigated whether periodic leg movements in sleep (PLMS), measured by polysomnography (PSG), were associated with subjective quality of sleep in people with RLS, primary insomnia and secondary insomnia. They found a significant correlation between PLMS and subjective sleep quality in those with RLS (n=33) on the first night. It was not significant on the second night and they concluded that the first night result may be due to more superficial sleep as a result of being in the laboratory environment. However the night-to-night variability of the

PLMS index has been well-documented (Montplaisir et al, 1997). Monitoring PLMS over more than 2 nights and within the person's home environment may elucidate whether such an association exists.

Owing to new actigraph technology it is now possible to measure PLMS in a person's home environment. A new technique has developed by Cambridge Neurotechnology Ltd that measures Periodic Limb Movement (PLM) in both legs simultaneously by an actiwatch device on each foot, which is then combined to give an index of PLM (PLM per hour). This gives a direct objective measurement of movement in the lower limbs. Using actigraphy as apposed to polysomnography and EMG means that you can obtain measurements over a longer period of time, assessing of the night-to-night variability of PLMs, without the need for lengthy inpatient investigation.

In order to elucidate further the link between RLS and depression this study will measure positive and negative affect following a Suggested Immobilization Test (SIT) and whether there is a relationship to RLS severity. Assuming that sleep disturbance modulates the level of depression in people with RLS, this study postulates that PLMS play a role in the sleep disturbance in those with RLS and is correlated with severity of RLS and therefore with the level of depression.

AIMS AND HYPOTHESES

The aim of the present study is to compare levels of depressive symptoms, positive and negative affect in three groups: *RLS group* (RLS), *restless control group* (RC) and *non-restless control group* (NRC). In order to establish whether RLS is an independent risk factor for depression, taking into account PLMS, which may influence the level of sleep disturbance. The main hypothesis postulates that the groups will differ in levels of positive and negative affect following the SIT. The RLS group is expected to have higher levels of negative affect than RC group and NRC group. The NRC group will have higher levels of positive affect than the RLS and RC groups. There are a number of secondary hypotheses: a) higher PLM index scores as measured by actigraphy will be positively related to the level of depression reported on the BDI in the RLS group; b) the mean level of sensory discomfort score (MDS) during the SIT will be highest in the RLS group and

lowest in the NRC group and will be positively correlated with level of negative affect; c) participants with RLS will have a greater SIT PLM and PLMS index than RCs and NRCs. The RCs will have a greater SIT PLM and PLMS index than NRCs; and d) the PLM index will be negatively correlated with subjective reports of sleep quality in the RLS group.

In addition a subset of the sample will be examined using objective laboratory based tests to check that the methodology for separating those with and without RLS has been reliable.

METHOD

Design

The study employs a between-groups design. It will compare three groups: RLS group (RL), restless control group (RC) and a non-restless control group (NRC). The independent variables will be the presence or absence (depending on the group) of: (1) sleep disturbance, (2) "Restlessness", (3) motor disorder, and (4) primary psychiatric disorder. There are three primary dependent variables which consist of three different measures of psychological distress over different time periods: a retrospective measure, the BDI, will be used as a standard measure of depressive symptomatology over the previous two weeks; an attributional measure, the PANAS, looking at the feelings related to the 60 minutes duration of the SIT; and a concurrent measure of mood, a visual analogue scale, taken throughout the SIT.

Participants

The participants will be recruited for the study from the general population by advertisements inviting people fulfilling certain criteria to contact the researcher (see appendix for a flowchart of participant flow through the study). A telephone screening will establish those meeting the minimal diagnostic criteria as outlined by the International RLS study group, which state that RLS is characterised by *(1) an urge to move accompanied by unpleasant sensations in the legs and symptoms that (2) occur mostly in the evening and at night, (3) worsen during periods of rest, and (4) are relieved by movement* (Allen et al, 2003). Volunteers who provide written informed consent will enter the study and be allocated to one of three groups based on the outcome of the face-to-

face interview and their responses to the screening questionnaires: RLS group (RLS); restless control group (RC); or non-restless control group (NRC). Exclusion criteria screened for include: age, <18years old or >80years old; diagnosis of major depression or bipolar disorder; prescribed medication to aid sleep; sleep apnoea, kidney disease; and pregnancy. Those in the restless control group will complain of restlessness that affects the quality of their sleep but will not fulfil criteria for RLS (verified by a high score on the Pre-Sleep Arousal Scale; PSAS; Nicassio et al, 1985). The normal control or non-restless control group must have no motor problems or movement disorders and a score < 8 on the Insomnia Severity Index (ISI; Morin; 1993). A subset of the sample will be randomly selected for review by the Director of the University of Glasgow Sleep Research Laboratory to ensure that the grouping criteria are reliable.

Sample Size Estimation

Given that the relationship between SIT-PLM (as a measure of RLS severity) and psychological distress has not been directly compared in previous studies the effect size is unknown. The power of the present study will be increased by strict adherence to the grouping protocol in order to reduce within-group variability. Using data from the study by Saletu et al (2002) a very large effect size is found (f = 0.6) for the difference between PLS, PLMD and controls on measures of anxiety and depression. Therefore *a priori* sample size calculations for a one-way ANOVA design, using an effect size of 0.5 (a more conservative estimate), significance level set at 0.05 and standard power of 0.8, suggests a sample size of 14 per group. It is proposed that at least 15 participants will be recruited to each of the three groups and with a maximum of 20 in each group. These numbers are also similar to that in the study by Montplaisir et al (1998) who recruited 16 people with RLS with 16 age-matched controls, and detected a significant difference in SIT PLM (28.4 vs. 5.0; $p < 0.01$) and PLMS index (76.1 vs. 26.9; $p < 0.001$).

Measures

Screening and Group Allocation

Potential participants will be screened using the following measures:

- The IRLSSG essential criteria for RLS.

- Pre-Sleep Arousal Scale (PSAS; Nicassio et al; 1985)
- Insomnia Severity Index (ISI; Morin;1993)
- Sleep history questionnaire

For each participant the following data will be collected and reviewed before the groups are allocated.

- RLS severity (IRLSSGRS; The International Restless Legs Syndrome Study Group rating scale; 2003)
- Subjective sleep quality (PSQI Pittsburgh Sleep Quality Index ; Buysse et al; 1988)

Descriptive Measures

- Quality of life (SF-36)
- Other important information gathered at interview will include Alcohol, smoker/non-smoker, medical history, medications, BMI etc.

Hypotheses Testing

- Positive and Negative Affect (Positive and Negative Affectivity Schedule; PANAS; Watson et al; 1988)
- Depression (The Beck Depression Inventory Second Edition; BDI-II; Beck et al; 1996). Although the BDI has a strong somatic component, it has been commonly used in studies of RLS. However for the present study it shall be used as a secondary measure, with the PANAS being the primary measure.
- Visual Analogue Scales (VAS) as a measure of sensory discomfort in their legs throughout the SIT.

Experiment

Participants will be asked to complete a daytime Suggested Immobilization test (SIT) in which they will be instructed to sit on a bed at a 45º angle and not to voluntarily move their legs for a period of one hour. Every 5 minutes participants will be asked to rate the discomfort in their legs on a visual analogue scale (VAS). The descriptors on the 100mm horizontal line will be taken from an established VAS that was added to the standard SIT procedure by Michaud et al (2002a); ranging from “no discomfort” on the left to “extreme discomfort” on the right.. The 12 discomfort scores

will then be averaged to give a mean discomfort score (MDS). The MDS has been found to correctly classify 82.7% of all subjects in a RLS group and a control group with a sensitivity of 82% and a specificity of 84% (Michaud et al, 2002b). Periodic Leg movements (PLM) will be measured using electromyogram channels attached to the anterior tibialis muscles of both legs. The SIT PLM will be calculated in accordance with recent criteria defined by Michaud et al (2001). Criteria for scoring PLMS are appropriate for the SIT apart from leg movement duration which has been increased from 0.5-5s to 0.5-10s. A cut-off score for SIT PLM of 12 was found to have a sensitivity of 62% and a specificity of 84% and is recommend when testing people with varying levels of symptom severity (Michaud et al, 2002b). Participants will then be asked to rate their performance on the test on another VAS and current level of positive and negative feelings on the PANAS (Watson et al, 1988). The test will be taken by the participants in a 3 hour time period, to minimise the affects of individual differences in circadian rhythm.

Actigraphy

The participants' leg movements during sleep will be measured at home using the Actiwatch, produced by Cambridge Neurotechnology which is taped to each foot at the base of the big toe. The analysis software allows movements that occur simultaneously in both legs to be scored as a single movement. The adaptations made by Moorish et al (2002) to the American Sleep Disorders Association (ASDA) criteria for scoring PLMS normally measured by EMG during PSG will also be used in the present study in order to reduce the chance of artificially inflating the number of PLMS due to the lowest epoch being two seconds. Participants will be given instructions to wear the actiwatch devices on both feet for four nights and fill out a sleep diary each morning. Four nights will enable an average PLM index to be produced within a limited timeframe.

Confirmatory Measures

- Daytime Sleepiness (Epworth Sleepiness scale)
- The SIT PLM index, PLMS index and the MDS will also contribute to the confirmation of group allocation. NRCs should have a PLMS index < 10. RLS sufferers should have a SIT index > 12 and a MDS >11

- Those not meeting the above criteria will be excluded from the study.

Procedure

Volunteers will be screened by telephone using information regarding sleep history, medical history and restlessness. Potential participants who do not meet any of the exclusion criteria will be invited to attend the University of Glasgow Sleep Laboratory, where they will be given more information about the study and provide informed written consent before proceeding to the next stage - a face-to-face interview with the researcher and completion the self-report measures. At this stage any evidence of a sleep-related breathing disorder will require further assessment and review by the clinical team and will be withdrawn from the study. They will be either placed in the RLS positive group or the RLS negative group. A group of good sleeper controls will also be recruited in a similar way. Participants from all three groups will be asked to complete the Suggested Immobilization Test (SIT). The researcher will then set up the EMG equipment and carry out the necessary biocalibration procedure. Participants will rate their sensory discomfort and mood on a visual analogue scale every 5 minutes throughout the 1 hour duration of the test. After the test they will be asked to rate their affect during the SIT using the Positive and Negative Affect Schedule (PANAS; Watson et al; 1988). If the data from the self-report questionnaires indicate that they do not meet criteria for the allocated group, they will be re-allocated or excluded from the study. Following the SIT, participants will be given instructions regarding the use of the Actiwatches. They will be required to wear the Actiwatches on both legs for a period of four nights. They will also be required to fill in a sleep diary during this period. Following the actigraph measurement they will be asked to return with the monitors and diaries, when they will be given the opportunity to discuss and any problems. The actiwatch data will be electronically summed using PLM software designed by Cambridge Neurotechnology. The average PLM index for each participant will be calculated from all four nights' data. Data from the SIT and actigraphy will be used to confirm that the group allocation was accurate.

PRACTICAL ISSUES: SETTING, TIMING AND EQUIPMENT

Setting

Contact details will include a mobile number and an email address. The mobile will have answer machine set to ask for a name and phone number for those times when it cannot be answered. The appointments will take place at the University of Glasgow Sleep Laboratory at the Southern General Hospital. The participants will be able to use the actiwatch to monitor their sleep/leg movements at home.

Timing

The timing for the study once the main recruitment has taken place is estimated to be approximately 4 months based on recruiting 3 participants per week. This will largely depend on the number of Actiwatches we are able to obtain for the study and therefore how many participants may be going through the monitoring stage of the study.

Equipment

- EMG equipment and monitor
- Mini actiwatch from Cambridge Neurotechnology Ltd.
- PLM Software also from Cambridge Neurotechnology Ltd.

DATA ANALYSIS

Preliminary analysis will be conducted on the demographic data to check that the groups are similar. Any differences will be added as a covariate in the main analysis. Confirmatory analysis will be carried out on the screening measures to check that groups differ as appropriate on each of the independent variables. The main hypotheses will be tested by analysing the differences between the groups using three univariate ANOVAs for each of the 3 dependent variables. If a significant difference is found a Bonferroni correction for multiple comparisons will be applied to the analysis and the ANOVAs repeated. Also correlation analyses of the actigraph data in the form of the PLM index and subjective sleep quality, RLS severity and depression will be performed. If found to

significantly correlate with either of the dependent variables, PLMS will be introduced to the analysis and the ANOVAs will be modified to ANCOVAs were necessary.

ETHICS

- Informed Consent
- Confidentiality and data protection – anonymised data and secure data storage.
- Evidence of a severe affective disorder will be reviewed by the clinical team and appropriate referrals made.
- Evidence of a sleep-related breathing disorder e.g. sleep apnoea will necessitate further assessment which will be carried out by Prof. Espie.
- Ensure good instructions re actiwatch to prevent failure and wasting participants time
- Participant time kept to a minimum
- This is not an intervention study, however if there are concerns regarding any of the participants scores on the BDI their General Practitioner will be contacted.
- A feedback mechanism will be put in place to enable participants to gain more knowledge about the nature of their condition and its impact on sleep.

HEALTH AND SAFETY ISSUES

- Lone working: local NHS policy will be followed at all times.
- EMG electrodes are adhesive and may cause minor skin irritation.
    - Care will be taken when applying and removing the EMG electrodes.
- The Suggested Immobilization Test is expected to be challenging but not distressing for the RLS group.

FINANCIAL ISSUES

- A full costing checklist will be submitted separately for the study.

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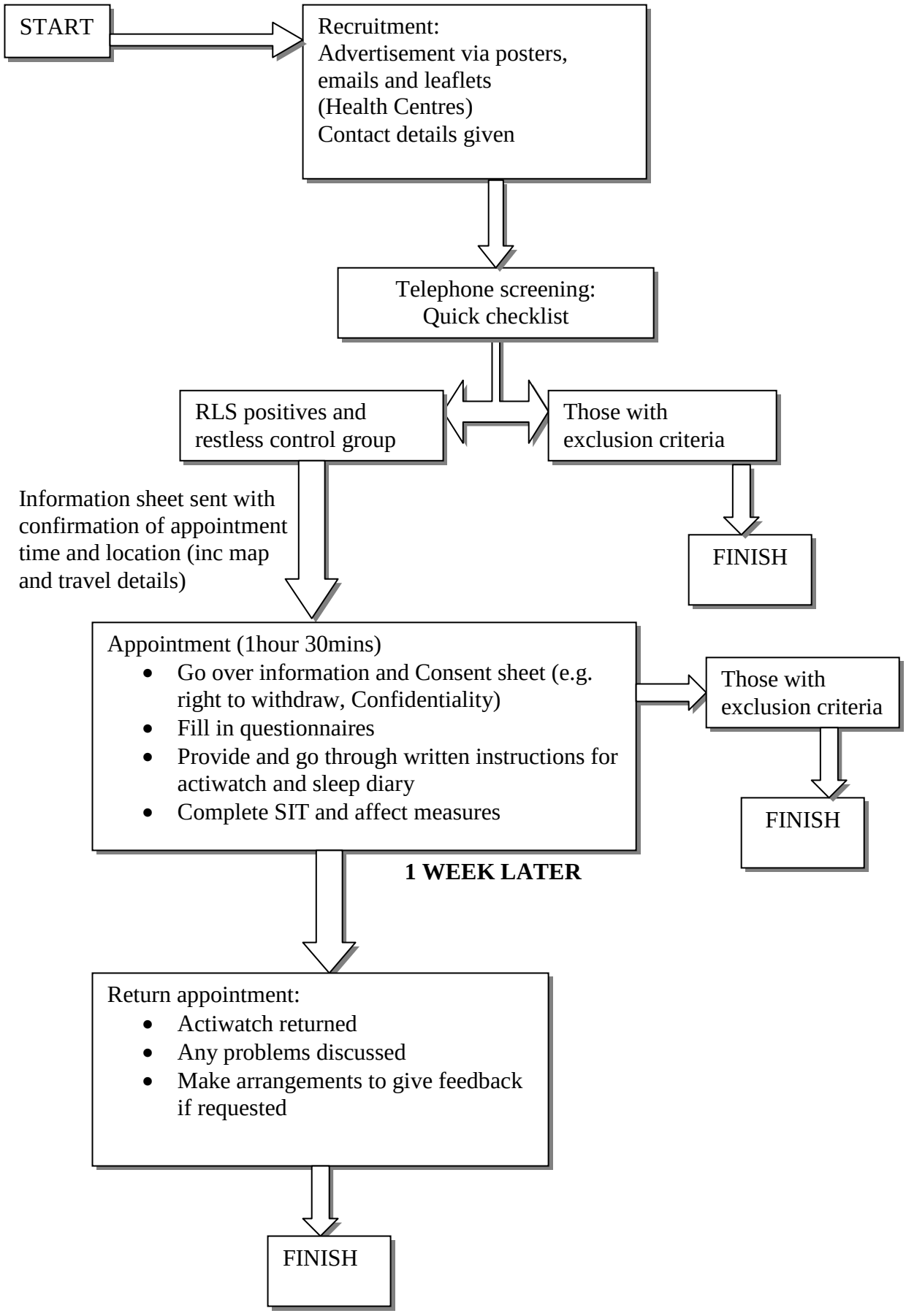
***Appendix**: Flowchart of Participant flow through the study*



ETHICS APPROVAL LETTER

Primary Care Division

NHS
Greater Glasgow and Clyde

Research Ethics
R&D Directorate
Gartnavel Royal Hospital
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www.nhsggc.org.uk

Mrs Lisa Galloway
Trainee Clinical Psychologist
University of Glasgow
Section of Psychological Medicine
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH

Date 11 September 2007
Your Ref
Our Ref
Direct line 0141 211 3824
Fax 0141 211 3814
E mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Mrs Galloway

Full title of study: **Investigating the Link between Depression and Restless Legs Syndrome: A Controlled Comparison of Mood and Motor Restlessness in Restless Legs Syndrome, with Restless and Normal Controls.**

REC reference number: **07/S0701/92**

The Research Ethics Committee reviewed the above application at the meeting held on 06 September 2007. Thank you for attending to discuss the study.

Ethical opinion

Members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation subject to the following issues being clarified to the Committee Co-ordinator as soon as possible.

1) The Participant Information Sheet should indicate that the EMG procedure could be potentially painful. A new PIS should be submitted.

2) The data should be retained for 5 years and not 3 years as indicated at Question A.44.

3) Question A39 - the use of a home computer is not allowed. This must be a computer in a secure workplace setting.

4) The Consent Form is not standard, i.e. the Yes/No answers should be boxes. A standard Consent Form can be found on the NRES website.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Application		
Investigator CV		
Protocol		
Covering Letter		19 August 2007
Advertisement	Version 1	17 August 2007
Participant Information Sheet	Version 1	17 August 2007
Participant Consent Form	Version 1	17 August 2007
Approval Letter Prof T McMillan		23 July 2007
Supervisor's CV	Prof Colin Espie	

R&D approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final approval from the R&D office for the relevant NHS care organisation.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/S0701/92 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Liz Jamieson

Liz Jamieson
Research Ethics Committee Co-ordinator on behalf of Dr Paul Fleming, Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
Standard approval conditions
Site approval form (SF1)

Copy to: *Mr Brian Rae,* R&D office for NHS care organisation at lead site

UNIVERSITY of GLASGOW

NHS Greater Glasgow and Clyde

PARTICIPANT INFORMATION SHEET

Investigation of the Link between Restless Legs Syndrome and Mood.

Introduction

You are invited to take part in a research study that is being carried out by the University of Glasgow. Before you decide, it is important for you to understand why the research is being carried out and what is involved. Please take some time to read the following carefully and discuss it with friends and relatives if you wish. Please ask if you would like more information or if there is anything that is not clear.

What is the purpose of the study?

Restless legs syndrome (RLS) can impact sufferers in a number of ways. We want to investigate further the impact of RLS on sleep quality and mood. It is important to understand how this condition affects sleep and mood. We want to find out whether people with RLS differ from others suffering from insomnia in their levels of positive and negative feelings. It is hoped that this study may increase awareness of the difficulties faced by sufferers of RLS.

Why have I been Chosen?

People who complain of the symptoms of RLS are invited to take part in the study. These are defined as: *(1) an urge to move accompanied by unpleasant sensations in the legs and symptoms that (2) occur mostly in the evening and at night, (3) worsen during periods of rest, and (4) are relieved by movement.*

We will also need some people to take part in the study who do not have any of the above symptoms in order to compare results.

Do I have to take part?

It is entirely up to you whether you take part or not. If you decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part, you will be contacted by the main researcher by telephone. Whether you are selected to take part in the study will depend on your answers to a number of questions. If selected at this stage you will be invited to the University of Glasgow Sleep Research Laboratory (Southern General Hospital) for a short interview and asked to fill out some questionnaires. We will then carry out a test (Suggested Immobilization Test; SIT) that

would be helpful to wear baggy clothing so that you are more comfortable. We will ask you to rate your discomfort and mood during and immediately following the test. The final stage of the study involves wearing a small device called an actiwatch at the base of the big toe for three nights and filling in a sleep diary each morning. You will be given full instructions before taking the device home. You will be asked to return the device and diaries to the sleep laboratory and given the opportunity to discuss any queries or problems.

What will the researcher do with the information?

The researcher will write a research dissertation on the effects of RLS on mood and sleep for the University of Glasgow, and will also aim to publish the results of the study in a relevant scientific journal. If you would like a summary of the results of the study, the researcher will provide you with one.

Will my taking part in the study be kept confidential?

Your identity and personal information will be completely confidential and known only to the researcher.

What are the possible disadvantages or risks of taking part?

There are no risks or disadvantages of taking part**.** However you might experience some discomfort when the electrodes are removed, much in the same way as removing a plaster.

What are the potential benefits of taking part?

The Suggested Immobilization Test is a reliable diagnostic test for RLS. Taking part in the study will provide further assessment of the condition and give an objective measure of symptom severity.

Who is organizing and paying for the research?

This research study is organised by Lisa Galloway, Doctoral Research Student (University of Glasgow), and funded by University of Glasgow. Educational supervision of this research is provided by Professor Colin Espie, University of Glasgow.

Contact for further information

If you have any questions about the study please contact Lisa Galloway at the:

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1345 Govan Road
Glasgow
G51 4TF
Email: restlesslegssyndrome@googlemail.com
Telephone: 07514 404 516

Thank you for your time and co-operation.