The Relationship Between Psychosocial Stress and 5-HTTLPR: Implications for the Workplace.

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Abstract

Current research on the relationship between the genetic marker 5-HTTLPR and psychosocial stress, shows a large amount of variation in the reported results between studies. In this thesis four meta-analyses using 14 independent samples were conducted to provide a consensus for these previous results and to provide a basis for how these varying results could be applied to the workplace.

All four meta-analyses used hedges g as the effect size and reported very small, negative effect sizes. Although the effect sizes were small, the negative direction indicates that the L/L 5-HTTLPR genotype has slightly greater cortisol reactivity to psychosocial stress. The limited amount of literature on 5-HTTLPR and psychosocial stress needs to be considered when reviewing the results as it is difficult to tell whether the small effect sizes are due to chance or if they are an accurate reflection.

The small effect sizes also mean that utilising these results in an organisational context is difficult as the relationship between 5-HTTLPR and psychosocial stress is not statistically significant. 5-HTTLPR is only one genetic marker out of hundreds so while psychosocial stress may have a statistically significant relationship with another marker, this has not been found yet. As a result of this, subjective measures of stress such as surveys are likely to continue to be more useful in identifying the stress levels of individuals in the workplace, rather than making inferences based on the 5-HTTLPR genotype of the individual.

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1 Chapter 1

Introduction and Literature Review

1.1 Overview of Chapter 1

This chapter provides background information on the topics integral to understanding the usefulness of this meta-analysis, and reviews relevant research. There is a focus on stress and its relevance in the workplace, and an additional focus on biological concepts such as genetic markers.

1.2 Stress in the Workplace

Stress is not a new concept however, it is becoming increasingly common in the workplace as work has become more complex, demanding, and technologically dependent. The side effects of stress, such as illness and absenteeism are very costly for organisations, making workplace stress an area of huge importance.

Several models have been proposed to explain the relationship between work and stress. The Job-Demand-Control (JDC) model theorised that the potential strain of a job could be predicted by the level of demand in the job, and the control the individual had over that demand (Karasek, 1979). The JDC was updated to become the Job-Demand-Support-Control (JDSC) model by Johnson & Hall, (1988). The JDSC included support as a way of improving the validity of the original model. In the JDC model, high strain jobs would involve high demand on the individual but they would have low control, while low strain jobs would have low demand and high control. There were two other categories of jobs; active and passive. Active jobs have high demands on the individual but the individual also has a high-level of control over the job, whereas, passive jobs involve low demands and low control. This model predicts that individuals in low strain jobs would be the healthiest, while those in high strain jobs are most at risk for illnesses. Passive jobs would not be challenging and this could become stressful, while active jobs would be challenging but the control would mediate the effect of the high level of demand. However, this control only refers to control over tasks in the job, not control over other aspects such as career opportunities or job security (De Bacquer, et al., 2005).

Other models have been put forward to explain the major causes of stress at work. A classification was developed by Cooper, Cooper, & Eaker (1988) that suggested stressors could be fitted within a six-factor model. These factors were; factors intrinsic to the job, role factors, relationships at work, career development, organisational factors, and the work-life relationship. Intrinsic factors referred to the content and context of the job, such as the quality and quantity of the work, and the conditions of work. Role factors referred to the aspects of job performance and the content of jobs. Relationships at work referred to the formal and informal relationships that individuals form with peers, supervisors and subordinates. Career development dealt with issues that arise around competition, opportunities for promotion, and appraisals. Organisational factors focused on the organisational culture and climate. The work-life relationship referred to the conflicting demands that work and personal life can have on an individual (Devonport, 2011).

1.2.1 Social Representation Theory and Social Identity Theory

Current research on workplace stress is utilising Social Representation Theory (Moscovici, 1984) and Social Identity Theory (Tajfel & Turner, 2004) to explain why individuals find some situations more stressful than others. Social Representation Theory suggests that when a group of individuals interacts frequently, they develop a shared system through which they view the world in similar ways. These similar views are often reflected in the culture of the group. There may be many separate 'common cultures' throughout an organisation as there are usually multiple groups, e.g. Management, individual departments, and individual teams. This theory helps to explain why individuals tend to behave in similar ways when in a work setting. Social Identity Theory suggests that an individual's sense of who they are is influenced by the groups that they belong to. This implies that an individual's behaviour in certain situations will be influenced by how strongly they identify with that group. Social Representation Theory and Social Identity Theory consider factors that might cause stress, which are outside of the factors that directly affect the individual. For example, in an organisation, a specific group, might feel undervalued or overworked, and this would be a source of stress to those individuals within that group.

1.3 Psychosocial Stress

Social Representation Theory and Social Identity Theory both link into the concept of psychosocial stress. Psychosocial stress arises from a cognitive appraisal of a perceived social threat, and the realisation that the threat may require resources that are not available to the individual (Caplan, 1985). Potential stressors include threats to social status, social-esteem, acceptance or rejection from a group, or a threat to an individual's self-worth (Spector & Jex, 1998).

These stressors threaten an individual’s ‘social-self’ and often invoke shame as the main emotional response, particularly when there is a decrease in an individual’s social status or social value, which can lead to social isolation (Dickerson, Gruenewald, & Kemeny, 2004). Several studies have looked at the effect that social isolation at work has on an individual. Wells (2018) found that individuals who were socially isolated at their work involuntarily, felt acute shame, a loss of respect and dignity, and had greater risks of mental health issues. The lack of respect and dignity as a result of social isolation at work often led to a decrease in individual’s self-esteem (Arora, 2013).

In a work-related context, psychosocial stress is an issue many individuals face as increasing emphasis is placed on managing and maintaining relationships with peers, subordinates, and supervisors, over and above the actual work in a role (Godlin & Kittel, 2004). These increased expectations can cause individuals to perceive that they do not have enough support to cope with the increasing demands on them. The lack of perceived support means that many stressors are perceived as threats rather than challenges that can be managed.

Many previous studies highlight the significant effect psychosocial work stressors have on employees. Clausen & Borg, (2010) found that psychosocial stressors in the workplace significantly predicted employee turnover, while Pal & Savsvik (2008) found that there was a correlation between work-family conflict, and the severity of stress felt by employees at work. Increased psychosocial stressors are also often associated with high levels of work-place bullying (Tuckey, Dollard, Hosking, & Winefield, 2009., Agervold & Mikkelsen, 2004), as well as a significantly increased likelihood of developing depression (Seigrist, 2008).

The effects of psychosocial stress extend further than just the workplace, as prolonged stress can increase the risk of contracting a range of health problems. Jansson & Linton (2006) found that individuals who had highly demanding work had a significantly increased risk of developing insomnia, compared to those who had low work demands, or those who had high levels of leader support. Low autonomy and high demands at work were also related to the continuation of insomnia. This was corroborated by Akerstedt, et al., (2015) who found that high demands at work increased the likelihood of disturbed sleep, and this was mediated by psychosocial stressors within the workplace such as social isolation and interpersonal conflict. Poor health symptoms were also associated with work to family conflict, while the organisational culture and values mediated the influence of psychosocial stress in the workplace (Hammer, Saksvik, Nytro, Torvatn, & Bayazit, 2004). Higher levels of psychosocial stress significantly contributed to the development of musculoskeletal disease, a condition which is costly to both the employee and the employer (Bongers, Kremer, & Laak, 1997).

1.4 Objective Stress Measures and the Trier Social Stress Test

With psychosocial stress having such varied and far reaching effects, there is a need for researchers and organisations to be able to collect accurate data and monitor the stress levels of employees (Sulsky & Smith, 2005). Current methods in organisational psychology tend to rely on subjective methods, such as surveys or interviews to collect this data. These methods allow for data to be collected easily and quickly but pose a range of problems to the validity and reliability of the data collected. Self-report measures such as surveys are prone to social desirability bias, where respondents tend to answer in a way that will be viewed favourably by others, which skews the results (Paulhus, 1991). In the workplace this poses a serious problem as respondents may either underestimate or overestimate how stressed they are, depending on what the accepted and expected attitudes are within the organisation.

Although subjective measures do have several issues, there are also issues with the objective measures of stress that have been commonly used in organisational psychology. Objective measures of stress in organisational psychology have largely relied on work-related outcomes, such as the absenteeism rate, the utilisation rate of employee assistance programmes, employee performance, and turnover rate amongst many others (Gupta & Beehr, 1979). While these measures are appealing because they provide objective and quantifiable data, it is impossible to claim stress as the sole causal factor of these measures as factors such as person-work fit and organisational culture can influence these measures (Spector P. E., 1998,. Westman & Etzion, 2001).

Outside of organisational psychology, these objective measures of stress are usually based on physiological changes that are linked with stress, to determine the level of stress present. These measurements usually only measure physiological changes, and do not consider the differences in how individuals feel stress. In biological research these measures include measuring heart rate variability, or measuring cortisol levels in blood or saliva, and tend to be far more invasive and time consuming than subjective measures such as surveys as they can involve blood tests or using heart rate monitors (Sulsky & Smith, 2005).

The Trier Social Stress Test (TSST), is currently considered the gold standard for objective stress testing (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014). The TSST involves taking cortisol samples at regular intervals to establish a baseline cortisol level, and then exposing participants to stressors. The stressors used in the TSST are forms of external stimulation that induce acute psychosocial stress.

As described above psychosocial stressors typically involve events which appear to pose a social threat to the individual (Frisch, Hausser, & Mojzisch, 2015). These stressors can include events such as performance reviews at work, difficulties with friendships and work relationships, and work place bullying. Each event translates as a perceived threat to the individual's social status, social esteem, respect and acceptance within a group, or as a threat to the individual's self-worth (Blom, 2012., Gruenewald, Kemeny, Aziz, & Fahey, 2004). In the case of the TSST, the stressors used involve the potential for public humiliation if the individual is unable to perform the task that has been assigned to them. This could be perceived as a threat to the respect the individual might get from the panel, as well as a threat to the individual's self-worth (Dickerson, Gruenewald, & Kemeny, 2004).

Once participants have been exposed to the stressors, cortisol samples are taken at specific time intervals afterwards to establish whether there was a significant increase in cortisol levels due to the stressor. The stressors used in the TSST are public speaking and mental arithmetic, both of which are conducted in front of a panel (Von Dawans, Kirschbaum, & Heinrichs, 2011). If the TSST is being used in conjunction with any subjective psychological measures such as surveys, these are administered both before and after the TSST (Hellhammer & Schubert, 2012).

Versions of the TSST where more support is available to the participants, either in the form of a friendlier panel, or the presence of a friend or dog, do not activate the stress response to the same extent that the normal TSST does

(Wiemers, Schoofs, & Wolf, 2012., Polheber & Matchock, 2013). The psychosocial stressors (and perceived threats) in the TSST are similar to situations and tasks that arise in the workplace, so the TSST was the best stress test to use to maximise generalisability of the results of the meta-analysis to the workplace.

1.5 The Biology of Stress Measurement (need to define genotypes)

Although common among psychological literature, stress is not solely a psychological phenomenon and the ability to measure stress objectively outside of organisational psychology is based on several biological processes. Stress occurs as part of the ‘fight or flight response’, which has four main steps. The flight or fight response is initiated when a stressor is encountered that could pose a threat to the individual, such as the potential for physical harm, or having to give a speech in public. This triggers the release of a series of hormones between the hypothalamus, pituitary gland, and adrenal glands (HPA axis), which results in the production of another hormone called cortisol (Hermana & Cullinanb, 1997). Cortisol can be used as a way of measuring stress, particularly in the TSST, as cortisol contributes significantly to the flight or fight response by elevating the sugar levels in the bloodstream as adrenaline is released. Cortisol also acts as the control which turns off the production of hormones in the HPA axis. When cortisol exceeds a certain level, it prevents the production the main hormones in the HPA axis, which in turn prevents cortisol itself from being produced (Miller, Chen, & Zhou, 2007).

When an individual is repeatedly exposed to stressors over a short period of time, the level of cortisol required to turn off hormone production increases, which can lead to several health problems as both heart rate and blood pressure remain elevated for longer periods of time (Bremner, 1999). Increased levels of stress can also lead to increased vulnerability to a wide range of mental health conditions such as anxiety and depression (Schulz, et al., 2011).

1.6 5-HTTLPR

5-HTTLPR has been a genetic marker of great interest to researchers in for some time. It is found in a section of DNA within one of the serotonin genes (SLC6A4). This section of DNA is found within a region of the gene that is responsible for controlling production of a protein, which is a major step in the production of serotonin.

5-HTTLPR has two variations in humans - a short (s) and a long (l) variation. These variations are called alleles, and each individual has two alleles of the same gene. In this respect, an individual can be; homozygous for the short allele which is where they have two short alleles, homozygous for the long allele which is where they have two long alleles, or heterozygous which is where the individual has one short and one long allele (Yip, 2002). This is important to note as differences in the combination of alleles can affect individuals quite differently. This combination of alleles is called an individual's genotype.

Several studies have looked whether one of the different combination of 5-HTTLPR alleles could be a potential factor that indicates predisposition to a range of conditions such as chronic fatigue, depression, anxiety, and stress. Meyer, et al., (2015) studied the relationship between 5-HTTLPR genotypes and maintenance of Chronic Fatigue Syndrome (CFS), using 120 youth who had been diagnosed with CFS. This study found that individuals who were homozygous for the short 5-HTTLPR allele had worse outcomes with CFS maintenance than those who were heterozygous, or homozygous for the long 5-HTTLPR allele.

Differences within the 5-HTTLPR genotype have returned mixed results in relation to depression. Veterans who had the short allele had a significantly higher risk for adjustment after combat, and reduced quality of life, than those who were homozygous for the long allele (Ashley-Koch, et al., 2015). Queirazza & Cavanagh, (2014) found that while variations within 5-HTTLPR may be involved in post-stroke depression, this variation is unlikely to have a significant effect on the severity of depression. A meta-analysis which reviewed 14 studies on the interaction between 5-HTTLPR, stressful life-events, and depression found no evidence that any of the 5-HTTLPR genotypes were associated with an increased risk of depression. These was no sex-specific effect, nor was there an interaction effect between 5-HTTLPR genotype and stressful life-events (Risch, et al., 2009). Another study found that individuals who were homozygous for the short allele, had a greater vulnerability to depression that those who were heterozygous or homozygous for the long allele (Beevers, Scott, McGeary, & McGeary, 2009).

The 5-HTTLPR allele variations have also been linked with issues in the workplace. Wirtz, et al., (2013) found that individuals with short alleles were more likely to over commit at work, and in turn this increased the risk of developing depression. Differences between the 5-HTTLPR genotype have also showed significant interaction effects with job-related stress (Huang, et al., 2014). Individuals with short alleles had a significantly increased risk of developing insomnia, in conditions where there was perceived to be high-levels of job-related stress. This risk increased significantly again for individuals who were homozygous for the short allele rather than heterozygous (Huang, et al., 2014).

Conversely in another study, individuals who were homozygous for the long allele were more likely to develop anxiety disorders when frequently exposed to high-levels of job related stress (Long, et al., 2013).

There is a large amount of variation in the current research on 5-HTTLPR and whether or not it indicates a predisposition to anxiety, and depression. The current research on 5-HTTLPR and psychosocial stress also shows a large amount of variation, indicating the need for a meta-analysis to summarise and condense the results.

1.7 Why do a Meta-Analysis?

Over time large volumes of research is generated on any given area, which makes it difficult to summarise and analyse by both researchers and practitioners. However, for researchers and practitioners to remain up to date in their field they need to be able to acquire this knowledge (Field & Gillett, 2010). Meta-analyses use data from several independent studies that address the same question, to produce an estimate of the relationship between two variables (Hunter & Schmidt, 1990). This estimate is generated by statistical analysis from the data from all of the studies included in the meta-analysis. The role of the meta-analysis is to statistically summarise the available data, thereby reducing the quantity of data to be sorted through by researchers and practitioners (Field & Gillett, 2010). In this respect, meta-analyses can add great value to any area of research where there are conflicting and confusing results, and are more useful for concisely summarising results than systematic reviews. A systematic review refers to the entire process of collecting, reviewing, and presenting the available evidence, whereas a meta-analysis refers to the statistical method of combining data to produce a summarised result (Gopalakrishnan & Ganeshkumar, 2013).

Meta-analyses are also able to provide a statistically stronger conclusion than an analysis of a single study, due to the increased number of subjects, and accumulated results. This is particularly useful in areas of research where significant results have not been found in multiple studies. In this case, single studies may not be reliable enough to detect differences between two treatments, populations, or samples. By using multiple studies, different populations are integrated into the analysis which accounts for different variations between groups, as well as reducing the risk of incurring Type I and Type II errors (Freiman, Chalmers, Smith, & Kuebler, 1978). Meta-analyses use statistical analyses to create a weighted effect size for each study. Each effect size is then added together and an average is calculated. By weighting the effect sizes using the inverse of the variance, meta-analyses can avoid skew in their results caused by the uneven sample sizes between studies in a meta-analysis (Field & Gillett, 2010).

1.8 Aims and Objectives

There are three main aims of this thesis;

1) To summarise the previous research surrounding relationship between psychosocial stress induced by the TSST, and the 5-HTTLPR genetic marker by calculating an average weighted effect size,
2) To highlight the relevance of genetics in relation to psychosocial stress in the workplace, and make recommendations on how this research could be utilised in the workplace.

3) And to discuss the implications of this research and make recommendations for future research.

2 Chapter 2

Materials and Methods

2.1 Data Set

A total of 9 studies were analysed in this meta-analysis. These studies consisted of published articles (n=8), and a Doctor of Philosophy thesis (n =1), and were found in a literature search that extended between December 2016 and August 2017. One article had two separate data sets, which were calculated as separate studies in the meta-analysis. All studies included used cortisol responses to a Trier Social Stress Test to analyse the effect the different 5-HTTLPR genotypes had, on psychosocial stress in humans. The TSST used in 8 of the 9 studies included in these meta-analyses did not have any alterations to the usual format. The 9th study included a condition where the TSST was performed in front of an evaluative audience, and a control condition where no audience was present (Way & Taylor, 2010). Effect sizes (Hedge’s g) and standard deviations were calculated for each study, and were then used to calculate an overall, average effect size.

Although there were only a small number of studies used in this meta-analysis, there are several justifications for this. Firstly, the subject area being reviewed in this analysis is still quite small and there are limited studies available for analysis. This was further compounded by being unable to get raw data for two studies for this analysis. Secondly, a meta-analysis does not need many studies to be statistically reliable or valid. Valentine, Pigott, & Rothstein (2010), suggested that a meta-analysis only needs a minimum of two studies, however this does change depending on the size of the samples within each study, as weighted effect sizes are often calculated using sample sizes. This issue has been eliminated as the inverse of the variance is used to calculate weighted effect sizes, preventing extreme skew towards larger studies. The current meta-analysis has 9 studies, with 14 independent samples, which coincides with calculations made by Higgins, et al., (2011) that show that a minimum of 10 independent samples are required to test for bias in a meta-analysis by funnel plot. Thirdly, while there are only a small number of studies, the results vary between these studies. This provides an opportunity to conduct a meta-analysis to provide a consensus of the effect 5-HTTLPR genotype has on the cortisol response in individuals exposed to a psychosocial stressor.

2.2 Search Strategy

Studies were searched for between December 2016 and August 2017 using four databases; PsycINFO, Web of Science, Google Scholar and Research Gate. The search terms used were stress*, Psychosocial stress*, 5-HTT*, 5-HTTLPR, gene*, coping, and cortisol. The exclusion and inclusion criteria below provides further explanation on how these search terms were used to find studies for inclusion. All retrieved studies had their bibliographies and citations reviewed for relevant studies. Meta-analyses in relevant areas also had their bibliographies and citations reviewed.

To offset the publication bias, previous theses and dissertations at New Zealand Universities were searched through for relevant studies. Research Gate was also used to find other unpublished studies. All English Language studies published up until August 2017 were considered, to determine whether they met the inclusion or exclusion criteria.

2.3 Inclusion and Exclusion Criteria

Potential studies were reviewed in three parts. An initial cut was made based on the title of the articles, a second cut was made after reviewing abstracts of the articles, and a third and final cut was made after reviewing the full text of suitable articles. Studies only progressed past each cut if they met at least one of the inclusion criteria, and none of the exclusion criteria. Studies included in the meta-analysis had to meet all the final inclusion criteria, and none of the exclusion criteria. Three databases were used to find studies suitable for this meta-analysis. The primary searches were conducted in PsycINFO, Web of Science, and Research Gate. Google Scholar was used for as a secondary search tool, if the full text was not available in any of the other three databases.

2.3.1 Initial Review Exclusion Criteria

In the initial stage, studies were excluded if they met any of the following criteria;

1. The study used non-human subjects.
2. The participants were children under 18 years old.
3. The paper focussed on a specific group such as those with autism, cardiac disease, or insomnia.
4. The study was on an unrelated topic such as post-traumatic stress disorder (PTSD) or fear conditioning.
5. The study looked solely at a topic other than stress.

Studies that used non-human subjects and children under 18 were excluded as the purpose of this meta-analysis was to make inferences relevant to the workplace. Studies that targeted specific groups such as those with cardiac disease or autism were excluded so that the results would be more applicable to the general population.

2.3.2 Initial Review Inclusion Criteria

Studies had to meet at least one of the inclusion criteria for the abstract to be reviewed. The inclusion criteria were;

1. Not one of the exclusion criteria was met.
2. Both search terms were in the title or the title had terms which were synonyms of the search terms.
3. The study was a meta-analysis of a similar topic.
4. Acute or psychosocial stress was mentioned in relation to genes in the title.
5. Serotonin gene and stress were mentioned in the title.
6. Risk factors and stress were mentioned in the title.
7. Cortisol was mentioned in the title.
8. Depression or anxiety were mentioned in the title in conjunction with stress.

Meta-analyses and systematic reviews were kept so that the bibliographies and citations of each could be reviewed for potential studies, however, they were not included in this meta-analysis. Depression and anxiety are often studied in conjunction with stress, so any titles that included these terms with stress were kept for further review.

2.3.3 Secondary Review Exclusion Criteria

Once the initial review was finished, the selected articles had their abstracts analysed. Articles were excluded if they met any of the following criteria;

1. The study was solely a mediator or moderator study.
2. The abstract specifically mentioned that the Trier Social Stress Test (TSST) or similar was not used in the method. Studies were included if the TSST was mentioned, or if no methods were mentioned.
3. Emotional coping was being studied rather than stress.
4. Any gene or genetic marker other than SCL6A4 or 5-HTTLPR was mentioned as the sole focus of the study.
5. The topic was unrelated to stress and genetic markers.

Studies that looked at emotional coping were excluded if they did not also look at stress, as emotional coping is the regulation that occurs after the stress response, rather than the stress response itself. Studies were also excluded if they only looked at genetic markers other than 5-HTTLPR. Studies which mentioned the SCL6A4 gene in the abstract were not excluded as this is the gene where 5-HTTLPR is located.

2.3.4 Secondary Review Inclusion Criteria

Studies were kept for a review of the full article if they met at least one of the follow inclusion criteria;

1. It did not meet any of the exclusion criteria.
2. There was no abstract provided.
3. The topic was relevant.

4. The TSST or similar was specifically mentioned, in relation to the Serotonin gene/5-HTTLPR.

If a study did not meet any of the exclusion criteria, but also did not meet any of the inclusion criteria, a judgement call was made on whether the full article was reviewed based on the relevance of the abstract to the topic, and the relevance of similar abstracts already reviewed. Studies that had no abstracts were searched for using Google Scholar.

2.3.5 Final Review Inclusion Criteria

Studies were included in the meta-analysis if they met all the following criteria;

1. The Trier Social Stress Test (or similar) was used in the research design.
2. Saliva or blood cortisol samples were taken.
3. The gene being studied was 5-HTTLPR.
4. Polymorphisms within the 5-HTTLPR gene were genotyped.
5. The study had enough statistical information to calculate Hedge’ and variance.
6. The population sample was unique.

These inclusion criteria were important to ensure that all studies used in the meta-analysis were as similar as possible, to avoid confounding variables.

2.3.6 Final Review Exclusion Criteria

Studies were excluded from the meta-analysis if they met any of the following criteria;

1. Not all the inclusion criteria were met.
2. The research design, validity, or reliability of the study was poor.

3. The full article was not available, e.g. Conference abstract.
4. The topic of the article was unrelated to this meta-analysis.
5. The study only looked at anxiety, depression, or emotional coping, rather than stress.
6. The study did not look at acute stress or psychosocial stress.

2.4 PsycINFO

Table 1.

Search terms used, and results obtained from the PsycINFO database.

Search string	Search terms	Number of results	Abstracts reviewed	Full text reviewed	Studies included
1	Stress*, 5-HTTLPR.	400	41	23	4
2	Psychosocial stress*, 5-HTTLPR.	44	8	6	1
3	Gene*, Psychosocial stress*, Human studies only.	5964	0	0	0
3b	5-HTTLPR	42	0	0	0
4	Coping, 5-HTTLPR*.	21	5	0	0
5	Cortisol, Stress*	7812	150	0	0
5b	5-HTTLPR.	443	15	4	0

The initial search was carried out in PsycINFO. This consisted of five sets of search strings being used, all of which were sorted by relevance rather than publication date. Table 1 summarises this information. The third search and fifth searches conducted returned over 5000 results which were too many to review, so the both searches were further narrowed down using another search term. This is shown under 3b and 5b in Table 1. The full term ‘5-HTTLPR’ was used when searching abbreviations of this did not return any results.

2.5 Web of Science

The second search was carried out using Web of Science. This search engine searches through the Web of Science Core Collection, Current Contents Connect, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index.

Web of Science did not have the option of searching in any field as PsycINFO did. Instead duplicate searches were performed, searching in both the topic and title fields. All search items were sorted by relevance rather than publication date. Table 2 summarises this information.

Similar to PsycINFO, three searches in Web of Science initially returned more results that was feasible to review. All three of these searches were further narrowed down using the search term ‘5-HTT*’. 5-HTT* was used over the longer 5-HTTLPR as it returned more results, and included results that mentioned the serotonin transporter (or 5-HTT), as well as those that mentioned the serotonin transporter polymorphic region (or 5-HTTLPR). These searches are shown as 7b, 9b and 10b in Table 2.

Table 2.

Search terms used and results obtained from the Web of Science database.

Search string	Search terms	Search field	Number of results	Abstracts reviewed	Full texts reviewed	Studies included
1	Stress*, 5-HTT*	Topic	952	47	20	2
2	Stress*, 5-HTT*	Title	135	17	3	1
3	Psychosocial stress*, 5-HTT*	Topic	78	10	0	0
4	Psychosocial stress*, 5-HTT	Title	5	0	0	0
5	Acute stress*, 5-HTT*	Topic	57	5	1	0
6	Acute stress*, 5-HTT*	Title	5	0	0	0
7	Gene*, Psychosocial stress*	Topic	4751	150	0	0
7b	5-HTT*	Topic	76	6	1	0
8	Gene*, Psychosocial stress*	Title	61	4	0	0
9	Cortisol*, Stress*	Topic	30,060	n/a	n/a	n/a
9b	5-HTT*	Topic	103	7	2	0
10	Cortisol*, Stress*	Title	2667	25	0	0
10b	5-HTT*	Title	21	0	0	0

2.6 Research Gate

Research Gate was used primarily to find unpublished studies to offset the publication bias, which skews results towards significant results. Research Gate did not give exact numbers for each search, rather it rounds the results down to the nearest 100 or 1000. Table 3 summarises this information. Articles that had already come up in searches in the previous data bases, were not reviewed at all, regardless of if they met the inclusion criteria.

Table 3.

Search terms used, and results obtained from Research Gate.

Search string	Search term	Field search	Number of results	Abstracts reviewed	Full texts reviewed	Studies included
1	Stress*, 5-HTTLPR*	Publications	100+	11	2	1
2	Psychosocial stress*, 5-HTTLPR	Publications	25+	0	0	0
3	Gene*, Psychosocial stress	Publications	1000+	0	0	0
3b	5-HTTLPR*	Publications	25+	0	0	0
4	Cortisol*, Stress*	Publications	1000+	0	0	0
4b	5-HTTLPR*	Publications	0	0	0	0

2.7 Previous Meta-Analyses and Systematic Reviews

Meta-analyses and systematic reviews in similar areas were kept aside during the search, so that their bibliographies and citations could be reviewed. In this search, relevant meta-analyses or systematic reviews were those that looked at the genetic marker 5-HTTLPR, and stress. Articles which also looked at depression or anxiety, as well as stress, were also kept aside for further investigation. Six meta-analyses and one systematic review had their citations and bibliographies reviewed. No unique or relevant studies were found for inclusion in the meta-analysis that had not already been identified.

In total, 9 unique studies were kept aside. Five studies had two separate samples, however there were no known duplications between the sample populations. Figure 1 shows the review process for including studies in the meta-analysis.

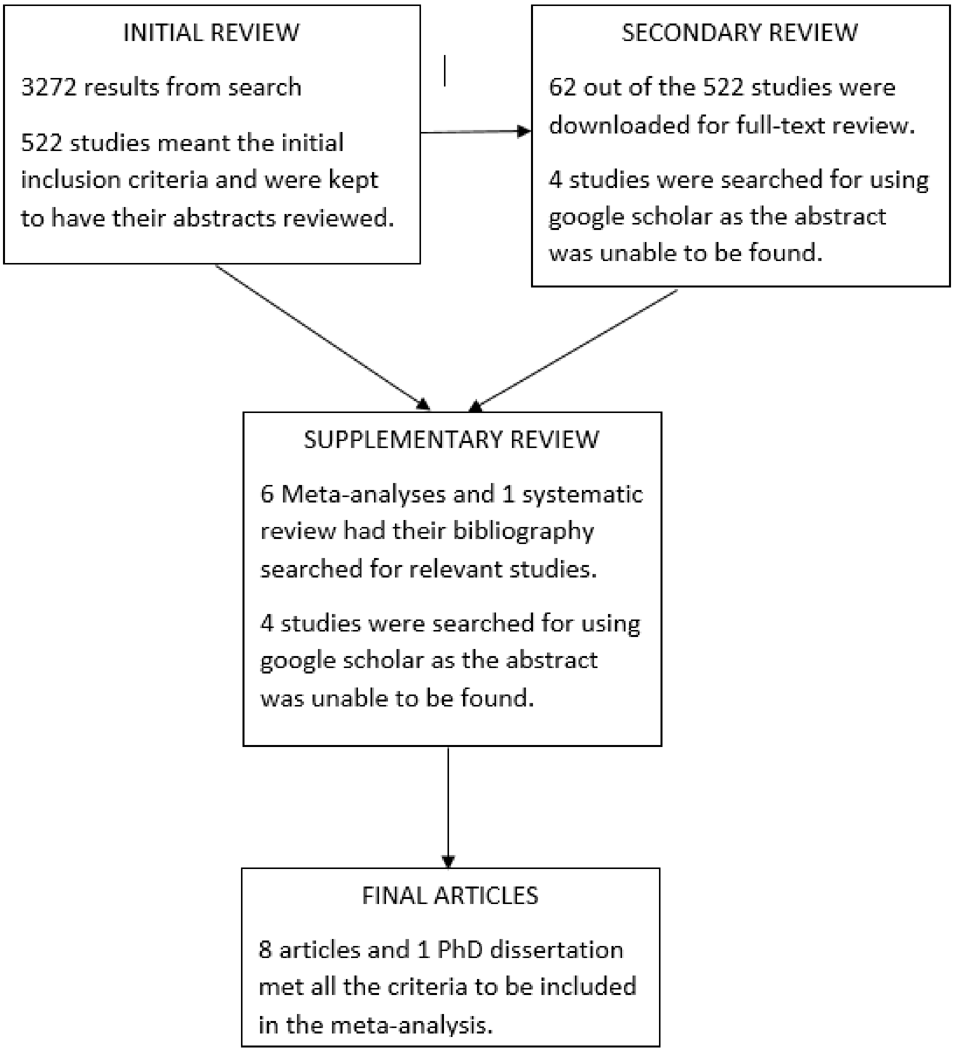

Figure 1. Review process for studies to be included in the met-analysis.

2.8 Data Extraction

Each study had the following information extracted so that variance and Cohen’s d could be calculated; sample size of each group, means, and standard deviation of the baseline and peak cortisol concentrations in response to the Trier Social Stress Test for the different 5-HTTLPR genotypes; S/S. L/S and L/L. Each study also had basic bibliographic information extracted such as the title, authors, year the study was published, and the journal the study was published in. This information was used to assess if the sample in each article was unique.

2.8.1 Condensing genotypes

Four studies reported their information as a SS/SL group and a LL group, rather than in three separate genotypes (SS, SL, and LL). To ensure consistency throughout the meta-analysis all studies had their data condensed into two groups, which were an SS and SL genotype group and a LL genotype group.

2.8.2 Condensing Measurement Times

There was a large amount of variation between studies in the times that cortisol was measured as part of the TSST. To maintain consistency through the analysis, the cortisol measurements were grouped into four time-bands. These bands were Baseline, Post-TSST – 15 minutes, 20-50 minutes, and 60+ minutes. These bands were created for each independent sample by taking the average of all measurements that fit into that time band and averaging the mean and variance.

2.8.3 Hedge’s g and Cohen’s d

The effect size used in this meta-analysis was Hedge’s g, as Cohen’s d was not able to be calculated in Comprehensive Meta-Analysis. Subsequent data analysis using Comprehensive Meta-Analysis reports effect sizes using Hedge’s g.

Initially Cohen’s was calculated for each study using the mean difference from each sample and dividing this by the sum of squared errors (or pooled standard deviation). Cohen’s d was used as it indicates the standardised difference between the means of two or more sample groups, which in this case were the different 5-HTTLPR genotypic groups.

2.8.4 Pooled Standard Deviation

In this meta-analysis, the pooled standard deviation was used as there were multiple groups within in each study. In each study, the groups consisted of three samples. Each sample contained individuals with one of the three 5-HTTLPR genotypes; S/S, L/S, or L/L.

2.8.5 Variation

The variation was calculated using Cohen's d and the sample sizes from each independent subgroup, to give an indication of the spread of the data from each study.

2.8.6 Transformational Statistics

Table 4 summarises how the standard deviation and means were extracted from each study in the meta- analysis. Raw data was requested from eight articles, however only one author sent through raw data. One article reported all required data. Seven studies provided the standard error of the mean (SE_M) rather than the standard deviation (SD). This required some statistical transformation to calculate the SD. The SD was calculated by multiplying the SE_M by the square root of the sample size.

Three articles provided the necessary statistical information, however this was only reported in graph format. These graphs were put through Graphclick, which is a program that extracts data points from graphs. The data extracted from each graph was the means and SE_M for each sample. GraphClick was chosen as it has been the subject of several academic reviews, which reviewed its validity and reliability (Rakap, Rakap, Evran, & Cig, 2015., Boyle, Samaha, Rodewald, & Hoffmann, 2013., Flower, McKenna, & Upreti, 2016). All reviews found reliability and validity correlation coefficients of approximately 0.99, demonstrating that the data that GraphClick is very accurate in extracting data from graphs.

The final study included in the meta-analysis had all the required statistical data to calculate Cohen's d and the variance directly from the statistical notation in the article,

Table 4.

How means and standard deviations were extracted for each study.

Study	Authors	Raw data received from author	Required data reported in study	Data extracted from graph	SD calculated from SE_M
1	Wust et.al	No	Yes	Yes	Yes
2	Verschoor & Markus	No	Yes	Yes	Yes
3	Mueller et.al	No	Yes	No	Yes
4	Fogelman et.al	Yes	n/a	n/a	n/a
5	Way & Taylor	No	Yes	Yes	Yes
6	Alexander et.al	No	Yes	No	Yes
7	Alexander et. al	No	Yes	No	No
8	Armbruster et.al	No	Yes	No	Yes
9	Reid	No	Yes	No	Yes

2.9 Data Analysis

All data analysis was done using Comprehensive Meta-Analysis.

2.9.1 Weighted Effect Size

Once Cohen's d was calculated for each study, a weighted effect size was calculated by finding the inverse of the variance of an individual study's effect size. The studies were weighted by the inverse of the variance rather than the sample size to prevent extreme skew in the results from studies with large sample sizes. After the weighted effect sizes were calculated, a mean weighted effect size was calculated. This was the overall effect size for the meta-analysis, so all weighted effect sizes were averaged.

2.9.2 Confidence Intervals

Confidence intervals were calculated for the mean weighted effect size, to give an indication of how accurate the effect size was, and what variation could be expected due to sampling error. To calculate confidence intervals, variance of the mean weighted effect size and the standard effort of the mean were calculated first.

2.9.3 Testing for Variability

To provide further information on the variability around the effect size, tests for heterogeneity were conducted. Three different heterogeneity statistics were calculated; Q – the amount of variability across studies, T^2 - a parameter estimate of the variance of the true effect sizes, and I^2 – the percentage of the overall variability (Q) which exceeds that which is expected by chance from sampling error. Heterogeneity tests were important to check whether conflicting results were measuring the similar or completely different constructs.

2.10 Fixed Effect versus Random Effect Models

There are two ways to calculate the mean weighted effect size, the fixed effect model and the random effects model. The fixed effect model assumes that there is a single ‘true’ effect size, and that all studies measure that same effect, so any differences in effect sizes must be due to sampling error. The random effects model assumes that studies are not measuring the same effect, and that variation in methodology may lead to variation in the underlying effect size. The random effects model assumes that there is a distribution of true effect sizes and that the studies in a meta-analysis are a random sample of that distribution.

There are a few differences with calculations between the fixed and random effects models. In the random effects model, all calculations are the same except that the initial calculation of variance includes the estimate of the variance of the true effect sizes (T^2). This may have no practical effect if the variability across studies is no more than expected by chance, or if *Q* is less than or equal to the degrees of freedom (*df*). In this case T^2 will be equal to zero and the analysis for the fixed-effect and random-effects models are the same. Analyses for the two models will only be different when *Q* is greater than the *df.*

While the random effects model is the most appropriate model to use for these meta-analyses both the fixed-effect and random-effects analyses were conducted and reported. This was to allow further comparisons to be made and further discussion to be had in Chapter 4 regarding the differences between the two models and their significance to the meta-analyses conducted in this study.

3 Chapter 3

Results

3.1 Outline of Chapter

This chapter will start by summarising the reported results from all studies included in these meta-analyses. Further information will be provided on the time bands used for each of the four meta-analyses conducted. Results for each meta-analysis will be provided separately, along with tests for heterogeneity, and a publication bias analysis. The results for each meta-analysis will include the results from both the fixed effect model and the random effects model. The differences between these two models will be outlined for each meta-analysis and discussed further in Chapter 4.

3.2 Initial Summary from Studies

The studies used in this meta-analysis did not all use the same method, or all measure the same genotypes. Table 5 below summaries the genotypes measured in each study, the method used and whether the study found a significant effect of p = <0.05. Each study was reviewed, rather than the independent samples in each study.

This summary was conducted to show the reported results from each study used. It was used to demonstrate that there was substantial variation between the results reported by individual studies and provides further justification for the need for a meta-analysis in this area. In this meta-analysis, the large variation in the results of the studies indicated that there was little to no consensus on whether differences within the 5-HTTLPR genetic marker had an effect on the response to psychosocial stressors. This provides an opportunity to contribute to this area by not only calculating an average effect size for this research, but to apply this finding to the workplace, where psychosocial stress is a common issue for employees with wide ranging side effects (Heraclides, Chandola, Witte, & Brunner, 2009., Seigrist, 2008).

Table 5.

Summary of all studies included in this meta-analysis.

Author	Cortisol Measurement	Genotype	Method	Result
Wust et al, 2009	Saliva and Blood	SS, SL, LL	TSST	No significant effect
Verschoor & Markus, 2011	Saliva	SS, LL*	Adapted TSST and questionnaire	No significant effect.
Mueller et al, 2011	Saliva	SS, LL*	TSST and questionnaire	L allele associated with higher cortisol response.
Fogelman et al, 2016	Saliva	SS, LL*	TSST and questionnaire	No significant effect
Way & Taylor, 2010	Saliva	SS, SL, LL	TSST	Significantly higher response from SS genotype.
Alexander et al, 2009	Saliva	SS, SL, LL	TSST and questionnaire. Males only.	No significant effect
Alexander et al, 2014	Saliva	SS, SL, LL	TSST and questionnaire.	S alleles associated with slightly higher cortisol response.
Armbruster et al, 2009	Saliva	SS, SL, LL	TSST only.	No significant effect
Reid 2014	Saliva	SS, LL	TSST and questionnaire.	Higher response from SS

* Only individuals with L_AL_A genotype were counted as LL. All other individuals were counted as SS.

3.2.1 Condensing Information

There was large variation between studies on the exact times when the cortisol measurements were taken after the TSST. Consequently, all times were condensed into four bands for greater consistency of results. These bands were; Baseline, Post TSST-15 minutes, 20-50 minutes, and 60+ minutes, and a meta-analysis was conducted for each time bands.

3.3 Baseline Meta-Analysis

A meta-analysis of the baseline cortisol measurements was conducted to ascertain whether there was a difference between the SS/SL and LL groups before the TSST was administered.

Table 6 shows the summary statistics for each study used in the meta-analysis. When applicable this was separated into independent samples within studies. The effect sizes for each independent sample ranged from -0.4 to 0.268 and no significant differences between the genotypic groups were found.

Table 6.

Summary statistics showing the effect sizes for each independent sub-group for the baseline time band.

Study Name	Subgroup	Hedge's g	Variance	Lower limit	Upper Limit	P Value
Wust et al	Men	-0.205	0.049	-0.641	0.230	0.356
Wust et al	Women	-0.203	0.045	-0.619	0.212	0.338
Verschoor	High	0.268	0.081	-0.291	0.828	0.347
Verschoor	Low	-0.400	0.082	-0.963	0.162	0.163
Mueller et al	Older Adults	0.194	0.050	-0.246	0.633	0.388
Mueller et al	Younger Adults	-0.170	0.048	-0.599	0.260	0.439
Fogelman et al	Older Adults	-0.110	0.067	-0.619	0.398	0.671
Fogelman et al	Younger Adults	0.078	0.049	-0.355	0.512	0.723
Way (2010)	Audience Evaluation	0.009	0.050	-0.429	0.448	0.966
Way (2010)	No Audience	-0.026	0.107	-0.668	0.616	0.937
Alexander et al (2009)		-0.017	0.051	-0.460	0.426	0.940
Alexander et al (2014)		0.140	0.023	-0.158	0.438	0.356
Armbruster (2016)		-0.032	0.062	-0.521	0.457	0.898
Reid (2014)		-0.000	0.105	-0.634	0.634	1.000

Table 7 shows the weighted effect sizes for the fixed and random effects models, as well as the upper and lower limits of the 95% confidence interval, and the p value. Both the fixed and random effects model had identical results, with a very small weighted effect size of g = 0.018 and a p value = 0.767, indicating that there was almost no difference in cortisol measurements between the two genotypes at baseline.

Table 7**.**

Weighted effect sizes using the fixed and random effects models.

Model	Hedge's g	Variance	Lower limit	Upper limit	P Value
Fixed	0.018	0.004	-0.140	0.103	0.767
Random	0.018	0.004	-0.140	0.103	0.767

Figure 2 below shows a forest plot of the effect sizes of each independent sample and the overall effect size using the random effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 6 and Table 7.

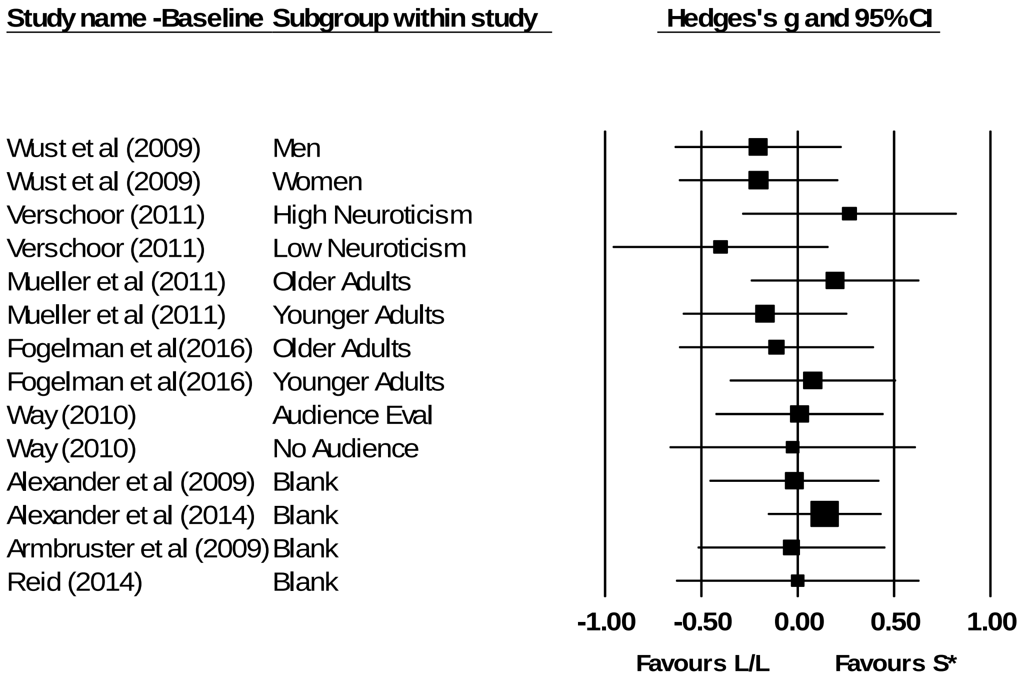

Figure 2. Forest plot showing all independent samples and the overall Hedge’s g effect size and 95% confidence interval using the random effects model.

Figure 3 below shows a forest plot of the effect sizes of each independent sample and the overall effect size using the fixed effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 6 and Table 7.

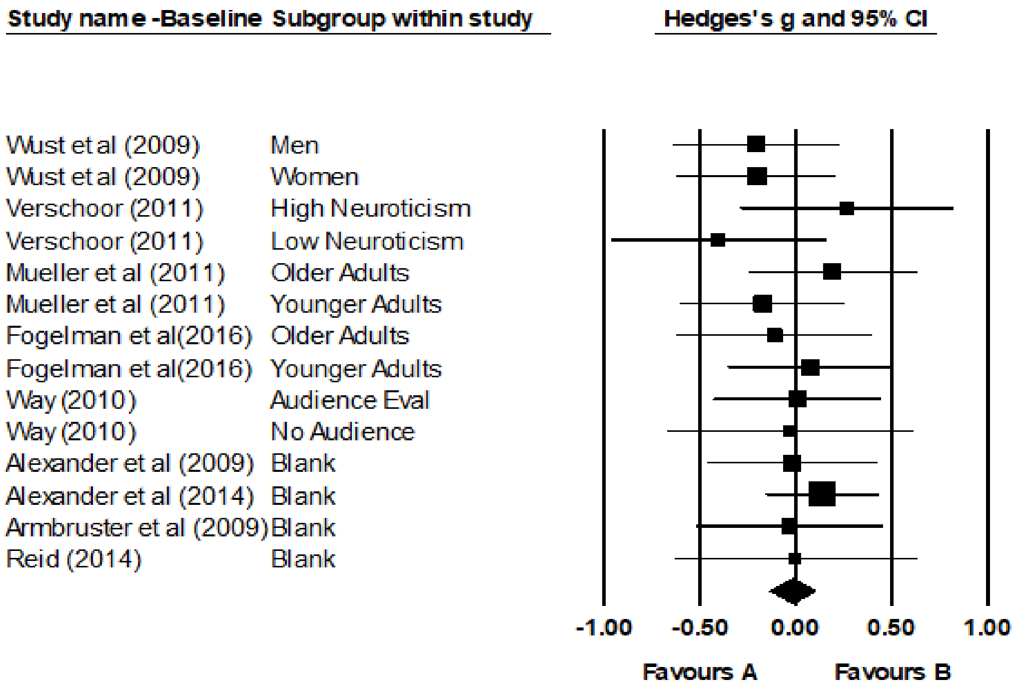

Figure 3. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the fixed effects model.

3.3.1 Heterogeneity

Heterogeneity tests were conducted to assess the variation in the outcomes between studies. Cochran's *Q*, the I^2 statistic, and Tau^2 (or T^2) were calculated and are shown in Table 8 along with the degrees of freedom for *Q*. Cochran's Q is less than the degrees of freedom indicating that there is not heterogeneity present between the samples analysed. Both the fixed and random effects model had the same results for heterogeneity with $Q = 7.05$ and degrees of freedom (df) =13.

Table 8.

Tests for heterogeneity for the baseline meta-analysis.

Model	Q	$Q\ df$	I^2	T^2
Fixed	7.050	13	0.00	0.00
Random	7.050	13	0.00	0.00

3.4 Post- TSST to 15-minute Meta-Analysis

A second meta-analysis was conducted for the post TSST to 15-minute measurement band. The post TSST to 15-minute band had several independent samples that did not measure cortisol during this time period, however a meta-analysis was conducted using the 10 independent samples that did fit within this band. Table 9 shows the summary statistics for the post TSST to 15-minute band for each of the independent samples. Individual effect sizes ranged from a moderate effect for the L/L genotype of g = -0.430 to a smaller effect for the S/S genotype of 0.304. Only one subgroup had a statistically significant p value under the 0.05 threshold, with p = 0.037.

Table 9.

Summary statistics showing the effect sizes for each independent sub-group for the Post TSST to 15-minute time band.

Study name	Subgroup	Hedge's g	Variance	Lower limit	Upper Limit	P Value
Wust et al (2009)	Men	-0.113	0.049	-0.549	0.321	0.608
Wust et al (2009)	Women	-0.408	0.046	-0.826	0.010	0.056
Mueller et al (2011)	Older Adults	-0.430	0.049	-0.862	0.003	0.052
Mueller et al (2011)	Younger Adults	-0.247	0.050	-0.687	0.193	0.271
Fogelman et al (2016)	Older Adults	-0.549	0.069	-1.064	-0.034	0.037
Fogelman et al (2016)	Younger Adults	-0.012	0.049	-0.446	0.421	0.956
Alexander et al (2009)		0.304	0.052	-0.141	0.750	0.180
Alexander et al (2014)		0.265	0.023	-0.033	0.564	0.081
Armbruster et al (2009)		-0.065	0.062	-0.555	0.424	0.793
Reid (2014)		0.054	0.019	-0.217	0.325	0.698

Table 10 shows the weighted effect sizes using both the fixed and random effects models. Both models showed a small effect size, however the random effects model showed the largest effect size with *g* =-0.092 with p = 0.371, while the fixed effect model had an effect of g = -0.057, with p = 0.312. These values indicate a small effect towards the L/L genotype showing an increased cortisol response to psychosocial stress, however neither of these results are statistically significant.

Table 10.

Weighted effect sizes using the fixed effects and random effects models for the Post TSST to 15-minute band.

Model	Hedge’s g	Variance	Lower Limit	Upper Limit	P Value
Fixed	-0.057	0.004	-0.181	0.068	0.371
Random	-0.092	0.008	-0.271	0.087	0.312

Figure 4 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the random effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 9 and Table 10.

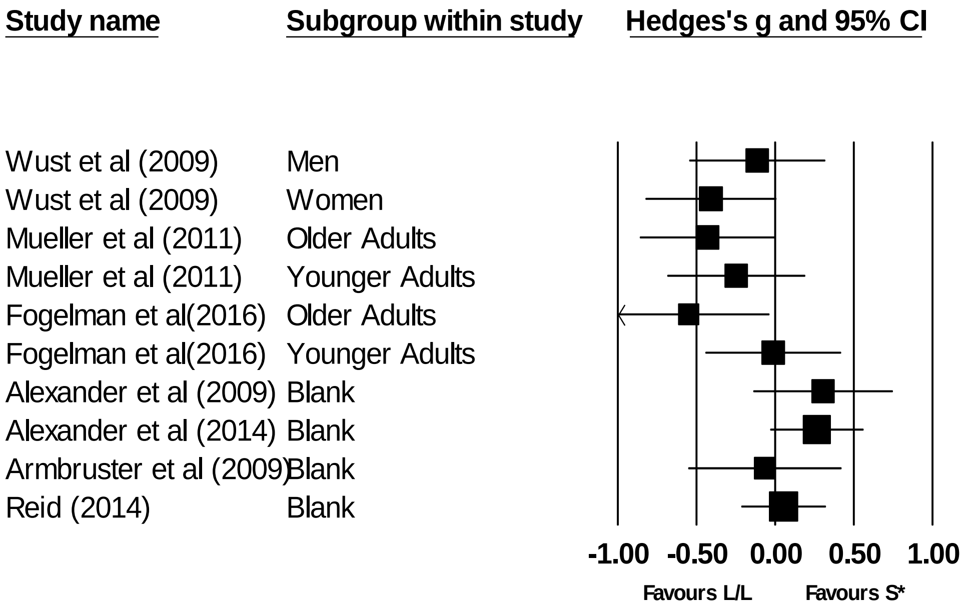

Figure 4. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the random effects model.

Figure 5 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the fixed effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 9 and Table 10.

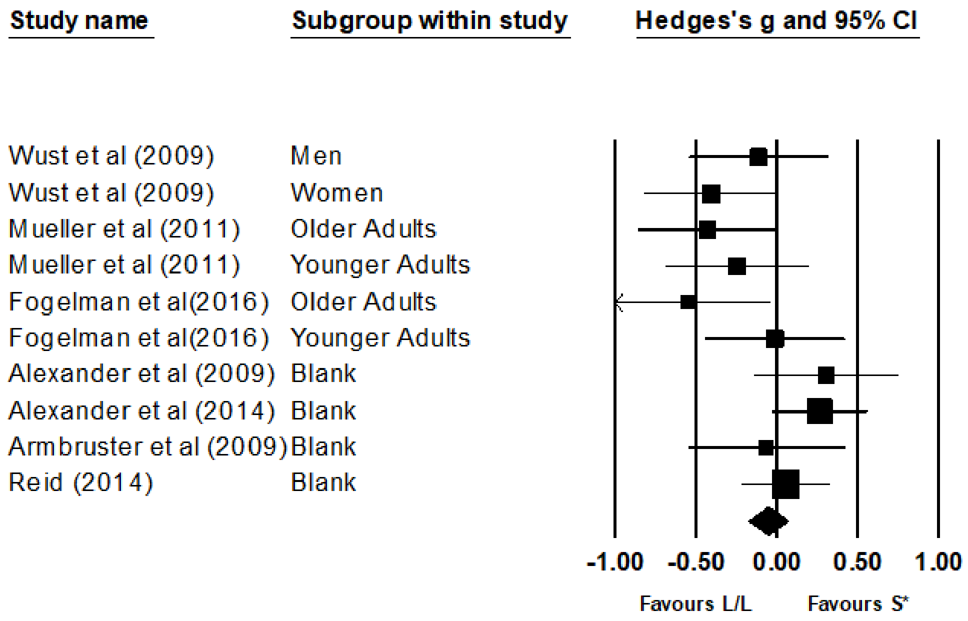

Figure 5. Forest plot showing all independent samples and the overall Hedge’s g effect size and 95% confidence interval using the fixed effects model.

3.4.1 Heterogeneity

Table 11 shows the results for the heterogeneity tests conducted. The fixed and random effects models differed in the results for heterogeneity with the fixed model having a Q value = 17.54 which was greater than the degrees of freedom, df = 9, while the random effects model had Q = 8.901 which was less than the degrees of freedom, df = 9. There was also a large difference in the I^2statistic between the two models, with the fixed effect model showing a large I^2 of 48.689, while the random effect model had an I^2 value of 0.00. There was no difference between the models for the T^2result.

Table 11.

Tests for heterogeneity for the Post-TSST to 15-minute meta-analysis.

Model	*Q*	*Qdf*	I^2	T^2
Fixed	17.54	9.000	48.689	0.039
Random	8.901	9.000	0.000	0.039

3.5 20-50-Minute Meta-Analysis

A third meta-analysis was conducted for the 20-50-minute time-band. All 14 independent samples were included in this meta-analysis. Table 12 shows the summary statistics for each independent sample. The effects sizes for these independent samples ranged from the L/L genotype showing a large effect of g = -0.876 to a small effect for the S/S genotype of g = 0.182. Only one subgroup had a significant p value of under the 0.05 threshold, with p = < 0.01.

Table 12.

Summary statistics showing the effect sizes for each independent sub-group for the 20-50-minute time band.

Study Name	Subgroup	Hedge's g	Variance	Lower limit	Upper Limit	P value
Wust et al	Men	-0.196	0.049	-0.631	0.240	0.378
Wust et al	Women	-0.216	0.045	-0.632	0.200	0.309
Verschoor	High	0.149	0.081	-0.409	0.706	0.601
Verschoor	Low	0.060	0.081	-0.496	0.617	0.832
Mueller et al	Older Adults	-0.369	0.041	-0.766	0.027	0.068
Mueller et al	Younger Adults	-0.366	0.039	-0.754	0.022	0.065
Fogelman et al	Older Adults	-0.876	0.053	-1.329	-0.424	0.000
Fogelman et al	Younger Adults	-0.251	0.068	-0.760	0.259	0.335
Way (2010)	Audience Evaluation	-0.016	0.050	-0.455	0.423	0.943
Way (2010)	No Audience	0.041	0.107	-0.600	0.683	0.899
Alexander et al (2009)		-0.031	0.051	-0.474	0.412	0.891
Alexander et al (2014)		0.325	0.023	0.026	0.624	0.033
Armbruster (2016)		0.092	0.062	-0.397	0.582	0.711
Reid (2014)		0.182	0.019	-0.089	0.453	0.189

Table 13 shows the weighed effect sizes using both the fixed and random effects models. Using the random effects model, a slightly larger weighted effect size of g = -0.1 was produced compared to the fixed effects model where g = -0.065. These results indicate a small effect towards the L/L genotype showing an increased response to cortisol after exposure to psychosocial stress. These results were not statistically significant as the p value for both models were greater than 0.05.

Table 13.

Weighted effect sizes using the fixed and random effects models.

Model	Hedge's g	Variance	Lower Limit	Upper Limit	P value
Fixed	-0.065	0.003	-0.176	0.046	0.250
Random	-0.100	0.008	-0.272	0.073	0.258

Figure 6 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the random effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 12 and Table 13.

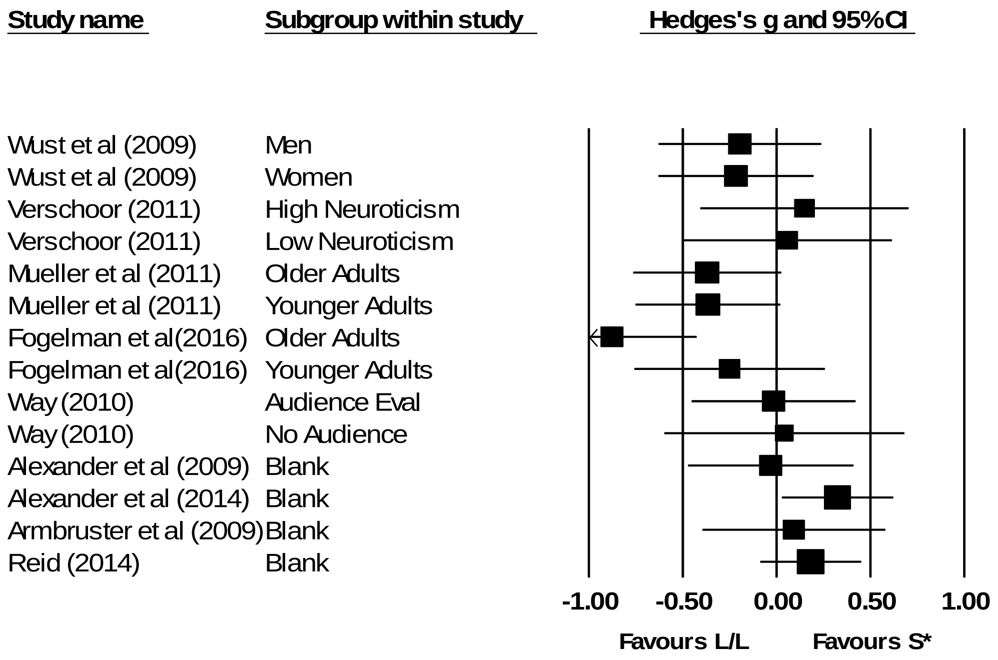

Figure 6. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the fixed effects model.

Figure 7 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the fixed effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 12 and Table 13.

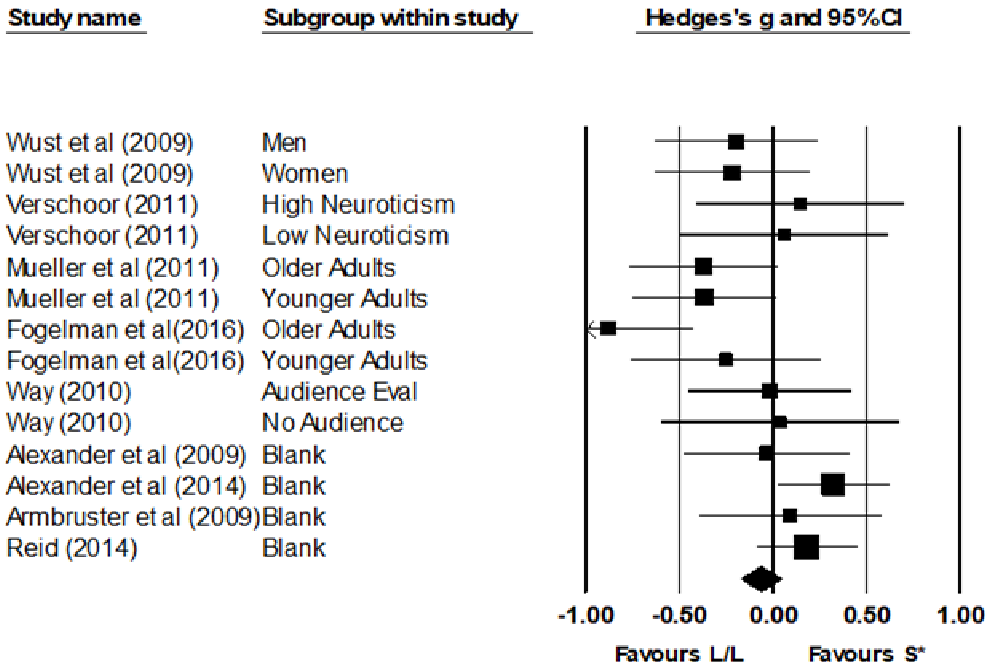

Figure 7. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the fixed effects model.

3.5.1 Heterogeneity

Tests for heterogeneity were conducted for the 20-50-minute meta-analysis. Table 14 shows the results of these tests. The fixed effects model produced a higher Q than the random effects model (Q = 29.334 and Q = 11.718 respectively). The I^2statistic was very different between the two models with the fixed effect model producing a high I^2value of 55.682, while the random effect model had a lower I^2 value of 0.00. There was no difference in the T^2value between the models.

Table 14.

Tests for heterogeneity for the 20-50-minute time band meta-analysis.

Model	Q	Qdf	I^2	T^2
Fixed	29.334	13.00	55.682	0.058
Random	11.718	13.00	0.00	0.058

3.6 60+ Minute Meta-Analysis

A final meta-analysis was conducted for the 60+ minute time band. Only one independent sample did not have measurements for this time band so 13 independent samples were able to be included in this analysis. Table 15 summarises the effect sizes for each unique subgroup. These effect sizes ranged from a moderate effect for the L/L genotype with g = -0.40, to a larger effect for the S/S genotype with g = 0.636. Only one independent sample had a significant p value under the 0.05 threshold, with p = 0.005.

Table 15.

Summary statistics showing the effect sizes for each independent sub-group for the 60+ minute time band meta-analysis.

Study name	Subgroup	Hedge's	Variance	Lower Limit	Upper Limit	P Value
Wust et al	Men	-0.161	0.050	-0.599	0.278	0.473
Wust et al	Women	-0.403	0.046	-0.824	0.018	0.061
Verschoor	High	0.042	0.083	-0.524	0.608	0.883
Verschoor	Low	0.023	0.083	-0.543	0.589	0.937
Mueller et al	Older Adults	-0.369	0.052	-0.815	0.076	0.104
Mueller et al	Younger Adults	-0.365	0.049	-0.800	0.069	0.099
Fogelman et al	Older Adults	-0.395	0.070	-0.911	0.122	0.134
Fogelman et al	Younger Adults	0.636	0.052	0.188	1.084	0.005
Way (2010)	Audience Evaluation	-0.012	0.051	-0.454	0.429	0.956
Way (2010)	No Audience	0.029	0.110	-0.620	0.679	0.929
Alexander et al (2009)		-0.328	0.053	-0.777	0.121	0.152
Alexander et al (2014)		0.296	0.023	-0.004	0.596	0.053
Reid (2014)		0.067	0.019	-0.205	0.338	0.629

Table 16 shows the results for the weighted effect sizes calculated using the fixed and random effects models. Both models reported very small effect sizes, with the random effects having g = -0.062, and the fixed effect model having g = -0.033. These effect sizes indicate a very small effect towards the L/L genotype having greater cortisol reactivity after exposure to psychosocial stressors. These results were not statistically significant as both models had p values greater than 0.05.

Table 16.

Weighted effect sizes calculated using the fixed and random effects models.

Model	Hedge's g	Variance	Lower limit	Upper limit	P value
Fixed	-0.033	0.004	-0.150	0.084	0.579
Random	-0.062	0.008	-0.237	0.113	0.489

Figure 8 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the random effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 15 and Table 16.

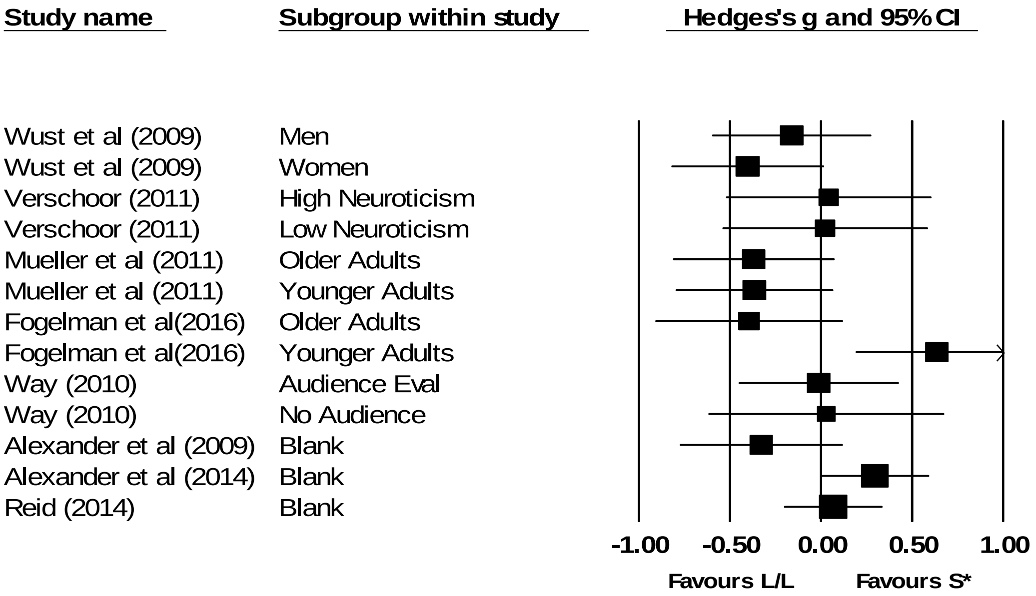

Figure 8. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the random effects model.

Figure 9 shows a forest plot of the effect sizes of each independent sample and the overall effect size using the fixed effects model. The 95% confidence interval for each of the independent samples are also shown. These results were previously reported in Table 15 and Table 16.

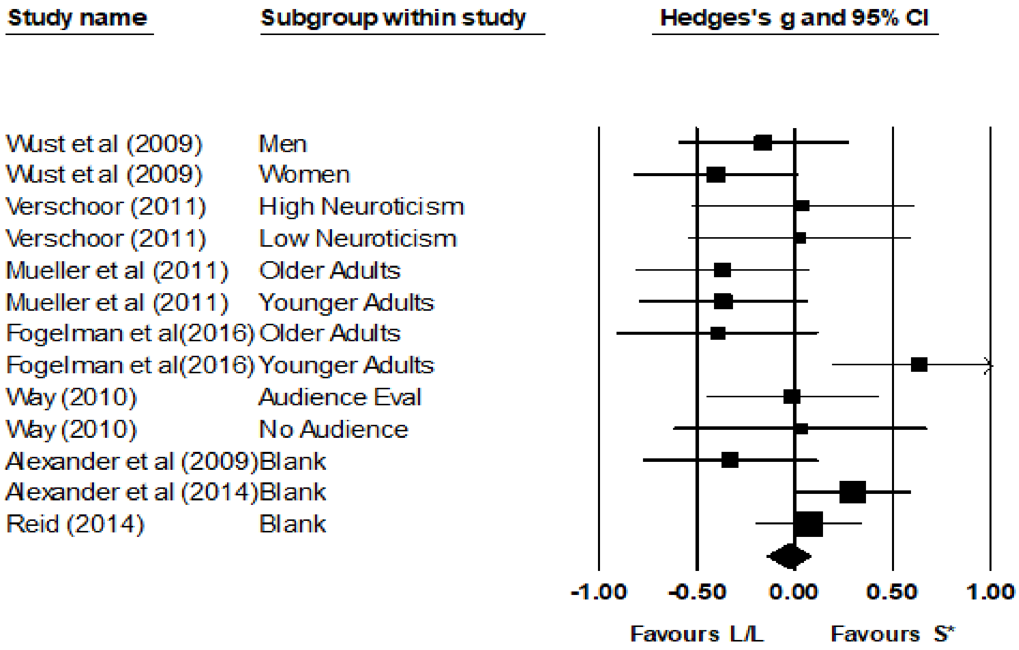

Figure 9. Forest plot showing all independent samples and the overall Hedge's g effect size and 95% confidence interval using the fixed effects model.

3.6.1 Heterogeneity

Tests for heterogeneity were conducted for this meta-analysis and Table 17 shows these results. The fixed effects model reported a larger Q value with Q = 25.183, than the random effect model with Q = 11.529. The fixed effect model also had a larger I^2statistic than the random effects model with I^2= 52.263 and I^2= 0.00 for the fixed and random effect models respectively. There was no difference in the T^2value between the fixed and random effects models.

Table 17.

Tests for heterogeneity for the 60+ minute time band.

Model	**Q**	**Qdf**	I^2	T^2
Fixed	25.183	12.00	52.263	0.052
Random	11.529	12.00	0.000	0.052

3.7 Publication Bias Analysis

A publication bias analysis was carried out using the data from the baseline time band as this band contained all 14 independent samples. Figure 9 below shows Hedge’s g for each study plotted against the standard error. The overall effect size is represented by a diamond under the graph. Usually the results for the fixed and random effect model are shown on separate graphs, however the for the baseline meta-analysis the results for these models were the same, so only one graph is shown. The funnel plot shown below is roughly symmetrical indicating that publication bias is not present.

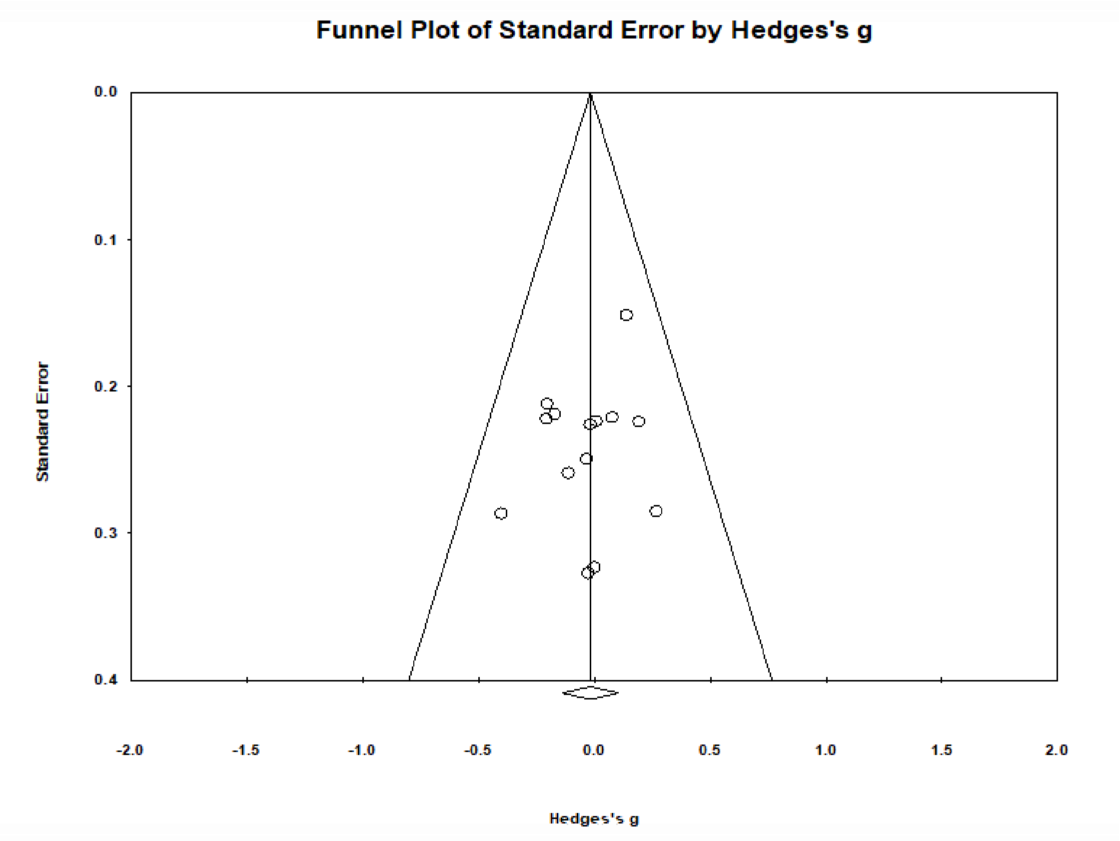

Figure 10. Funnel plot showing Hedge’s g for each independent sample plotted against the standard error.

3.8 Explanation of Results

3.8.1 Baseline Meta-Analysis

The baseline meta-analysis found a very small positive effect of g = 0.018(± 0.122), $\sigma^2 = 0.004$, with a p value =0.767. There was no difference in effect size when using the fixed or random effects models. This very small effect size is not unexpected if it is assumed that the 5-HTTLPR genetic marker only has an effect once an individual has been exposed to a psychosocial stressor.

The tests for heterogeneity showed the same results for the fixed effect and random effects models. For this meta-analysis Cochran’s Q has low power as a test of heterogeneity as the number of subgroups included is small, (n =14). In meta-analyses with a small number of studies included, the I^2statistic is a more useful indication of heterogeneity as it does not depend on the number of studies considered (Higgins & Thompson, 2002). The low I^2 indicates that there is very little variation between the sub groups – in this case while it would be possible to use the fixed effects model as there appears to be very little variation between studies, preference should be given to the random effects model results, as it assumes that variation between studies lies in a normal distribution (Fleiss & Gross, 1991).

3.8.2 Post-TSST to 15-minute Meta-Analysis

The Post-TSST to 15-minute meta-analysis had a very small effect size, however the results differed between the fixed and random effects models. The fixed effect model had a small negative effect of g = -0.057 (±0.124), σ^2 = 0.004, with a p value = 0.371. The random effect model had a slightly larger, negative effect size of g = -0.092 (±0.179), σ^2 =0.008, with a p value of 0.312. While the random effects model shows an effect size of almost double the fixed effect model, this is still very small and is not significant as p is not < 0.05. The negative direction of the effect size suggests that there is a slight trend towards those with the L/L genotype showing an increased cortisol after the TSST.

The results from the random effects model should be used for the Post-TSST to 15-minute meta-analysis. There were only 10 subgroups included within this meta-analysis so although Cochran’s Q differs between the two models, it does not hold a lot of power as a test for heterogeneity. The I^2 statistic was high for the fixed effects model, I^2=48.689, whereas I^2= 0.00 for the random effects model. This indicates that the studies included in this meta-analysis are from the same population as the variation between studies is due to chance rather than heterogeneity.

3.8.3 20-50-Minute Meta-Analysis

The 20-50-minute meta-analysis also had a small negative effect size which differed between the fixed and random effects models. The fixed effect model had a small, negative effect size of g = -0.065 (±0.111), σ^2 =0.003, with a p value of 0.250. The random effects model also had a small, negative effect size of -0.1 (± 0.172), σ^2 =0.008, with a p value of 0.258. These results are similar to those found in the post-baseline-15-minute meta-analysis, with the small, negative effect size indicating a slight trend towards the L/L genotype having an increased stress response to the TSST.

The results from the random effects model should be used for the 20-50-minute meta-analysis, as there were only 14 subgroups included in this meta-analysis. The I^2 statistic was high for the fixed effects model, I^2=55.682, whereas I^2= 0.00 for the random effects model. This indicates that the studies included in this meta-analysis are from the same population as the variation between studies is due to chance rather than heterogeneity.

3.8.4 60+ Minute Meta-Analysis

The 60+ minute meta-analysis had the smallest effect sizes after the baseline analysis with the fixed effects model producing a very small, negative effect size of g = -0.033 (± 0.117), σ^2 =0.004, with a p value = 0.579. The random effects model had an effect size of -0.062 (± 0.175), σ^2 =0.008, with a p value = 0.489.

The results from the random effects model should be used for the 60+ minute meta-analysis, as there were only 13 subgroups included in this meta-analysis. The I^2 statistic was high for the fixed effects model, I^2 =52.2.63, whereas I^2= 0.00 for the random effects model. This indicates that the studies included in this meta-analysis are from the same population as the variation between studies is due to chance rather than heterogeneity.

3.9 Conclusion

With the exception of the baseline meta-analysis, which had a negligible effect size, all meta-analyses conducted found a small effect size indicating that individuals with the L/L genotype had greater cortisol reactivity after exposure to psychosocial stressors. The results for both the fixed effect and random effect models were reported in table format. The publication bias analysis was conducted on the baseline meta-analysis data as this time-band included all independent samples, and there was no difference between the random and fixed effect modes. Heterogeneity tests were conducted for each meta-analysis, to support the choice to use the random effect model over the fixed effect model.

The heterogeneity tests also indicated whether the variation in all individual samples included were due to chance or to sampling errors between the samples.

The implications of these results will be discussed further in Chapter 4.

4 Chapter 4

Discussion and Future Research

4.1 Discussion

The four meta-analyses conducted show various effect sizes, however all are relatively small. In Chapter 3, the results acquired using the fixed and random effects models were reported regardless of which model was more appropriate for this meta-analysis. The results for both models were briefly discussed in the Chapter 3, however it should be noted that the results from the random effects model should be given greater weighting as the studies used are from separate populations and as such it is unlikely that there is a ‘true’ effect size as is assumed with the fixed effects model. In this situation it is more likely that there is a distribution of effect sizes and the studies used in this series of meta-analyses lie within that distribution. Results for both models were reported as it is worth noting the differences in effect sizes for each analysis between the two models, as it shows how discrepancies between different meta-analyses using the same studies may arise. Both the fixed effects and random effects model results were reported as a way of conducting a sensitivity analysis due to the small number of studies included and the small effect sizes reported. It is worth reviewing both sets of results to determine whether the TSST was more effect in studies with small sample sizes (random effect model), or if studies with larger sample sizes were more robust in their methodology (fixed effect model).

As previously reported in Chapter 3 these results indicate that there was no significant effect of genotype on the cortisol responsivity to the TSST, as all meta-analyses had very small effects sizes and large p values. While there were not any statistically significant results in these meta-analyses, there does appear to be a small trend towards the L/L genotype having a greater cortisol response after the TSST, as all effect sizes were negative except in the baseline analysis. These results indicate that overall there is no consistent effect.

There are several reasons that may have contributed to the lack of significant results obtained from the four meta-analyses conducted. Firstly, the lack of statistically significant results may be an accurate reflection of the relationship, or lack thereof, between the 5-HTTLPR genetic marker and cortisol reactivity to psychosocial stress. While several of the studies analysed in these meta-analyses did report effects, these were not large effects and differed noticeably in both direction and magnitude. The small effects found may also reflect the current small area of research that reviews 5-HTTLPR and psychosocial stress. More studies would be needed to confirm whether the small effects found are an accurate representation of the relationship between 5-HTTLPR genotype and cortisol reactivity to psychosocial stress, or if the effects found were purely chance. Further investigation is needed to confirm the presence of any larger effect, as well as the consideration of other genes.

It should also be noted that the four meta-analyses conducted only used results obtained from physiological measures of stress, and do not use any accounts of perceived stress reported by participants. Although there is a correlation between perceived stress and cortisol measurements this is not a 1:1 relationship, and it may be mediated by factors such as coping strategies and perceived support (Sladek, Doane, Luecken, & Eisenberg, 2016.,Walvekar, Ambekar, & Devaranavadagi, 2015). While several studies in the four meta-analyses did measure perceived stress, these measurements were not incorporated into the analysis due to a lack of consistency between the psychometric stress scales.

4.2 Implications for the Workplace

One of the original aims of conducting this study was to discuss ways that research involving genetic markers and psychosocial stress could be applied to the workplace, with a view for suggesting personalised interventions for employees. This is difficult to do with the results obtained as there is no certainty that the effect sizes calculated are due to relationship between 5-HTTLPR and a pre-disposition to psychosocial stress, rather than just down to chance. It is also difficult to make any suggestions for how the results from these meta-analyses could be applied to the workplace when they do not consider the participants' own perceptions of the stress they felt.

These results do indicate that while there may be a genetic pre-disposition to an increased stress response to psychosocial stressors, this is not a large effect, and that there are likely to be other factors that contribute to issues with psychosocial stress in the workplace. With further research it may be possible to develop employee assistance or employee prevention programmes that are tailored to individual employees, which consider any genetic predisposition to increased sensitivity to psychosocial stress. This may involve implementing coping mechanisms early on in an employee's job to try and mediate sensitivity to psychosocial stressors.

It should also be noted that any use of genetic information in the workplace needs to be carefully considered as it brings a unique set of ethical, legal and social considerations. While information regarding the genetic predisposition to stress, depression, or anxiety, particularly under specific occupational circumstances can be used to create employee prevention programmes or to tailor jobs to suit individual employee needs, this needs to be balanced against the potential for new forms of stigma, discrimination, or social alienation (Brandt-Rauf & Brandt-Rauf, 2004).

It is also worth noting that while there were no significant results produced and there appears to be a very small relationship between 5-HTTLPR and psychosocial stress at best, there are many other genetic markers that may have a stronger relationship with psychosocial stress. However, until such relationship is found, personalised interventions in the workplace will need to continue to utilise some of the more subjective measures of psychosocial stress, such as surveys.

4.3 Limitations

There are several limitations with how the meta-analysis was conducted that need to be noted and improved upon for any future replications of this study.

4.3.1 Literature Search

There were several areas that have the potential for bias to affect the outcome of the meta-analyses conducted. The biggest area for concern was the inclusion and exclusion criteria. While care was taken to not deselect any potential studies in the early stages of the literature search, there was no way to guarantee that this has not happened. The search strategy and search engines used during the literature search may not have been as comprehensive as required to ensure all relevant studies were found. There was the potential that some relevant search terms may have not have been used in the search leading to missed studies. In any future replications of this study, the literature search should be conducted concurrently with at least one other research. The results from all researchers should then be cross-checked to calculate the inter-researcher reliability of the literature search.

4.3.2 Data Extraction

Although all studies reported the required data, only the raw data for one study was able to be obtained. This meant that those studies which reported the required information in graph format had to have the data extracted from the graph for the studies to be able to be used. The software Graphclick was used for this, and while previously studies (Flower, McKenna, & Upreti, 2016., Boyle, Samaha, Rodewald, & Hoffmann, 2013) have reported high validity and reliability of the results obtained using Graphclick, there is still room for human error in the results obtained. It would have been beneficial to have had the raw data from at least one of the studies where Graphclick was involved in obtaining the data, so that the results obtained could have been cross-checked to check if human error was an issue in this study.

Secondly, getting the data into an analysable format required a large amount of statistical transformations in several cases. Two studies reported the log or natural log of the original data, and this had to be converted back to the original results. This data then had to be converted from pg/ml to nmol/L, and from there converted from the standard error of the mean to the standard deviation. While the conversion of units from pg/ml to nmol/L does not create statistical noise, this is not true when converting the standard error of the mean to standard deviation, or when reversing the logarithm of reported data. Without the raw data it is impossible to ascertain how significant this statistical ‘noise’ is, and whether the data used in this analysis differs significantly from the original data.

Thirdly, two of the three samples within studies had to be combined into one sample. In several studies the S/S and S/L genotypes were combined into one sample to keep consistency between all studies. Without having done another meta-analysis with the S/S and S/L samples separate it is difficult to tell if combining these groups together affected the size of the weighted Hedge’s g found for each time band. While having the S/S and S/L genotypes as separate samples would have increased the number of meta-analyses required, it would have allowed the data to be analysed to see if there was a difference between the heterozygous genotype (S/L) and the homozygous genotypes (S/S and L/L). The meta-analyses conducted only allow comparisons between the L/L genotype and the S* genotype. The S* genotype included individuals who had the S/L alleles. Analysis of the three separate genotypes may have revealed information on if the slight effect found inset of meta-analyses, is unique to the L/L genotype or if it extends to any genotype that has an L allele (eg. S/L). Without further analysis utilising all three possible genotypes it is impossible to make even correlation claims regarding this.

Fourthly, all measurements were condensed into time bands due to the inconsistency between each study on the timing of when the cortisol measurements were taken. By condensing the individual measurements into time-bands it means that there may have been stronger effects at different times which are not reported in this study. For example; by combining measurements into a 20-50-minute band, the peak cortisol measurements at approximately 30 minutes may be significantly reduced when combined with measurements at 50 minutes, as cortisol levels may have dropped significantly by this point.

It is also worth mentioning that the timing of the cortisol measurements in the original studies may have had an effect on the data as cortisol measurements can fluctuate within subjects depending on the time of day that the measurements are taken (Lovallo, Farag, & Vincent, 2010). Although having a baseline measurement taken before the TSST does reduce this limitation, the results found may still be variable depending on the time the TSST was conducted. The studies used in the four meta-analyses did not all state when the TSST was conducted so it was not possible to determine if the time that cortisol measurements were taken had an effect on the results.

4.3.3 Data Analysis

A major limitation of this study was that there was room for human error in several stages of the data analysis. All data was extracted manually from each study, with no cross-checking by a second researcher. Once this data was extracted an excel spreadsheet was used to calculate the initial standard deviation from SEM, as well as conversion between units (pg/ml to nmol/L) and reversing the log of two studies. All calculations in excel were done using the formula function in excel, rather than being calculated manually, however the formulas had to be input manually rather than using an existing template or syntax. The use of excel for some limited data transformation was necessary so that the data could be formatted in a way that was able to be analysed in CMA.

It is also likely that the results of the four meta-analyses conducted are subject to publication bias, as all bar one of the studies used in the meta-analysis were published articles and the unpublished study was a PhD thesis. The potential publication bias may be reduced as several of the studies used in this meta-analysis do not report significant results, which is relatively unusual for published articles, although less unusual in medical research. It would have been beneficial for more unpublished studies to have been obtained for use in the meta-analysis, but time did not permit the search and subsequent inclusion of other unpublished studies. The funnel plots created for each of the meta-analyses also indicate that some bias is present as they are all asymmetrical, with a large gap on the bottom left of the plot.

4.4 Areas for Future Research

The meta-analyses conducted raise many interesting avenues for future research. One of the main limitations with this research is that with the limited number of studies available it is difficult to assess whether the results found were accurate or just down to chance. To overcome this, further studies need to be conducted looking at the relationship between the 5-HTTLPR genotype and psychosocial stress. In particular it would be beneficial to conduct research using a modified version of the TSST that more closely reflected the workplace, rather than a predominantly laboratory based test, as this would increase the generalisability of the results.

To increase the applicability of this research for use in the workplace, it would be beneficial for future research to incorporate perceptions of felt stress with any future studies on 5-HTTLPR and psychosocial stress. There appears to be a limited relationship between 5-HTTLPR and cortisol responsivity to psychosocial stress, however there may be a relationship between 5-HTTLPR and perceived or felt stress after exposure to psychosocial stress. This area of research is also important to look at as physical stress reactions, such as the increase in cortisol, may not translate directly into how stressed individuals perceive that they are. For example, while an individual may have elevated cortisol levels, they may not feel like they are stressed.

It would also be interesting to look at the mediating effects of coping mechanisms and previous experiences in relation to cortisol responsivity after being exposed to psychosocial stress. Current research has looked at the effects of previous stressful life events in relation to cortisol reactivity and psychosocial stress, however it does not consider coping mechanisms which may be a mediating factor on the relationship between cortisol reactivity and psychosocial stress (Wan, Couture-Lalande, Lebel, & Bielajew, 2017., Mazurka, Wynne-Edwards, & Harkness, 2016). With the long-term goal of being able incorporate genetic research into the workplace it may also be beneficial to evaluate the effectiveness of employee assistance programmes, or stress related interventions, on the individuals with different 5-HTTLPR genotypes to see if there is a genetic pre-disposition to interventions being successful.

While further research on the relationship between 5-HTTLPR genotypes and psychosocial stress is needed, it would also be beneficial to conduct further research on individual attitudes to the use of genetic testing in the workplace. This research is important to see if genetic differences are a viable option for designing personalised interventions for the workplace. A pilot study was conducted in 2005 by Roberts, Warner, Geppert, Rogers, & Hammond, however this could be further developed to include individuals who have been part of an organisation where genetic testing is used, rather than as a hypothetical situation.

4.5 Conclusion

While the results found in the four meta-analyses were not statistically significant, this does not mean that the results obtained are not important or should be discounted. These results contribute to the current field of knowledge by summarising a set of diverse results from 8 previous studies and provide a discussion point for future research to be based on, although this meta-analysis should not be taken as a final and accurate viewpoint of the effect 5-HTTLPR genotypes have on the stress response individuals have to the TSST. There are multiple limitations with this analysis as mentioned previously, and while limited recommendations could be made for incorporation of these results into the workplace, new research is constantly being added to this field which will change and improve our understanding of this area and how it can be used in an organisational context.

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