Neurobiological mechanisms of affective touch and their role in depression

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Abstract

The aim of this investigation was to determine whether i) affective touch has a role in mediating beneficial social influences on resilience to depression and ii) whether affective touch acts through specific skin CT afferents to enhance central serotonin function.

To develop and validate the Touch Experiences and Attitudes Questionnaire (TEAQ), 117 items about experiences and attitudes to touch were completed online by 618 participants. Principal components analysis reduced this to 57 items and 6 factors. Three factors concerned touch experienced; in social situations (CST), in intimate relationships (CIT) and during childhood (ChT) and 3 factors concerned attitude to touch; in intimate relationships (AIT), with unfamiliar people (AUT) and in Skin Care (ASkC). The shortened TEAQ was completed by a second sample of 704 participants. Confirmatory factor analysis found the 6 factor structure to be a good fit of the data, suggesting the TEAQ to be valid and reliable.

Participants completed some demographic questions and some questionnaires to determine their current psychiatric symptoms, social circumstances, recent life events, childhood adversity and personality alongside the TEAQ. Currently depressed participants had lower touch scores for all factors compared to healthy controls. Remitted depressed participants had significantly lower touch scores on all factors except CST, ASkC and AIT compared to healthy controls. A multiple regression analysis found neuroticism, satisfaction with social support, recent life events, CIT and childhood adversity (CHA) to be predictive of depression, whereas extraversion, number of social supports, ChT and CST, did not significantly predict depression score. Logistic regression analysis found ChT, CHA and neuroticism to predict vulnerability to depression, but not AIT or AUT. It was concluded that CIT was the most important aspect of affective touch for promoting resilience to depression.

The CNS effects of pleasant and unpleasant touch were investigated using fMRI in healthy female volunteers. It has been hypothesised that a novel class of CT afferent fibres in hairy skin encodes affective touch. Therefore, CNS responses to pleasant stroking of the forearm with stroking of the fingers were compared. No differential CNS effects of forearm stroking over finger stroking were seen. Indeed, more brain regions were activated by pleasant brush stroking of the fingers which lack CT afferents. Pleasant brush responses in left inferior frontal gyrus were attenuated by tryptophan depletion. However, the midbrain raphe was activated by unpleasant brush stroking and de-activated by pleasant and this effect was abolished by tryptophan depletion. This study found little evidence that CT afferents in hairy skin have a specific role in affective touch and serotonin cells of the raphe appear engaged by unpleasant stimuli rather than pleasant.

In conclusion, the results of the questionnaire study indicated touch (hugs, kisses, stroking) in intimate relationships may promote resilience to depression whereas touch with other social contacts does not, suggesting type of affective touch to be important. It is suggested that future studies of the role of current social support and of early adversity in depression should include assessments of the correlated dimension of affective touch. The fMRI study found little evidence for a specific peripheral touch receptor encoding pleasant affective touch. The median raphe nucleus was inhibited by pleasant touch and this is in keeping with the idea that that aversive stimuli activate serotonin projections to the forebrain but not that this is strengthened by affective touch. Further investigation is required to identify CNS mechanisms of affective touch.
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Alternative format thesis

This thesis has been submitted in alternative format as it allowed me to incorporate the manuscripts I have prepared for publication into my thesis. This thesis consists of a general introduction to this research field, with a discussion of previous literature and the contribution this thesis makes to the research field. This is followed by a general methods section which details the methods used during this investigation and why they were chosen. Three manuscripts prepared for publication as journal papers then follow. The first two manuscripts have been prepared for submission to the journal Psychological Medicine and details the results found during my questionnaire study. The third manuscript has been prepared for submission to Cerebral Cortex and details the results found from my imaging investigation. The final section contains a general discussion of the research presented in this thesis and provides an overall conclusion for the thesis as a whole.
1. Introduction

According to the World Health Organisation, depression is the leading cause of disability, as measured by years lived with disability (YLDs) and was ranked the 4th leading contributor to global burden of disease in the year 2000. It is expected that by 2020, depression will be the 2nd leading contributor to global disease (World Health Organisation, 2010). Major depressive disorder (MDD, also known as unipolar depression) has a lifetime prevalence of 5-10%. Women have an almost two-fold greater probability of being affected by MDD than men (Hamet and Tremblay, 2005).

The factors that have been implicated in the pathogenesis of depression are schematically illustrated in figure 1. This figure illustrates that environmental and physiological factors contribute to pathogenesis, the physiological component including dysfunction of the neurotransmitter serotonin or 5-hydroxytryptamine (5-HT). The environmental risk factors are childhood neglect and abuse which may act by affecting development of the brain and how it processes emotional and cognitive information giving rise to vulnerable personality traits such as neuroticism (Brown et al., 1999). In adult life, stressful life events often trigger the onset of a depressive episode and research has shown that a lack of social support during a stressful life event increases the risk of depressive onset (Brown et al., 1986). Adverse experiences during child and adulthood and a lack of social support increase an individual’s cognitive vulnerability to depression.

Serotonin is the main neurotransmitter involved in the aetiology of depression, a conclusion supported by the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression (Nestler et al., 2001) and the fact that experimentally reducing serotonin levels in the brain through acute tryptophan depletion causes a return of depressive symptomology in individuals who have recently recovered from depression (Delgado et al., 1990). Genetic factors account for about half the risk of depression and genetic variation in some specific genes appears to increase risk. The genetic polymorphism most strongly implicated in depression is found in the serotonin transporter gene linked polymorphic region (5-HTTLPR). A mutation in this region has led to the existence of two alleles for this gene; a long and a short form. Individuals with one or two short alleles have
been found to have reduced serotonin function causing them to be more vulnerable to depression (Caspi et al., 2003). Serotonin regulates stress hormone release and raised cortisol levels have been associated with vulnerability to depression (Lanfumey et al., 2008). The combination of serotonin and cognitive vulnerabilities to depression, increases the risk of a depressive episode, especially in the context of life adversity.

The question discussed during this thesis is whether early and current social risk factors act entirely through cognitive biases that increase vulnerability to depression, or whether social factors may have direct neurobiological effects that increase vulnerability. For example, animal models of social isolation have shown serotonin neurotransmission is affected by pre-weaning isolation. These studies also found pre-weaning isolation affected the neurochemical ability of the brain to adapt to stress (Meaney et al., 1988, 2000, 1994). In adulthood, animals isolated following restraint stress were found to be more anxious than those not isolated following restraint stress (Dourish et al., 1989). These findings suggest social isolation has a neurobiological effect on the brain which increases the risk of a depressive episode developing. This neurobiological effect appears to involve a change in brain serotonin function (Deakin, 1996).
Affective touch is a major factor which is lacking for socially isolated individuals. One possible mechanism by which social isolation increases the risk of a depressive episode would be if affective touch is specifically encoded by the brain. The encoding of affective touch by the brain is likely to involve serotonin transmission, as this has been shown to be altered by animal models of social isolation (Meaney and Szyf, 2005). The aim of this thesis is to investigate the hypothesis that affective touch promotes resilience to depression through enhancing central serotonin function.

1.1. The role of serotonin in depression

1.1.1 The symptoms of depression

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) states the symptoms an individual would present if they were depressed. Symptoms of depression include low mood, a loss of interest in pleasure (anhedonia), weight change, sleep disturbances, psychomotor change (eg. moving more slowly than usual), loss of energy, feeling worthless, an inability to concentrate or recurrent thoughts of death, for at least two weeks (American Psychiatric Association, 1994). In order for an individual to be diagnosed with depression, they must present a total of five of the above symptoms with at least one of them being low mood or anhedonia. Depression is recurrent and often chronic. Depression can be subdivided into two forms; bipolar and unipolar, which is classified by depression with or without periods of mania respectively (Hamet and Tremblay, 2005). This thesis considers unipolar depression only.

1.1.2. The anatomy and function of the serotonin system

As shown in figure 2, the majority of serotonin cell bodies of the brain are located in the median and dorsal raphé nuclei (MRN and DRN respectively) which are located in the brainstem. From these nuclei, serotonin pathways innervate almost all brain regions, including the cerebral cortex, cerebellum and the midbrain (Deakin, 1996, Törk, 1990). The DRN and MRN overlap in the areas of the brain they innervate, but the cerebral cortex, thalamus, caudate, putamen, nucleus accumbens and dopamine nuclei of the midbrain are
mainly innervated by DRN projections. The hippocampus, septum and other limbic regions are mainly innervated by the MRN (Nestler et al., 2001). The habenula, part of the epithalamus, is one of the few forebrain structures which projects to the DRN. The habenula influences the activity of the serotonin neurons found in the raphe and modulates the release of cerebral serotonin (Morris et al., 1998).

Figure 2: The serotonergic projections of the human brain from the raphe nuclei to various parts of the central nervous system.


### 1.1.3. Serotonin modulates the stress response

The forebrain serotonin system has been implicated in minimising the impact psychosocial stressors have on behaviour. When severe life events occur, depression and anxiety occurs. Serotonin pathways are concerned with preventing and adapting to stress. Aversive events cause the release of serotonin, but the system is complicated, with different forms of stress producing different coping responses, modulated by different serotonin
projections which signal via different receptor subtypes (Deakin and Graeff, 1991, Gardner et al., 2009, Lowry et al., 2005).

As depicted in figure 1, there are two major locations in the brain from which serotonin neurons project. These regions are known as the DRN and the MRN. Neuronal pathways arising from the DRN innervate the basal ganglia, nucleus accumbens and amygdala and are closely associated with dopamine pathways. These pathways are associated with locomotor guidance and incentive-motivation. The MRN is at the same level as the locus coeruleus and innervates the thalamus, neocortex and hippocampus and modulates sensory transmission.

The DRN has been implicated in facilitating motor defence and avoidance in anticipation of aversion and the MRN mediates sensory defence mechanisms, minimising the impact of aversion once it has happened. The DRN innervates areas rich in 5-HT\textsubscript{2}, 5-HT\textsubscript{2A} and 5-HT\textsubscript{1D} receptors. DRN innervation of 5-HT\textsubscript{2} receptors in the basal ganglia and the amygdala acts as an anticipatory anxiety mechanism, warning the organism of impending noxious stimuli and guiding the organism away from danger. Over-active DRN projections could underlie the aetiology of generalised anxiety disorder (GAD). Under-active DRN projections could lead to more impulsive behaviour.

The MRN innervates the temporal lobe and brain regions associated with memory. The MRN modulates memory processes, enabling one to adapt to an aversive event by denial or dissociation if the event becomes chronic or repeated. A reduced MRN response to a threatening life event would lead to the onset of depression as an individual would be unable to adapt. 5-HT\textsubscript{1A} receptors are particularly associated with the terminals of the MRN. Reduced 5-HT\textsubscript{1A} provides one mechanism by which depression could occur and a mechanism of action of antidepressants could be to increase 5-HT\textsubscript{1A} signalling in MRN projections (Deakin, 1996).
1.1.4. Serotonin and depression

The monoamine theory of depression was proposed by Schildkraut in 1965 and is still the main biochemical theory of depression. It states that depression is caused by reduced monoamine neurotransmitters in the brain. This hypothesis was proposed based on evidence that drugs effective in treating depression all increase monoamine levels, despite having differing mechanisms and sites of action. Serotonin is thought to be the main monoamine involved in depression (Hensler, 2006, Rang et al., 2005). Evidence for a role of serotonin in depression comes from three main sources. Genetic investigations have identified a polymorphism in the serotonin transporter gene which increases vulnerability to depression (Caspi et al., 2003). The most commonly prescribed and efficacious treatment for depression is selective serotonin re-uptake inhibitors (SSRIs) (Nestler et al., 2001). Acute tryptophan depletion is an experimental technique used to reduce serotonin levels in the brain. Following tryptophan depletion, recovered depressives experience a return of depressive symptomology (Delgado et al., 1990). This evidence mainly implicates reduced serotonin function in the mechanism of action of antidepressant drugs, but direct evidence that reduced serotonin function occurs in depression remains inconsistent.

1.1.4.1. Pharmacological treatment of depression

The first clinically used antidepressant was iproniazid, a monoamine oxidase inhibitor (MAOI). Iproniazid was first reported to be effective as an antidepressant by Nathan Kline in 1957. Also in 1957, Roland Kuhn reported imipramine, a tri-cyclic antidepressant (TCA) to be an effective antidepressant (Ayuso-Gutierrez, 2002). Other MAOIs such as phenelzine and isocarboxazid were developed shortly after these discoveries. Now there are three main classes of antidepressant drugs; MAOIs, TCAs and selective serotonin re-uptake inhibitors (SSRIs) (Baldessarini, 2006).

MAOIs reversibly inhibit monoamine oxidase, the enzyme which converts monoamines to inactive metabolites. The cytoplasmic concentration of monoamines in nerve terminals is thus increased by MAOIs, which in turn increases the leakage of monoamines into the synaptic cleft and therefore monoaminergic stimulation of postsynaptic receptors.
MAOIs affect serotonin levels the most and dopamine levels the least (Nestler et al., 2001, Rang et al., 2005).

Tricyclic antidepressants such as imipramine inhibit the reuptake of noradrenaline and serotonin and to a lesser extent dopamine into nerve terminals, thus increasing their synaptic concentration. Originally it was thought that the monoamine of importance was noradrenaline, but then it was realised that it could be serotonin. The most commonly prescribed antidepressant is fluoxetine, a selective serotonin reuptake inhibitor (SSRI). The efficacy of SSRIs implicates serotonin, not noradrenaline as the principle neurotransmitter involved in depression. The fact that all antidepressant drugs take at least two weeks to induce a physiological effect, despite their pharmacological effects being produced immediately, suggests that a simple lack of serotonin in the brain is not the cause of depression. It is likely that a secondary mechanism is induced by an increased serotonin level, which then reduces the symptoms of depression. The nature of this secondary mechanism is unknown at present (Nestler et al., 2001, Rang et al., 2005), although many theories have been proposed. The theories proposed include 5-HT\textsubscript{1A} autoreceptor desensitisation (Elena Castro et al., 2003, Le Poul et al., 1995) and the induction of hippocampal neurogenesis (Santarelli et al., 2003) following chronic SSRI treatment.

1.1.4.2. Acute tryptophan depletion (ATD)

Further evidence implicating reduced serotonin function in depression comes from ATD studies. Tryptophan is the precursor of serotonin. As tryptophan is an essential amino acid, levels of tryptophan and therefore serotonin can be dramatically reduced by a dietary method known as ATD. Subjects follow a low tryptophan diet for 24 hours prior to the experiment. This diet is typically 2500 calories, 48 g protein and 160 mg tryptophan. Following this 24 hour period, 100 g of powdered amino acids in flavoured solution is administered orally. The amino-acids are in proportions similar to that found in human milk. Tryptophan is omitted in the tryptophan depletion drink, but not in the control drink. Aspartic acid and glutamic acid are omitted from both drinks, due to concern over their
toxicity at high doses. The sulphur containing amino-acids have an unpleasant taste and can induce nausea and vomiting (Delgado et al., 1990, Hood et al., 2005).

Plasma tryptophan is 95% albumin-bound. Free plasma tryptophan traverses the blood-brain barrier via the large neutral amino acid (LNAA) transporter. Tryptophan therefore competes with all other LNAAAs for transportation from the plasma into the brain. If the ratio of tryptophan to all other LNAAAs is lowered, then this will cause all other LNAAAs to be transported into the brain and not tryptophan, thus lowering brain tryptophan levels (Hood et al., 2005). The second mechanism by which ATD reduces brain tryptophan levels is by hepatic protein synthesis induction. Protein synthesis reduces plasma amino acid levels, which were increased by ATD. As no tryptophan is administered orally, this must be derived from an endogenous source, thus further depleting the ratio of plasma tryptophan to other LNAAAs. This method decreases plasma tryptophan levels by approximately 90% within 3-5 hours (Delgado et al., 1990).

Sex differences in the response to tryptophan depletion have been reported. ATD has a greater tendency to lower mood in females even if tryptophan is depleted to an equal extent in males and females (Bell et al., 2005). Nishizawa et al., (1997) found the rate of serotonin synthesis in healthy males was 52% greater than females. ATD caused serotonin synthesis to be reduced by a factor of 9.5 in males, compared to a factor of 40 in females. Women with the SS polymorphism of the serotonin transporter gene have been found to be particularly susceptible to the mood altering effects of ATD. People with the SS alleles have lower serotonin re-uptake activity which could account for this finding (Bell et al., 2005).

Tryptophan depletion induces a temporary depressive relapse in remitted depressed patients (Deakin, 1996, Delgado et al., 1990), but only in patients who were treated with SSRIs, not in those treated with other classes of antidepressant drugs (Nestler et al., 2001). Symptoms induced include depressed mood, psychic anxiety, decreased energy, reduced interest and anhedonia. This effect usually occurs 5-7 hours after the administration of the amino acid solution, but effects can occur after only two hours, or sometimes the day after the administration of this solution. Unwanted effects of tryptophan depletion include nausea and vomiting, drowsiness, sweating and feeling faint. Healthy male subjects who underwent
tryptophan depletion showed a mild impairment of attentive performance and increased negative mood, but did not show clinical depression (Delgado et al., 1990). A meta-analysis by Ruhe et al., (2007) found no effect of ATD on mood for healthy volunteers, or individuals who were currently depressed. Participants in remission from depression or with a family history of depression were found to experience mood lowering effects following ATD. It appears that ATD has an effect only on individuals vulnerable to depression. The results of ATD studies therefore suggest that lowering of serotonin does not directly induce a lowering of mood.

One patient reported an ‘electrical feeling’ in their arms when depressed, which was not present after the subject recovered. This is likely to be due to a malfunction in the serotonin system, supported by the finding that 4 hours after ATD, this ‘electrical feeling’ returned and was alleviated following tryptophan repletion. This finding suggests serotonin may be involved in skin sensations (Delgado et al., 1990).

Another method of serotonin manipulation is to use parachlorophenylalanine, a serotonin synthesis inhibitor. Parachlorophenylalanine has also been found to cause depressive relapse. The serotonin system interacts with the norepinephrine system, GPCRs, neuropeptides and other signalling systems, therefore these systems may also be involved in the aetiology of depression. Rather than lowered serotonin levels directly causing depressive symptoms, it could be the balance between serotonin, norepinephrine and dopamine being altered in serotonin manipulation studies which causes depressive relapse (Delgado et al., 1990).

1.1.4.3. Genetic risk factors for depression

The pharmacological treatments of depression described above and the effects of acute tryptophan depletion indicate that manipulation of serotonin affects mood, but is serotonin function actually disturbed in depression? Genetic variation is a natural experiment of serotonin manipulation. The serotonin transporter (5-HTT), which is responsible for the re-uptake of serotonin from neuronal synapses, has been the focus of a large number of genetic investigations, particularly as it is this transporter which is blocked by SSRIs.
A polymorphic region located on the proximal 5’ regulatory region of the serotonin transporter (5-HTT) gene, found on chromosome 17q, has been linked to a predisposition to depression, as well as being linked to anxiety, aggression-related personality traits and affective disorders (Bennett et al., 2002, Caspi et al., 2003, Hamet and Tremblay, 2005). This region is called the 5-HTT gene-linked polymorphic region (5-HTTLPR). A long (‘L’) and a short (‘S’) form of the 5-HTTLPR allele exists. The S form is associated with lower transcriptional efficacy of the promoter than the L form and therefore a reduced 5-HTT density (Caspi et al., 2003).

The G x E interaction has been illustrated by four separate lines of evidence involving in vivo, primate and clinical studies (Caspi et al., 2003). 5-HTT knockout mice developed normally, but their serotonin levels were reduced by 40-60% for the (-/-) strain. Basal ACTH levels were similar for all three strains, but the two knockout strains had a greater increase in ACTH levels in response to stress with the (+/-) strain having a lower increase than the (-/-) strain. Results produced by a light/dark box experiment showed the knockout mice to have greater fearfulness and anxiety than the wild-type mice, although their behaviour under normal conditions was the same as that of wild-type mice (Murphy et al., 2001).

Rhesus macaques also show a variation in the length of the promoter region of their 5-HTT genes. Rhesus monkeys with an allele analogous to that of the human S allele, showed reduced CSF 5-HIAA concentrations when peer-reared compared to L/L monkeys. When monkeys with an S allele were parent reared, no difference in CSF 5-HIAA concentration was found. Early adverse life events were therefore required to differentiate between L/L and L/S monkeys (Bennett et al., 2002).
A study of the effect of life events on people with different genotypes for this allele was investigated. The findings were significant and support the hypothesis that a G x E interaction is required for the onset of depression and other related mental illnesses to develop. The results obtained are illustrated in figure 3 (Caspi et al., 2003).

These findings implicate that serotonin function is disturbed in depression and that stressful life events increase the risk of depressive onset. A treatment that decreases stress, or alters the serotonin system, or both is therefore likely to help reduce the onset of depression. It was found that 33% of subjects with an S allele and four or more stressful life events over the past 5 years became depressed whereas only 17% of LL homozygotes became depressed. Although this is a significant difference, it also suggests other factors are involved, otherwise one would expect the prevalence to be greater than this (Caspi et al.,
Evidence to support the hypothesis that stress often acts as a trigger for a depressive episode is clearly illustrated by these findings.

1.1.4.4. Is serotonin function decreased in depression?

In the 1960’s and 1970’s, many attempts were made to measure serotonin function using peripheral measures. These included measuring uptake of serotonin by blood platelets. Depressed and remitted depressed individuals were found to have a reduced rate of serotonin uptake by blood platelets compared to individuals with no psychiatric history (Coppen et al., 1978). The reliability of this finding was reported as high by Cowen et al., (2008), but this is an indirect measure of brain serotonin function. Another indirect measure used at a similar time was plasma tryptophan levels, which were found to be lower in depressed patients (Cowen et al., 1989).

Imipramine is a tricyclic antidepressant. Many investigations into platelet imipramine binding were carried out, again with conflicting results. A meta-analysis carried out by Ellis and Salmond (1994), concluded that imipramine binding to platelets was lowered in depressed individuals. Despite this conclusion, platelet imipramine binding is an indirect, static measure of brain serotonin function, which limits the conclusions which can be drawn from these findings in terms of brain serotonin function in depressed individuals.

Another indirect method used to investigate differences between serotonin function in depressed individuals and healthy controls was to measure cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations. The results from these investigations suggested a subtype of depressed individuals, who were more likely to attempt suicide, had reduced CSF 5-HIAA, but other depressed individuals had normal CSF 5-HIAA (Owens and Nemeroff, 1994). Post-mortem investigations of the brains of suicide victims reported contradictory results, with some investigations reporting increased 5-HIAA, some decreased and other investigations no difference between 5-HIAA levels in suicide compared to non-suicide victim’s brains (Cheetham et al., 1989, Ferrier et al., 1986).
Post-mortem investigations into 5-HT₁₆ receptor binding have provided contradictory findings with some investigations reporting increased 5-HT₁₆ radioligand binding in the prefrontal cortex and hippocampus of suicide victims, but other investigations have reported no differences. Post-mortem studies of 5-HT₂₆ binding have also been contradictory with some investigations reporting increased prefrontal receptor binding in suicide victims compared to non-suicide victims and others reporting a decreased binding and still others reporting no change in prefrontal 5-HT₂₆ binding. Some investigations of 5-HT₂₆ binding in the hippocampus report decreased binding while others report no change. Decreased 5-HTT binding in post-mortem brains from individuals with a lifetime history of depression has been reported, as well as antidepressant free suicide victims. This finding is again contradicted by other investigations which have reported no change in 5-HTT binding in suicide victims with a depressive disorder (Stockmeier, 2003). While studying post-mortem brains is advantageous over measurements of platelet binding and CSF 5-HIAA concentrations in that it is a direct measure of brain serotonin function, it is a static measure and many artefacts may be present in post-mortem brains.

A more direct measure of brain serotonin function was obtained using drug challenge tests. An acute dose of SSRI was found to cause a reduced prolactin release in depressed and remitted depressed individuals compared to healthy controls, suggesting impaired serotonin mediated prolactin release in individuals prone to depression (Cowen, 2008). Further neuroendocrine challenge tests supported these findings. Depressed patients were found to have a blunted release of prolactin in particular and also growth hormone, in response to intravenous tryptophan in depressed patients who had lost less than 10 pound in weight (Charney et al., 1982, Cowen and Charig, 1987, Deakin et al., 1990). These methods of investigating serotonin function were advantageous over the previous methods described in this section in that they were measuring brain serotonin function more directly, although this was limited to the response of the hypothalamus, and the measurement was static rather than dynamic.

More recently, more direct in vivo quantification of serotonin binding have been made possible through the use of positron emission tomography (PET). There was hope that by using PET, conclusive evidence could be obtained that depressed individuals had disrupted
serotonin function. Investigations using radioligands of 5-HT_{1A} receptors have found binding density to be reduced in both depressed and remitted depressed individuals, indicating this to be a trait rather than state marker for depression.

PET investigations into 5-HT_{2A} and 5-HTT binding have produced contradictory results, with some investigations reporting decreased binding, some increased and some comparable binding densities compared to healthy controls (Cowen, 2008). A PET investigation carried out by Selvaraj et al., (2009) found that unmedicated, depressed individuals had reduced 5-HTT binding compared to healthy controls.

Despite the many investigations using many different methodologies, conclusive evidence for abnormal serotonin function in depressed individuals has failed to materialise. Neuroendocrine studies have provided evidence of a serotonin deficit in depressed individuals and PET studies suggest post-synaptic 5-HT_{1A} receptor density to be reduced in depression. Studies of serotonin uptake sites, at best show only a small decrease in serotonin terminals in depressed individuals, rather than the major loss expected. These investigations highlight the complexity of the neurobiology of depression and show that despite half a century of investigations, the precise differences in serotonin function between depressed and healthy individuals still remains elusive.

1.2. Negative cognitive biases in depression

Many investigations have compared the cognitive biases of individuals with either one or two S alleles of the 5-HTT transporter gene compared to those homozygous for the L allele of the transporter, as individuals with an S allele are more prone to depression. Some investigations into differences in affective processing between individuals with L and S 5-HTT alleles are discussed below.

An fMRI investigation found that subjects either homo- or hetero-zygous for the S 5-HTT allele showed greater amygdala neuronal activity in response to fearful stimuli than individuals who were homo-zygous for the L allele. The amygdala is thought to be
responsible for the emotions of fear and anxiety, suggesting a correlation between increased
fear and anxiety in humans and the presence of an S allele (Hariri et al., 2002).

A further study by Hariri et al., (2005) confirmed the above findings. This study found
amygdala activity to increase in response to fearful or threatening facial expression for all
subjects. Participants who carried the S allele for the 5-HTT gene were found to have greater
right amygdala activation during this response than subjects homozygous for the L allele.
There was no significant difference between left amygdala activity for different 5-HTT
genotypes.

Another gene implicated in the aetiology of depression is the monoamine oxidase A
(MAOA) gene. It could be that subjects with a polymorphism in this gene and an S 5-HTT
allele are even more likely to develop depression if this is combined with the occurrence of
stressful life events. The MAOA gene is located on the X-chromosome. Deficiencies in MAOA
activity has been correlated with aggression in mice and humans, for example childhood
maltreatment had less effect on males with high MAOA activity than low MAOA activity.
MAOA decreases norepinephrine, dopamine and serotonin levels in the brain. Males with
low-activity MAOA represented 12% of the subjects in one investigation, but represented
44% of the criminal convictions obtained by that investigation group. In a group of male
subjects with low-activity MAOA, 85% developed some form of antisocial behaviour (Caspi et
al., 2002).

Negative cognitive biases in depression are present when processing a variety of affective
stimuli in various paradigms. Negative biases are evident when processing emotional stimuli
such as emotional faces. It has been found that depressed individuals tend to report neutral
facial expressions as negative. Tasks involving recall of affective information have found that
depressed individuals recall negative affective stimuli more easily than positive affective
stimuli (Harmer, 2008). Depressed individuals also have a tendency of over general
autobiographical recall. When asked to think of a specific autobiographical memory in
response to a negative affective cue, such as loneliness, depressed individuals tend to give a
categorical, rather than specific autobiographical memory (Hermans et al., 2008).
Evidence to implicate serotonin as the neurotransmitter responsible for negative cognitive biases and therefore some of the symptoms of depression, was recently reviewed by Harmer, (2008). In this review it is observed that acute tryptophan depletion (ATD) has been found to reduce the processing of positive compared to negative affective stimuli in a variety of paradigms, even in healthy individuals who do not experience any mood altering affects following ATD. Increasing serotonin function with antidepressants has been found to have the opposite effect on affective processing on healthy and depressed individuals, with acute as well as chronic antidepressant administration. This provides evidence to support the theory that the negative cognitive biases experienced in depression are caused by reduced serotonin function.

1.3. Personality type and depression

Numerous investigations have been carried out to investigate the relationship between certain personality traits and depression. The personality trait most strongly associated with depression is neuroticism. This trait describes individuals whose emotions are easily aroused by negative stimuli. Neuroticism has a genetic component and is greater in those vulnerable to depression and remitted from depression and higher still in those currently depressed. This shows neuroticism to be state and trait dependent. Neuroticism has been found to be a vulnerability factor for anxiety as well as depressive disorders, which makes it not a specific depressive personality trait. One criticism of the construct of neuroticism is that this personality trait is not evaluated independently of current symptomatology (Enns and Cox, 1997). The neuroticism extraversion openness personality inventory revised (NEO-PI-R) (Costa and McCrae, 1992), a widely used personality measure, actually includes a depression facet within its construct of neuroticism. This makes it difficult to differentiate the personality trait predisposing the individual to depression from depressive symptoms which an individual could potentially experience in a mild form long before the onset of a major depressive episode.

Extraversion describes the personality trait of sociable individuals who show positive emotionality, energy and dominance (Enns and Cox, 1997). Low extraversion has been
associated with depression, although findings are less robust than those for neuroticism. Low extraversion appears to be state rather than trait-dependant for depression with depressed individuals having lower extraversion scores than those who have recovered from depression (Kerr et al., 1970).

Interpersonal dependency is another personality trait associated with some forms of depression. These individuals are thought to be vulnerable to depression when an interpersonal relationship breaks down, causing affection, love or caring from another individual to be reduced. Dependency has been found to be increased in remitted depressed participants compared to levels before depression, suggesting a depressive episode itself may increase dependency (Hirschfeld et al., 1989).

Self-criticism has also been associated with vulnerability to depression. Beck’s concepts of sociotropic and autonomous individuals describe dependent and self-critical individuals. Dependent individuals are sociotropic; they need positive interactions with others and are sensitive to disapproval from others. They find it important to please others and secure attachments. Autonomous individuals are self-critical. They have a need for independence and achieving personal goals. Their concern is personal failure. These personality types are thought to predispose an individual to different types of depression. Beck proposed that highly sociotropic individuals are vulnerable to neurotic/reactive depression, whereas highly autonomous individuals are vulnerable to endogenomorphic depression (Beck et al., 1983). Research has found this proposal to be true. Different stressful life events increase the risk of depression for highly sociotropic or autonomous individuals. Sociotropic individuals are more likely to become depressed following an event relating to an interpersonal relationship, such as a relationship breakdown, whereas autonomous individuals are more prone to depression following an achievement event, such as failure in an exam (Hammen et al., 1989).

An obsessional personality type describes someone who is preoccupied with orderliness, perfectionism, control and conscientiousness. Obsessionality has been found to be higher in depressed individuals, but studies of premorbid obsessionality are currently contradictory. This is thought to be due to the measure of obsessionality used. Perfectionism is thought to exacerbate the perceived failures of an individual, increasing their vulnerability to depression and this trait has been found to be elevated in depressed patients (Enns and Cox, 1997).
1.4. Environmental risk factors for depression

1.4.1. Stressful life events trigger the onset of a depressive episode

Many life events have been identified as risk factors for the onset of depression. These life events include employment, financial, housing, health and relationships stressors. In childhood, stressful life events which are thought to increase the likelihood of a major depressive episode occurring in later life include emotional and physical neglect, childhood abuse and parental loss (Levinson, 2006; Sàenz et al., 2006). Out of these risk factors, a large amount of evidence exists to show childhood risk factors and social isolation are of particular importance. The majority of these stressors involve either a lack of physical contact or bad physical contact. As isolation has also been linked to depression (Deakin, 1996), this suggests touch may affect the development of depression.

1.4.2. The neuroendocrine response to stress and its role in depression

Stress is known to often precede the onset of depression (Wurtman, 2005). Acute stress causes the release of corticotrophin releasing factor (CRF) from the corticolimbic regions of the brain. CRF activates the major noradrenergic nucleus of the brain, the locus coeruleus, causing increased sympathetic tone and therefore increased anxiety and arousal. Acute stress also causes the release of CRF from the hypothalamus, causing adrenocorticotropic hormone (ACTH) release from the anterior pituitary, which induces cortisol release from the adrenal cortex. This cortisol then inhibits further release of CRF and ACTH by a negative feedback mechanism acting on the hypothalamus and anterior pituitary. Acute stress causes cortisol receptors in the brain to be rapidly desensitised and therefore this negative feedback mechanism of cortisol to be less effective. Shortly after the acute stress, cortisol levels decrease and cortisol receptors return to their normal level of sensitivity (Leonard, 2005).

Some subjects are able to adapt to chronic stress and their ACTH and cortisol levels are lower than that seen in acute stress. Subjects unable to adapt to chronic stress
hypersecrete cortisol. This leads to a desensitisation of brain glucocorticoid receptors, which leads to compromised negative feedback control of ACTH secretion. Chronic stress also increases the levels of arginine vasopressin (AVP) and pro-inflammatory cytokines which also stimulates the secretion of cortisol from the adrenal gland. AVP has a synergistic effect with CRF on ACTH secretion (Levine, 2002). Glucocorticoids inhibit 5-HT<sub>1A</sub> receptor expression and increase 5-HT<sub>2A</sub> receptor expression. Central CRF administration to rats has been shown to increase anxiety and increase the concentration of dopamine, noradrenaline and 5-HIAA in the hypothalamus (Leonard, 2005). Animal experiments involving uncontrolled stress, such as inescapable shock or restraint stress, increase serotonin turnover and decrease serotonin levels in the amygdala, prefrontal cortex, nucleus accumbens and lateral hypothalamus (DeBellis, 2005). This suggests CRF could be responsible for the decreased serotonin levels induced by stress. Depression is associated with reduced serotonin function, thus suggesting a possible mechanism by which chronic stress may cause the development of depression.

A greater neuroendocrine response to stress was produced by rhesus macaques with an S 5-HTT allele than with two L 5-HTT alleles (Vicentic et al., 2006). This suggests subjects with an S 5-HTT allele have a greater predisposition to depression as they have increased CRF release and are less able to adapt to chronic stress. This is further supported by findings that 5-HTT knockout mice have been shown to have reduced 5-HT<sub>1A</sub> receptor function and an increased corticosterone response when stressed (Li et al., 2004, Vicentic et al., 2006).

1.4.3. Individuals who have suffered childhood adversity have an increased rate of depression and increased cortisol levels

Five types of childhood trauma have been identified: sexual, emotional and physical abuse and emotional and physical neglect (Moskvina et al., 2006). Out of these five types of trauma, two involve negative physical contact and one involves a lack of good physical contact. Moskvina et al., (2006) studied depressed individuals and used the childhood trauma questionnaire to identify participants who had suffered childhood trauma. Over two-thirds of the participants reported childhood trauma of some sort. A negative correlation was identified between age of onset of depression and the severity of childhood trauma experienced and it was found that total childhood trauma score significantly predicted age of
onset of depression, as determined by regression analysis. A stepwise regression analysis showed emotional abuse and physical neglect were the types of childhood trauma which predicted age of onset of depression most strongly (Moskvina et al., 2006).

Harkness & Monroe (2002) also investigated the correlation between depression and childhood adversity, but used only female participants. This study used only depressed participants. The structured interview for DSM-IV axis I disorders (SCID) was used to identify participants who were suffering from depression. Research Diagnostic Criteria was used to categorise subjects as suffering from endogenous or non-endogenous depression. The Hamilton Depression Rating Scale was used to determine the presence and severity of depressive symptoms. The Childhood Experience of Care and Abuse interview (CECA) was used to determine childhood adversity.

This study found endogenous depression to be twice as likely if subjects had suffered severe physical abuse, sexual abuse, antipathy or neglect as those who suffered no severe adversity. Endogenous depression was also twice as likely if the subject had experienced marked levels of discord compared to moderate or little/no discord. Participants who had experienced lax or high levels of supervision and discipline as compared to those who experienced moderate levels, were twice as likely to suffer from endogenous depression. The majority of these adverse experiences involve either bad physical contact or a lack of good physical contact, providing further evidence for the relationship between physical contact and depression. High levels of supervision may be associated with reduced good physical contact and increased bad physical contact as physical punishments are likely to occur more often with high levels of supervision. Sexual abuse was significantly associated with a higher severity of depression and greater suicidal ideation than participants who were not sexually abused (Harkness and Monroe, 2002).

Hill et al., (2001) also illustrated the effect of early childhood adversity on the development of depression in later life. This study involved 1181 female participants aged 25-36 completing a questionnaire asking about childhood experiences and mental health problems as an adult. The second part of this study involved categorising participants depending on the childhood adversity they experienced, then interviewing a random
selection of the members allocated to each category. The CECA was used to obtain information about participants’ childhood experiences.

This study found child sexual abuse and poor parental care to be associated with the onset of major depression and poor love relationships at age 21-30 years. A link was also found between poor love relationships and the onset of depression at age 21-30 years. Poor love relationships at age 26-30 years was not predicted by major depression at age 21-25 years, but major depression at age 26-39 years was predicted by poor love relationships at age 21-25 years. This suggests poor love relationships to predispose an individual to depression. The relationship between intimate relationships and childhood adversity was also investigated. The majority of participants who experienced no sexual abuse or poor parental care in childhood experienced good love relationships as an adult. Two thirds of the participants who reported both sexual abuse and poor parental care during childhood experienced poor relationships as adults. When childhood adversity was not present, poor love relationships caused an increased rate of depression from 2.5% to 16.0%. Participants who experienced poor parental care, but good love relationships showed a depression rate of 22.0% compared to 53.7% of participants who experienced poor parental care and poor love relationships. Participants who had experienced child sexual abuse showed similar rates of depression whether they had experienced poor parental care or not and showed an average depression rate of 33%.

Bifulco et al., (1998) carried out a study of 105 non-depressed working-class mothers over a period of 14 months. This population was selected as they are a group at particular risk from depression. Two vulnerability factors were investigated: psychological and interpersonal vulnerability. Psychological vulnerability was present if the subject had a negative image of themselves. Interpersonal vulnerability was present if the subject was experiencing conflict with their partner or children or a lack of support outside the home if the subject was a single mother. Every woman in this study had either psychological or interpersonal vulnerability. It was found that of these women, 37% became depressed with an average episode length of 18 weeks. Over two-thirds of the women in this study experienced at least one severe life event, defined as an event involving high threat or unpleasantness and lasting for at least two weeks. Little difference was found in the rate of
onset of depression between women who had one vulnerability factor and women who had both. A significant difference was seen between women who experienced a severe life event and those who did not, with those who didn’t having a lower rate of depression compared to those who did. Over half the participants had experienced childhood adversity, defined as either severe neglect, physical or sexual abuse before age 17.

Childhood adversity was linked to a greater risk of onset of depression during this study. A significant link between a prior episode of depression and another episode occurring during this study was found. For participants who experienced their first episode of depression as a teenager, their risk of becoming depressed during this study was 2.5 times greater than those with a later onset of depression. The majority of subjects who reported depression as a teenager had also experienced childhood adversity. This therefore illustrates the importance of childhood adversity as a risk factor for the onset of depression in later life. The presence of a severe life event and teenage depression was the best predictor for the onset of depression. All of the factors in this study which defined childhood adversity involve either a lack of good physical contact or the presence of bad physical contact. This study thus highlights the importance of touch experience, particularly during childhood and the risk of a depressive episode in later life.

The relationship between childhood adversity and depression is thought to be due to changes in neurotransmitter systems, particularly the serotonin system. Serotonin is important in the early development of the CNS. Throughout life, it is involved in regulating HPA axis function (Vicentic et al., 2006).

1.5. Social support prevents onset of depression

A study by Brown et al., (1986) investigated the relationship between self-esteem, social support and depression. The study involved the use of semi-structured interviews and involved 400, mainly working class women with at least one child living at home. Married and single mothers were included in the investigation. This investigation studied whether social support following a stressful life event reduced the risk of depression. Having a close, confiding relationship with someone was not found to have any association with depression,
however, receiving crisis support from another individual, defined as high confiding with active emotional support and no negative response, was found to be highly associated with a reduced risk of depression. The women who were found to be most vulnerable to depression following a stressful life event were those that were ‘let down,’ that is, women who reported they had a close, confiding relationship with an individual at first interview and then when interviewed one year later, had experienced a stressful life event, but had not received crisis support from that individual. These women were found to have a 20 fold increase in risk of depression compared to those who did receive crisis support and these women had a comparable risk of depression with women who reported having no confidante at first interview and as having received no crisis support following a life event. One can speculate that active emotional support would be likely to involve affective touch, particularly when support is given by a woman’s husband. Unfortunately, the term active emotional support was not defined in this paper.

A study performed by Dourish et al., (1989) investigated the effect of social support on an animal model of depression. Rats were subjected to acute, uncontrollable restraint stress for 2 hours. Following a period of 18-21 hours, animals were placed on a circular open field for 3 minutes, during which time locomotion was measured. Control animals did not undergo restraint stress. Animals in the control or treatment group were then subdivided into isolated before/grouped after stress, isolated before and after stress, grouped before and after stress or grouped before/isolated after stress. The only animals to show decreased locomotion following stress were those animals which underwent restraint stress and were then isolated. This decrease in locomotion following restraint stress is thought to mimic the effects of depression on the brain. It can therefore be suggested that group housing acts to prevent rats from depressive symptoms and can be likened to the findings in humans that social isolation poses as a risk factor in the aetiology of depression (Dourish et al., 1989).

Harlow et al., (1971) investigated the effect of early isolation on development in primates. Monkeys were completely isolated from birth to an extent such that they did not see or physically interact with another monkey and saw only the experimenter’s hands and arms when necessary for feeding purposes. Monkeys were observed through a one-way vision
window. Following isolation for 90 days, monkeys were housed with age-mates. These monkeys suffered from severe anorexia and had to be forced fed in order to survive. After one month of group housing though, these monkeys were comparable to their age mates in their behaviour.

Monkeys isolated for the first 6 months of life did not develop normal behaviours following housing with age mates. These monkeys showed autistic-like behaviours, increased fear and aggression compared to non-isolated monkeys and were unable to socially interact with age-mates. Monkeys isolated for the first year of their life were even more severely affected. When housed with age-mates they showed no exploratory or playful behaviour. These monkeys were not aggressive and would fail to protect themselves against age-mates, resulting in these monkeys being separated for their own protection (Harlow et al., 1971).

A further investigation carried out by Harlow managed to reverse the depressive symptoms of monkeys isolated for their first six months. This was achieved by housing the monkeys after 6 months individually, but next to 3 month old monkeys, selected as monkeys at this age do not show aggressive tendencies. Isolates were allowed to physically interact with monkeys for two hours per day both in the cage and in a playroom. Initially, the isolated animals responded to the 3 month old monkeys by retreating to a corner, rocking and huddling. The 3 month old monkeys responded to the isolate by following and clinging to the isolates. The isolates soon clung back and after a few weeks the isolated monkeys and the younger monkeys were playing enthusiastically with one another. The isolates’ abnormal behaviour was gradually reduced and the animals showed normal behaviour after 6 months. In this experiment it appears that good physical contact from another individual may have contributed to reversing depressive symptoms (Harlow et al., 1971).

1.6 Affective touch

1.6.1. Lack of affective touch as a risk factor for depression

Experimentally induced depressed mood causes unpleasant memories to be more accessible than pleasant memories. It has been suggested that one of the major cognitive changes which occurs when a person becomes depressed is that unpleasant memories
become more important and pleasant memories less important to a depressed person. Past events may also be perceived as less pleasant and unpleasant events as more unpleasant. It has not been concluded whether negative thinking is the cause or the effect of depression, but there is evidence to show a link exists between negative thinking to depression. A negative perception of interpersonal relationships is thought to be particularly predisposing to depression (Cochrane, 1990).

Cochrane (1990) asked psychiatric patients who had been admitted due to depression to answer a questionnaire stating the amount of good and bad physical contact they received both as a child and at present. They were also asked whether or not they believed they were loved as a child and loved now. Patients were asked to fill in this questionnaire soon after admission to a psychiatric ward. Patients were then asked to fill in the same questionnaire within a few days of being discharged from the hospital, the assumption being that at this point their condition would be greatly improved compared to when they were first admitted onto the psychiatric ward. The non-depressed patients were also asked to complete these questionnaires using the same protocol as that described above. Non-depressed patients therefore had other psychiatric conditions. Out of the 254 patients questioned, only 18% reported satisfactory physical contact experience both in childhood and at present. Out of these subjects, 24% were depressed. Of the patients who did not receive satisfactory physical contact experience either as a child, or at present, or both, 58% were depressed. These results showed a significant correlation between depression and contact experience (Cochrane, 1990).

Although the evidence described above does implicate a lack of touch as a risk factor for the aetiology of depression, this study does not show a causal relationship between the two factors. This is difficult though because many factors contribute towards the aetiology of depression. It would also be interesting to see whether similar results would be obtained if healthy controls rather than non-depressed psychiatric patients were used to compare against the depressed people and also whether patients suffering from depression and no other psychological conditions showed the same results as the heterogeneous group of depressed patients questioned throughout this study. It would also be interesting to obtain more detail about the amount of contact experience received and whether this was
satisfactory or not, as it could be that the amount of good physical contact received was comparable between the depressed and non-depressed groups, but this was reported as unsatisfactory by the depressed group due to their negative cognitive biases. This is supported by 62% of subjects giving a more positive response to physical contact experience questions when asked shortly after being discharged from the psychiatric ward compared to their responses when first admitted onto the ward and 33% gave more positive responses to the love experience questions.

When people who had unsatisfactory contact experience were divided into loved and not loved and then depressed, not depressed or borderline, it was found that 43% of those loved and 76% of those not loved were depressed, which is a significant finding. Loved subjects with a satisfactory physical contact experience had a 23% incidence of depression. Loved subjects with an unsatisfactory physical contact experience had a 43% incidence of depression. Unloved subjects with an unsatisfactory physical contact experience had a 76% incidence of depression. This suggests an additive effect of love and physical contact in the prevention of depression. It could equally be argued that the level of depression corresponds to the negativity of the responses given by the subjects. This can be substantiated by the fact that the severity of the depression experienced by people who reported an unsatisfactory physical contact experience and perceived themselves to be unloved was much higher than that of loved and satisfactory physical contact subjects. On the other hand, it could be argued that an additive and causative effect of a lack of good physical contact and being unloved could be a significant risk factor for depression.

Unsatisfactory contact in the present as opposed to in childhood is associated with a higher incidence and greater severity of depression, suggesting current circumstances to be more important than past experiences in terms of predisposing a subject to depression.

Subjects were also asked when their last period of good physical contact ended and when their period of depression had begun. From this it was determined whether or not the unsatisfactory contact pre-dated the depression or whether the onset of depression pre-dated the period of unsatisfactory physical contact. It was found that, for 86% of subjects, unsatisfactory physical contact pre-dated the onset of depression. Prior to the onset of
depression, 65% of subjects experienced not being loved. This suggests lack of good physical contact and love to be causes, rather than effects of depression (Cochrane, 1990).

1.6.2. The relationship between affective touch during the neonatal period and stress response in adulthood in rats

Rat pups which underwent maternal separation for 180 minutes each day from post-natal day 2-14 were found to show increased depressive behaviour. These behaviours included a reduced consumption of sweetened solution, a measure of anhedonia. The rats also showed increased fear responses demonstrated by increased acoustic startle responses, increased freezing in an open-field and reduced exploration of a novel environment. One aspect these rats were lacking was affective touch from the mother during this period. These rats as adults were found to have decreased firing of serotonin neurons of the raphé nuclei in response to the SSRI citalopram, suggesting long-term alterations in either the 5-HT transporter or 5-HT₁A autoreceptors or both. Serotonin neurons innervate areas of the brain responsible for the stress response such as the hippocampus and prefrontal cortex (Heim and Nemeroff, 2001). These findings imply maternal separation during early development alters serotonin pathways leading to an increased stress response and increased depressive behaviour. It is possible that similar physiological effects occur in humans, providing a possible explanation why neglected children have greater than average plasma cortisol levels and an increased rate of depression in later life (DeBellis, 2005).

On the other hand, rat pups which underwent maternal separation for 15 minutes daily (MS15) from post-natal day 1-21 have a decreased stress response compared to untreated animals. It was found that maternal behaviour was altered as a result of this treatment. The dam responded to separation from her pups by increased licking and grooming and arched back nursing on their return. Following this period animals were housed normally and tested as adults (Hariri et al., 2002, Meaney et al., 1994, Smythe et al., 1994, Stamatakis et al., 2006, Vicentic et al., 2006).

MS15 pups were found to have a reduced HPA stress response, as determined by lower ACTH or corticosterone levels compared to non-handled animals, although basal levels...
were comparable between the two groups (Meaney et al., 1994). MS15 animals were less anxious during the elevated plus maze and had lower plasma cortisol levels than control animals (Andrews and File, 1993, Durand et al., 1998). Handled animals were found to have increased type II glucocorticoid receptor density in the hippocampus and frontal cortex, but not in the hypothalamus or the amygdala. This increased the negative feedback effect of glucocorticoids.

Increased type II glucocorticoid receptor density was linked to increased serotonin turnover in the hippocampus and frontal cortex. This has been attributed to an increase in circulating T₃ and T₄ hormone levels (Meaney et al., 1988, 2000, 1994, Mitchell et al., 1992, 1990, Smythe et al., 1994). Thyroid hormones are known to increase serotonin turnover and serotonin is known to increase the expression of type II glucocorticoid receptors (Mitchell et al., 1990). It is thought that in rats, maternal licking and grooming increases thyroid hormone levels which increases serotonin turnover in the hippocampus and frontal cortex. This increases 5-HT₂/₅C and 5-HT₇ receptor binding and therefore type II glucocorticoid receptor density (Laplante et al., 2002, Meaney et al., 1994). The responsiveness of the glucocorticoid negative feedback system to glucocorticoid exposure therefore increases, thus reducing the increase in plasma ACTH and cortisol levels produced in response to stress compared to non-handled animals (Meaney et al., 1994).

It has been shown that dopamine turnover, particularly in the hypothalamus, increased in MS15 pups. This effect was significantly greater in females than males. Serotonin levels were increased and turnover decreased in the hippocampus, striatum and hypothalamus of male and female pups, but the dopamine effects were present, suggesting dopamine changes may also be important in this mechanism (Papaioannou et al., 2002a, 2002b). As described above, stress predisposes an individual to depression, as does maternal neglect. It could be that the neurochemical basis of these risk factors can be explained by the above mechanism.

Acute maternal deprivation leads to increased plasma ACTH levels (Levine, 1994). Levine (1994) investigated the effect anogenital stroking had on ACTH levels in rat pups. If pups were maternally deprived for 24 hours, on post-natal day 9 or 12, but stroked three times in the anogenital region with a fine brush, plasma ACTH levels were as low as those of
maternally nondeprived animals, whereas simply picking up the pups did not produce this effect (Levine, 1994). This suggests that tactile stimulation may have specific effects on the developing brain, specifically on the development of the HPA axis.

1.6.3. Contact comfort aids neonatal monkey development and reduces their stress response

Harlow & Zimmermann (1959) illustrated the importance of early life-experiences, maternal separation and contact comfort on the development of neonatal Macaque monkeys. Monkeys develop strong and lasting emotional attachments to their mothers. In this series of experiments, Harlow investigated the development of this attachment using inanimate surrogate mothers. The experiment began with the isolation of 60 neonatal monkeys from their mothers, 6 to 12 hours after birth.

There were two types of surrogate mother. The first type of surrogate mother consisted of a cylindrical block of wood covered in a layer of sponge rubber over which was a layer of terry cloth. These surrogates were known as cloth mothers. Wire mothers were also designed and consisted of a cylinder of wire-mesh. Both surrogates were affixed to a base at 45°. Bottle holders were present in the upper-middle part of each cylinder for feeding (Harlow and Zimmermann, 1959). Each cylinder was given a head with a face. The cloth surrogate had an ornamental face and the wire surrogate a simple dog face. The difference between faces was proven not to be a confounding variable in a later experiment. The surrogates were the same size and shape, so the only tactile difference was the terry cloth present on the cloth, but not the wire surrogate. This terry cloth covering provided the monkey with contact comfort (Harlow and Suomi, 1970).

An early experiment investigated whether nursing or contact comfort drove maternal attachment in neonatal monkeys. Eight newborn Macaques were placed in separate cages, each one attached to two cubicles, one containing the cloth mother and the other the wire mother. Milk was provided by the cloth mother for half the monkeys and the wire mother for the other half. The mean number of hours spent with each mother was recorded. All monkeys spent more time with the cloth compared to wire mother. Initially, the wire mother
fed monkeys spent less time with the cloth mother than those fed by the cloth mother. The wire mother fed monkeys spent slightly more time with the wire mother than the cloth fed monkeys, but this was likely to be mainly for feeding purposes. By PND 16, the amount of time spent with each surrogate was comparable between the two groups and remained this way until the end of the experiment at PND 165. Monkeys spent up to 18 hours a day with the cloth mother compared to a maximum of about 2.5 hours with the wire mother. Lactation therefore does not seem to be the major developmental factor involved in maternal attachment (Harlow and Zimmermann, 1959).

Neonatal Macaques became emotionally attached to the cloth pads which covered the floor of their cages from PND 1, evident by the neonates clinging to the pads and having violent tantrums when the cloth pads were changed during cage cleaning. It appears the pleasant tactile stimulus of the terry cloth can induce a strong emotional attachment in neonatal macaque monkeys (Harlow, 1958).

The importance of contact comfort was illustrated by Harlow when he gave the monkeys fearful stimuli. Monkeys raised in the presence of both mothers and presented with a fearful stimulus in the presence of both mothers would usually respond by running to the cloth surrogate and rubbing their bodies against it. This caused a rapid loss of fear and after just a couple of minutes the monkeys were visually exploring the stimulus or could even approach the fearful stimulus. In a separate experiment, monkeys reared with either the cloth or wire mother were presented with a fearful stimulus. Monkeys reared with the cloth mother responded in a similar way to that described above. Monkeys raised with a wire mother on the other hand ran towards the wire mother, but did not rub against or cling to her and showed an emotionality score greater than that produced by the monkeys raised in standard laboratory conditions when presented with a fearful stimulus. The presence of the wire mother did not alleviate the monkey’s fear during the experiment (Harlow and Zimmermann, 1959).
1.6.4. Neurobiological responses to affective touch

A recent review by Dunbar (2010) examined the role of allo-grooming (the grooming of others) in primates and its role in social bonding. Allo-grooming is thought to release endorphins, although alternative theories suggest oxytocin and vasopressin to be of importance. Oxytocin is thought to be more active in females and vasopressin more active in males. Dunbar suggested oxytocin and vasopressin to have an important role during initial bond formation; they facilitate social engagement and allow two individuals to be interested in each other, whereas endorphins have a role in maintaining a relationship longer-term.

Maternal-infant bonding has also been reported to involve oxytocin, vasopressin and endogenous opioids, as well as norepinephrine. Norepinephrine has been implicated in social learning. It has been found that the administration of the norepinephrine antagonist, propranolol to neonatal rats, prevents the formation of a preference to an odour that has previously been associated with stoking the dorsal surface of the rat with a paint-brush. Maternal sheep have a 2-4 hour ‘bonding window’ following parturition, facilitated by oxytocin. This allows olfactory memories of the offspring to be formed by the ewe. This process has also been found to be dependent on norepinephrine. Intravenous infusion of propranolol into ewes during their bonding window reduced the ability of these ewes to identify their own offspring from other lambs. This implicates a role for norepinephrine in maternal learning (Nelson and Panksepp, 1998).

Serotonin has also been implicated in promoting affiliative behaviour, including increasing allo-grooming in adult male vervet monkeys. Monkeys were housed into three males per social group, which also included at least three adult females and their offspring. After a baseline period, the dominant male was removed and one of the remaining monkeys was treated. The remaining monkey was vehicle treated only and used as a reference monkey. During one treatment block, the treated monkey received either tryptophan or fluoxetine, both of which increase serotonin function. In another treatment block, the same monkeys were treated with either fenfluamine or cycloheptadine, which both decrease serotonin function. When serotonin function was increased, these monkeys became more dominant than the reference monkey and displayed more affiliative behaviours. When serotonin function was reduced, the monkey became more subordinate and the reference monkey
became the more dominant monkey. An increase in dominance was associated with increased affiliative behaviour, including allo-grooming, whereas a decrease in dominance was associated with increased aggression and locomotion. These results suggest serotonin may be involved in increasing positive tactile interactions between individuals (Raleigh et al., 1991).

1.6.5. Massage therapy reduces depression scores and cortisol levels

It is thought that early experiences of touch may affect infant development. It has been shown that Touching and Caressing, Tender in Caring (TAC-TIC) therapy used on premature infants improves their outcome; they have increased weight gain, decreased length of stay in hospital and are at an earlier age when they suck their first feed compared to premature neonates who are touched as little as possible (Hayes, 1998). A study of a student population showed that those subjects with greater intimacy with their parents had lower depression scores and those with less intimacy with their parents had higher depression scores (Field, 2002).

Field et al. (1996) investigated the effect of massage therapy on depressed adolescent mothers. This massage therapy involved slow stroking of the forehead, shoulders, neck, arms, hands, torso, legs and feet. Massaging was carried out once a day for half an hour two consecutive days each week for 5 weeks. Control participants received relaxation therapy sessions, the occurrence and duration of which were the same as the massage therapy group. Relaxation sessions involved yoga exercises and progressive muscle relaxation. The relaxation therapy sessions involved no physical contact from another person. Participants who received massage therapy showed reduced depression and stress after therapy compared to before, whereas the control group did not. The relaxation therapy group was less anxious, but the massage therapy group was less anxious, showed less anxious behaviour and had lower cortisol levels (Field et al., 1996). Serotonin levels, determined by urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, have been found to be increased and frontal EEG activation patterns normalised following massage therapy. Increased serotonin levels have been associated with decreased testosterone levels and decreased aggression (Field, 2002).
Similar studies have measured changes in urinary 5-HIAA and found increased urinary 5-HIAA concentration after massage therapy, compared to levels pre-treatment. Control participants who received no therapy showed no change in serotonin levels over the same time period (Hernandez-Reif et al., 1998). In a separate study, urinary 5-HIAA levels also increased following massage therapy. The control group received relaxation therapy and showed no change in 5-HIAA levels (Hernandez-Reif et al., 2001). Both of these studies also showed patients to have reduced depression following massage but not control treatment (Hernandez-Reif et al., 1998, 2001). These findings suggest affective touch increases serotonin in the brain, thus reducing depressive symptoms, although an increase in 5-HT metabolism does not necessarily reflect an increased neuronal activity (Adell et al., 1997).

1.6.6. Tryptophan depletion reduces pleasantness ratings of tactile stimuli

A preliminary investigation into the role of serotonin in affective touch processing was carried out by this department. During this investigation, acute tryptophan depletion was used to reduce brain serotonin. Stimuli were applied using a rotary tactile stimulator (RTS) at a force of 0.1 N and 0.3 N and a velocity 0.75 cm/s and 18 cm/s. Stimuli were applied in a proximal-distal direction over an area 8.5 cm long and 1 cm wide, except for the cosmetic brush which covered an area 3.5 cm wide. The stimuli applied were: burlap (sacking), the loop side of velcro, a large cosmetic brush and velvet. The participant’s arm was placed on a vacuum beanbag to allow it to remain static. Participants were provided with earplugs. They then put on headphones and white noise (below 80 dBA) was played to them through the headphones, thus eliminating auditory input into perceived sensations. A black curtain was placed between the participant and the RTS to eliminate visual input into the perceived sensations.

A force of 0.3 N was rated as more pleasant than a force of 0.1 N, but the two different velocities did not produce different pleasantness ratings. It was found that the pleasantness rating of tactile stimuli decreased following tryptophan depletion as shown in figure 4. This suggests serotonin may be involved in the encoding of affective touch. Results found burlap (sacking) most unpleasant, and the cosmetic brush the most pleasant. Velcro and velvet
produced the greatest difference in pleasantness rating following tryptophan depletion compared to control results with both stimuli perceived as more unpleasant following tryptophan depletion (Blackburn and Phillips, 2004).

1.7. Mechanosensation

Mechanosensation, the perception of pressure applied to the skin, is known to be predominantly encoded by Aβ afferents. Aβ neurons are traditionally the neurons implicated in sensing light touch. Their afferents include Merkel’s disks, lanceolate endings found around hair follicles and pacinian corpuscles. The neurons project from the skin to the spinal cord. Their cell bodies are found in dorsal root ganglion (DRG). These neurons have thick myelination and a large soma diameter. There are three types; slowly adapting type I which are associated with Merkel’s disks, slowly adapting type II and rapidly adapting, associated with Pacinian corpuscles (Lumpkin and Bautista, 2005). Table 1 summarises the properties of Aβ-fibre mechanosensory afferents of the fingerpad (Johnson et al., 2002, Kumamoto et al., 1993).
Aβ afferents found around hair follicles below the sebaceous gland (Fundin et al., 1997). Another mechanoreceptive afferent type found in hairy, but not glabrous skin is C-fibre tactile (CT) afferents.

### 1.7.1. C-fibre tactile (CT) afferents

CT afferents are associated with C-fibres, not Aβ fibres (Vallbo et al., 1999). C-fibres have small diameters, are non-myelinated and have a slow conductance rate of 0.5-2.0 m/s (Lumpkin and Bautista, 2005, Stander et al., 2006). C-fibres are traditionally associated with mechanoreceptive and polymodal nociceptors, as are Aδ fibres (Lumpkin and Bautista, 2005).

CT afferents were not identified in humans until 1990 when Nordin published a paper in which he described how two types of C-fibre afferents had been identified in human skin. Before this paper was published, CT afferents were known to exist in cats and primates, but not humans. The investigation carried out by Nordin involved microelectrode recordings.
being taken from eleven C-fibre afferents of the face of 3 healthy males. C-fibre afferents were identified by their conduction velocity of 0.6-1.4 m/s. Eight of the afferents had a mechanical threshold ≤ 2.3 mN and responded to weak tactile stimuli. The other three units responded to noxious stimuli only and had mechanical thresholds of 54 mN (Nordin, 1990).

The low-threshold afferents were strongly activated by slow stroking movements of low force. Rapid stroking reduced the response produced. These afferents showed after discharges. The afferents also showed fatigue following repeated stimulation (Nordin, 1990).

Further research was carried out by Vallbo et al., (1993, 1999), who investigated these afferents using microneurography. The first investigation confirmed the findings of Nordin (1990), that these afferents have a response threshold of 2.5 mN and are particularly responsive to stroking. The afferents described were from a larger sample size of 28 volunteers and were located on the forearm not the face, suggesting these afferents to be present at many body sites.

The second publication by Vallbo et al., (1999) compared nociceptive C-fibre afferents to CT afferents, again using microneurography. The sample size used was quite large with 17 volunteers and 38 afferents investigated. A bimodal distribution of mechanical thresholds was found, with CT afferents having thresholds of 0.3-5 mN and nociceptor thresholds were 10-80 mN, as determined by stimulation with von Frey bristles. CT afferents responded more to a blunt probe stimulus than the nociceptive afferents and responded less than nociceptive afferents to a sharp probe stimulus. High CT afferent impulse rates were induced by slow stroking of the forearm with the fingertip of the experimenter and by stroking with a soft brush, a stimulus which had very little affect on the nociceptive afferents, as shown in figure 5. This investigation confirmed CT afferents show fatigue and also found they show a biphasic response to stimulation (fast-slow-fast impulse firing rate). Figure 5 shows the response of CT afferents compared to C-fibre nociceptors to a brush being stroked over the skin.
Further investigations into CT afferents involved studying subjects with sensory neuropathy syndrome. Patients suffering from this condition do not have large myelinated somatosensory fibre function from the lower face or neck downwards. These subjects do not have Aβ fibres, which means that all mechanosensation that is coded for by these fibres is lost and proprioception at the level of the sensory neuropathy is not present in these patients (Cole et al., 2006). Skin sensations not encoded by large myelinated somatosensory fibres are still detected by these patients. Nociceptive and thermoreceptive stimuli are still perceived the same as a healthy subject as non-myelinated, small diameter C-fibres and medium diameter, thinly myelinated Aδ fibres, are still present (Cole et al., 2006, Lumpkin and Bautista, 2005).

Two patients with sensory neuropathy syndrome were tested with monofilaments. When the hairy skin of the forearm was tested, the stimulus could be detected at a force which was within the normal range for healthy individuals and was not perceived as painful. 2-point discrimination, light touch and vibration could not be deduced (Cole et al., 2006). Monofilaments applied to the palm of the hand which is covered by glabrous skin, could only be detected when applied at a much greater force than that detected by hairy skin. The stimulus was then perceived as slightly painful. The results obtained from the healthy control subjects were similar when the hand or the arm was tested. As CT afferents are only present in hairy skin, the results obtained suggest that in the sensory neuropathy patient, the CT afferents are responsible for the detection of the monofilament stimuli, whereas in the glabrous skin, it is the nociceptors which detect the monofilament stimuli, thus accounting
for the differences in stimulus perception obtained. fMRI analysis into brain activation of sensory neuropathy subjects following stimulus application showed the somatosensory cortex was not activated when the forearm of a sensory neuropathy subject was stimulated, implicating CT afferents to be involved in the detection of the affective, as opposed to the discriminatory aspects of touch (Cole et al., 2006).

Although this study by Cole et al., (2006) undoubtedly provided important information into CT afferents, one has to ask whether or not the results obtained are relevant to the general population, as only two subjects were available for use in these investigations, due to the rarity of this condition. It is well known that the brain can show a certain amount of plasticity. It should therefore be considered whether or not the brains of these individuals have altered their responses to stimulation of C-fibres to allow for their lack of myelinated fibres in some way. Despite this, stimuli were perceived differently when applied to hairy or glabrous skin, providing evidence for CT afferents. This is further supported by the finding that stimuli were perceived as painful when applied to glabrous, but not hairy skin.

1.7.2. The role of the insular cortex in affective touch processing

The lamina I spinothalamocortical pathway is illustrated in figure 6. Lamina I receives synaptic inputs from Aδ and C fibres which innervate all the tissues of the body. From lamina I, this pathway projects to the posterior part of the ventromedial nucleus of the thalamus and from here it projects to the posterior insula (Craig, 2002). CT fibres project through the spinothalamocortical pathway to the posterior insula. fMRI investigations into the brain response of sensory neuropathy patients to affective touch have provided evidence to support the theory that CT afferents project through the spinothalamocortical pathway. Sensory neuropathy patients lack large diameter Aβ fibres, typically responsible for transmitting mechanosensitive information to the brain, from the neck downwards. Stroking the forearm and thigh of these patients with a soft brush caused the activation of the posterior insula, but not the somatosensory cortex (Björnsdotter et al., 2009, Olausson et al., 2002, Olausson et al., 2008). This also implicates the role of CT afferents as responsible for the affective, rather than discriminative aspects of touch perception.
Information from the posterior insula is then projected to the anterior insula, anterior cingulate and OFC; brain regions responsible for affective processing (Craig, 2002, 2009).

1.8. Brain areas responsible for affective processing have been previously investigated using functional magnetic resonance imaging (fMRI)

fMRI is a sensitive method of measuring brain function. fMRI records physiological changes by measuring magnetic differences between oxygenated and deoxygenated blood (DeBellis, 2005). Studies investigating brain responses to affective touch have been carried out previously and the results obtained are discussed below.

The prefrontal cortex contains a variety of brain areas responsible for many different functions. Areas of the brain present in the prefrontal cortex include the prelimbic cortex, the infralimbic cortex, the anterior cingulate cortex and the orbitofrontal cortex. The prefrontal cortex is involved in working memory, cognition, attention, emotion, executive function and behavioural inhibition (Morgane et al., 2005). McGlone et al., (2001) showed activation of Brodmann Area (BA)10, a region of prefrontal cortex, correlated with the
perceived intensity of the itch.

The orbitofrontal cortex (OFC) is implicated in reward and judgement (Cotter et al., 2005) and is strongly innervated by serotonin neurons (Morris et al., 1998). The OFC also has strong connections to the limbic pathways of the brain, which are responsible for reward processing (Kulkarni et al., 2005). fMRI studies show pleasant touch strongly activates the orbitofrontal cortex (Francis et al., 1999, Rolls et al., 2003). The size of neurons in layer one of the OFC have been found to be reduced in post-mortem brains of bi-polar depressive patients. There was a trend for a reduction of neuronal size in layer 5 as well (Cotter et al., 2005).

A different study has implicated the OFC in affective responses. Mothers with no post-natal depression were asked to view photos in a scanner of their own and other people’s infants. The OFC was activated more strongly when viewing a photo of their own infant than viewing a photo of another person’s infant and subjects rated their pleasant mood rating as higher when viewing their own infant. This suggests a role of the OFC in processing pleasant, affective stimuli (Nitschke et al., 2004).

Acute tryptophan depletion decreases activity in the OFC, subgenual anterior cingulate and caudate nucleus. The anterior cingulate has projections to the OFC and the limbic striatum. This is thought to function abnormally in depression. Anterior cingulate lesions decrease motivation and decrease interest. The caudate nucleus has been associated with psychomotor changes, whereas the OFC has been associated with affective behaviour (Smith et al., 1999).

Serotonin pathways innervate cortical and subcortical brain regions including the OFC, caudate nucleus and anterior cingulate cortex. It has been suggested that serotonin function exerts its affects on mood by impairing neural activity in the caudate nucleus, the ventral anterior cingulate cortex and the OFC (Smith et al., 1999).

A study carried out by Kulkarni et al. (2005) investigated the brain regions involved in the affective components of pain. Healthy subjects were PET scanned while a radiant heat stimulus from a CO\textsubscript{2} laser was applied to one of four pseudo-randomly selected sites on the left dorsal forearm. A\textdelta and C-nociceptive afferents were targeted and A\textbeta fibres were
avoided. When subjects were asked to focus on the location of the stimulus, the primary somatosensory cortex and the inferior parietal cortices were particularly activated. When subjects focused on the unpleasantness of the stimulus, the perigenual anterior cingulate cortices, OFC, frontal pole, posterior insula, primary motor cortex and hypothalamus were particularly activated.

The anterior cingulate cortex has been divided into the perigenual and mid-cingulate cortex. The mid-cingulate cortex has been divided into the anterior and posterior mid-cingulate cortex. The anterior mid-cingulate cortex is associated with fear and affective processing and is anatomically and functionally distinct from the posterior mid-cingulate cortex, which is involved in executive functions (Vogt et al., 2003).

The perigenual anterior cingulate cortex in particular is strongly associated with affective responses such as vocalisation, autonomic control and fear. The anterior cingulate cortex is the most commonly activated region of the brain during functional imaging studies of pain. The OFC has connections with the limbic system. This region was activated when participants focused on the unpleasantness of a painful stimulus. This is a brain region involved in depression, implicating the OFC to be involved in the emotional response to pain. It is thought that the hypothalamus could be the common autonomic and neuroendocrine output system following OFC and amygdala activation. Both of these areas are associated with emotional processing (Kulkarni et al., 2005).

This study concludes that the perigenual anterior cingulate cortex and the anterior mid-cingulate cortex and associated structures are involved with processing the emotional aspects of pain. The primary somatosensory cortex and the inferior parietal cortex are involved in determining stimulus location (Kulkarni et al., 2005).

fMRI studies have shown that the OFC is activated more strongly in response to a pleasant stimulus of velvet or a painful stimulus of a stylus than a neutral stimulus of wood being applied to the skin. Different regions of the OFC were activated by pleasant and painful stimuli. The somatosensory cortex was activated more by the neutral rather than pleasant or painful stimuli, implicating the OFC to be responsible for the affective aspects of touch. This is supported by evidence showing that orbitofrontal taste and olfactory neurons decrease
activation in response to the taste and smell of food as satiety increases. A rostral part of the anterior cingulate cortex was activated by pleasant stimuli, whereas a more posterior region was activated by painful stimuli (Rolls et al., 2003).

Francis et al., (1999) implicated the OFC in the perception of pleasant tactile stimuli. As the stimulus was only applied to the palm of the hand, this suggests CT afferents are not the only afferents able to encode pleasant touch as CT afferents are absent in glabrous skin. Rolls et al., (2003) showed the OFC to respond to the affective aspects of touch as it was activated more by pleasant and painful rather than neutral touch.

Brooks et al., (2005) implicated the posterior insula in the perception of the affective component of painful stimuli. Olausson et al., (2002) showed that the insula region, but not the somatosensory cortex was activated by touch when one patient without large myelinated afferents was used. This experiment compared 24 healthy volunteers against only one patient. Although this was unavoidable, only one subject makes it questionable whether or not these findings are accurate and significant. Rolls et al., (2003) found the anterior insular cortex was activated by the painful stimulus, but not the neutral or pleasant stimulus.

fMRI imaging has identified the posterior insula cortex as an area of the brain activated by stimulation of hairy, but not glabrous skin and is thus implicated as being an area specifically activated by CT afferent stimulation. Stroking the forearm of a sensory neuropathy patient with a soft brush activated the posterior insula cortex, but not the primary or secondary somatosensory cortices when applied to the hairy skin of the arm, thus further implicating CT afferents in the detection of non-noxious skin sensations applied to hairy skin. When the same stimulus was applied to the palm of the hand, the stimulus could not be detected by the sensory neuropathy subject (Olausson et al., 2002). Rolls et al., (2003) found the anterior cingulate cortex was activated by pleasant and painful stimuli with painful touch activating a more posterior and dorsal part of the anterior cingulate cortex than the pleasant touch.

Linde et al., (2004) showed sumatriptan, a 5-HT1b/1d agonist produced a short-lasting allodynia following light touch to the dorsal side of the hand. Sumatriptan increased unpleasantness ratings in response to stimulation of the skin with a soft brush in both
healthy subjects and those who suffered from migraines. This provides evidence for a role of serotonin in touch perception.

Serotonin receptors involved in touch perception may be pre- or post-synaptic and may be found in the periphery or centrally. At present, there is no direct evidence as to whether the involvement of serotonin in touch perception is peripheral or central. In Linde’s (2004) and Blackburn’s (2004) investigations, manipulation of serotonin was systemic, so although these investigations implicate a role of serotonin in affective touch perception, it is unclear from these investigations whether serotonin is involved peripherally or centrally. The investigation by Linde (2004) implicates a role of the presynaptically located 5-HT\textsubscript{1B/1D} receptor in affective touch perception. Further investigation using microneurography investigations while manipulating serotonin peripherally by, for example iontophoretically delivering serotonin into the skin or delivering a serotonin agonist or antagonist into the skin, would determine whether serotonin has a peripheral role in affective touch perception. If no peripheral role was found, this would suggest serotonin has a central role in affective touch perception.

Animal studies have provided evidence to suggest the habenula to be involved in self-stimulation, mating, maternal behaviour, sleep, ingestive behaviour, naloxone reversible analgesia and exploration. Altered activity in this region in depressed patients is therefore a possible explanation for the changes in mood and cognition which occur. A feedback pathway converges on the habenula and then a projection from here innervates the dorsal raphe nucleus and controls the release of serotonin in the cerebral cortex. Alterations in habenula activity therefore, alter the whole serotonergic system and therefore affect behavioural, cognitive and affective brain mechanisms (Morris et al., 1998).

The above studies show fMRI to be an effective method of investigating brain response to affective stimuli, so this method was selected for use in our investigation of affective touch.
1.9. A proposed model for the role of affective touch in depression

Figure 7 depicts a proposed model of the role of affective touch in depression; the focus of the research contained in this thesis. We hypothesised that early deprivation and genetic vulnerability, such as the presence of the 5-HTT short allele, leads to impaired serotonin development, which in turn leads to the development of an ineffective affective touch system and an individual to be less responsive to affective touch. In order to be effective, the affective touch system must develop properly and must be maintained. Subjects less responsive to affective touch are less likely to engage in physical contact with other individuals, leading to them becoming more socially isolated, which in turn causes the affective touch system to be more ineffective and a vicious cycle to develop. This leads to serotonin vulnerability.

Impaired serotonin development leads to increased negative cognitive biases, which in turn leads to negative appraisal of self and future. Negative cognitive biases pre-dispose an individual to social isolation as they are more likely to perceive themselves as socially isolated.
and because their personality type makes them less likely to develop a strong social network. A vicious cycle begins with increasingly negative cognitive biases leading to further social isolation which leads to greater negativity about oneself and future. Affective touch encodes to the brain that you have social support and improves self-confidence and optimism about the future. Without affective touch, negative cognitive biases are further increased leading to cognitive vulnerability. In the presence of a stressful life event, a combination of serotonin and cognitive vulnerability may lead to the onset of depression.

In summary, serotonin is involved at several possible points in this model. Impaired development of the serotonin system may occur due to a genetic vulnerability or due to early touch deprivation. This may lead to an ineffective affective touch system and increased negative cognitive biases. Serotonin vulnerability may also develop during later life if an individual experiences little affective touch due to social isolation. It is proposed that the affective touch system involves serotonin and must develop properly in early life and then must be maintained in later life in order to prevent vulnerability to depression. A combination of an ineffective affective touch system and cognitive vulnerability causes an individual to be highly vulnerable to depression following a stressful life event.

To investigate this model, we carried out a questionnaire study into the role of affective touch in depression and an fMRI study into the effect of acute tryptophan depletion on affective touch processing in healthy volunteers. A questionnaire regarding individual’s attitudes to and experiences to touch was developed. Participants completed this questionnaire along with questionnaires about childhood circumstances, social isolation, stressful life events and whether or not they are currently depressed or have been in the past. When possible, genotypic data regarding the 5-HTT allele was obtained. The data collected was analysed using regression analysis to determine the relative contribution of these factors to the onset of depression.

An fMRI investigation was also carried out to determine the response of the brain to affective touch. Half the participants underwent acute tryptophan depletion to determine the role of serotonin in the perception of affective touch. Participants were stroked on the forearm and palmar aspect of the fingers with pleasant, unpleasant and neutral affective stimuli. This allowed brain response to different tactile stimuli to be determined and also
allowed further insight into the role of CT afferents in affective processing by contrasting the response of the brain to touch to the hairy skin of the forearm which contains CT afferents to the glabrous skin of the palm where CT afferents are absent.

Following these investigations, we determined whether the model proposed in figure 7 could be accepted or rejected, or whether further investigations are required before this conclusion can be made.
2. Methods

2.1 Questionnaire study methods

2.1.1. Participants

The study was approved by the University of Manchester ethics committee. Participants completed all questionnaires anonymously online to create large samples and to minimise the influence of embarrassment, social conformity and pressure to participate. The first sample was for principal components analysis and item selection of the Touch Experiences and Attitudes Questionnaire (TEAQ). A second, replication sample completed the reduced TEAQ and other questionnaires for the confirmatory factor analysis using structural equation modelling. All members of the University of Manchester received an emailed invitation to participate including undergraduates, postgraduates, academics, clerical and general staff, allowing a reasonably diverse age range. The study was also advertised through an online social networking site. A £50 prize draw provided an incentive to participate.

2.1.2. TEAQ item generation

Questionnaire items were generated and assessed for acceptability by discussion with colleagues and social contacts to cover the range of positive touch experiences including hugs, kisses, skin-skin contact and hair-skin contact in everyday circumstances such as greeting, consoling, intimacy and childhood contact. Items consisted of statements and a 5-point Likert scale of agreement. Statements were written to cover attitude to both giving and receiving touch, as well as questions about attitude to touch in general such as ‘I’m not a very tactile person.’

The terms ‘partner’, ‘boyfriend/girlfriend’, ‘husband/wife’ were avoided and instead any questions about intimate touch referred to ‘someone you are close to’. Questions about childhood touch were limited to the amount of various forms of touch they received and not their attitudes as the latter was considered harder to recall and to interpret. An example question is: ‘my parents regularly cuddled me as a child.’ Items also covered self-touch in
cleaning and grooming such as ‘I find taking a shower or bath very enjoyable.’ 117 items were created and presented at random using a random number generator. The TEAQ was included with other questionnaires, described below, as an online survey.

2.1.3. The questionnaire battery

A questionnaire battery was compiled with the aim of investigating the hypothesis that affective touch is a component of social support which reduces the risk of depression. The battery began with some general questions to obtain demographic data about gender, age, relationship status, number of children, living arrangements and employment status. The general questions also included questions about whether or not they had received any professional help for emotional or psychiatric problems, whether they had sought or needed help for depression in the last year, whether they had been feeling persistently depressed or in a low mood for the past two weeks and whether or not they had ever had a period of a month, excluding bereavement, during which time they felt very depressed, so much so that it interfered with their work and interests. They were also asked if they were currently being treated for depression and how good they think their current health is.

Following these general questions, participants were asked to complete the Brief Symptom Inventory (BSI) (Derogatis, 1993). Items belonging to the factors somatization, hostility, phobic anxiety, paranoid ideation and psychoticism were removed, as these factors were not of interest for this study. This shortened the BSI to 26 items. The BSI is a widely used and highly validated questionnaire (Juhasz et al., 2009, Juhasz et al., 2011). The BSI contains 6 items relating to depression: “During the past week how much were you distressed by ... thoughts of ending your life, feeling lonely, feeling blue, feeling no interest in things, feeling hopeless about the future, feelings of worthlessness.”

The BSI was followed by the TEAQ. In the original questionnaire battery, the TEAQ was 117 items. This was replaced with the 57 item TEAQ (appendix 1) following exploratory factor analysis. The TEAQ was followed by some questions about social problems and circumstances, including the SSQ6 (Sarason et al., 1987). The SSQ6 was altered slightly in that the first question: “Whom can you really count on to distract you from your worries when
you feel under stress?’ was replaced with an item from the original version of the SSQ ‘Whom can you really count on to be dependable when you need help?’ This item was chosen to replace the original first item as it was easier to understand, more general and more relevant, allowing a wider range of situations to be covered by the SSQ6. The SSQ6 was also simplified by asking participants to rate the number of people who they could depend on for each circumstance as ‘None’ ‘A Few’ or ‘Lots’ rather than asking participants to list who they could depend on.

The questions about social circumstances were followed by a childhood adversity questionnaire (CHA), derived from the 28 item Childhood Trauma Questionnaire (Bernstein et al., 1994). The CHA questions related to emotional and physical neglect and emotional and physical abuse. The CHA was derived for a different study carried out by the department and contains 6 items: “When I was growing up... 1. I was happy, 2. I believe that I was abused or neglected, 3. People in my family looked out for each other and 4. My parents/guardians weren’t able to take care of me.” Participants rated their agreement to each statement on a 5 point likert scale ranging from ‘Never True’ to ‘Very Often True,’ as used with the original version of the CTQ. Two additional items to which participants responded yes or no were ‘I lost my mother’ and ‘I lost my father.’ This questionnaire was used as it was much shorter than the CTQ and was found to correlate strongly with the original version of the CTQ in a previous study carried out by the department (Pearson’s correlation: R = 0.75, p < 0.001, N = 142) (Juhasz et al., 2011). Using the CHA also avoided the use of CTQ questions which are quite intrusive and potentially upsetting, particularly those regarding sexual abuse. Items 1 and 3 were reverse scored and a total score obtained by summing the scores, with a high score representing a large amount of childhood adversity.

The 44 item Big Five Inventory (BFI) followed the CHA and was used to determine personality type (John and Srivastava, 1999). Although the NEO-PI-R (Costa and McCrae, 1992) is the most validated Big Five questionnaire measure, a previous investigation carried out by the department has found the BFI to strongly correlate with the NEO-PI-R (Pearson’s correlation: extraversion R = 0.79; agreeableness R = 0.59; conscientiousness R = 0.75; neuroticism R = 0.81; and openness R = 0.66, p < 0.001, N = 142) (Juhasz et al., 2009). Due to
the BFI being much shorter than the NEO-PI-R (44 items compared to 240), the BFI was selected for this investigation.

The BFI was followed by the List of Life Threatening Experiences (LTE) (Brugha et al., 1985). The LTE is a life events schedule with items such as: ‘You yourself suffered a serious illness, injury or an assault.’, ‘Your parent, child, spouse died,’ ‘You broke off a steady relationship.’ Rather than participants simply stating whether or not they had experienced an event, as in the original LTE, participants in this investigation were asked to indicate how long ago the event happened by selecting either ‘in the last two months,’ ‘in the last year’ or ‘more than a year.’ Participants were also asked to indicate whether each event still strongly affected them. This enabled further details to be obtained about the life events an individual had experienced.

The LTE was followed by participants being invited to give any further information or comments they felt were relevant. They were then asked whether or not they wanted to be entered into the £50 prize draw or be contacted about further studies and to provide an email address if they did. Participants were then thanked for their participation.

2.1.4. Principal components analysis and item selection

Principal components analysis (PCA) establishes the components which exist within a dataset by assuming each variable has a communality of 1 and transposes the original data into constituent linear components. PCA also determines how a particular variable (in this case, a questionnaire item) contributes to the components identified. A limitation of PCA is that it assumes the sample used is the population, which means that the results obtained cannot be extrapolated beyond the sample obtained (Field, 2005). This method of deducing the factors present in the touch questionnaire dataset was selected as it is a well established technique and has been used to determine the factor structure of various questionnaires previously (Brinker and Dozois, 2009, Nyklicek and Denollet, 2009, Patton et al., 1995, Treynor et al., 2003, Vitaliano et al., 1985, Wagnild and Young, 1993).
Participants with greater than 5% missing values were excluded from the analysis to minimise inaccuracies caused by missing values (Tabachnick and Fidell, 2007). PCA with direct oblimin rotation was carried out on the data from the 117 item touch questionnaire. Direct oblimin rotation was selected as some correlation between factors was expected as all variables relate to affective touch. The covariance rather than correlation matrix was analysed as responses to all variables were made on the same 5-point Likert scale, so the data is commensurable and therefore suitable for covariance analysis (Field, 2005). Correlation coefficients are insensitive to differences in how much scores vary about the mean for different variables and any variables which are not normally distributed can cause significant inaccuracies in the analysis (Tinsley and Tinsley, 1987). This is not the case for covariance analysis, leading to its selection for this analysis. Missing values were excluded pairwise to minimise the amount of data removed from analysis. Scores for negatively phrased questions were reversed so that scores reflect greater touch experience or positive attitude. The number of factors to extract was determined using Cattell’s scree test (Cattell, 1966).

A correlation matrix was used to exclude redundant items that correlated significantly with more than 80% of the others or with another item at more than $r = 0.8$. Items with measures of sampling adequacy (MSA) values less than 0.6 were removed. Items with rescaled communalities less than 0.3, indicating that these items explained only a small proportion of the shared variance were also removed (Field, 2005). Stevens (1992) suggests only factor loadings greater than 0.4 should be considered of interest. Any items with factor loadings less than 0.4 for all factors were removed, as well as any items which loaded similarly on two factors. Reliability analysis was carried out for each factor. Any items which did not increase Cronbach’s alpha were removed.

2.1.5. Confirmatory factor analysis (CFA)

CFA is a multivariate technique which allows a previously hypothesised model to be tested for its validity. CFA is more accurate than regression or general linear model methods, as measurement error variance is explicitly estimated in CFA, but not in the other techniques.
CFA is also advantageous over other multivariate techniques as observed and unobserved (latent) variables can be incorporated into a model (Byrne, 2001). For these reasons, CFA was chosen to determine whether the factor structure obtained by principal components analysis in the first sample was valid in a second sample.

Confirmatory factor analysis was carried out using structural equation modelling (Amos™ 7; SPSS Inc.) on the data obtained from completion of the 57 item TEAQ by the replication sample. In addition, a hierarchical model was tested. The criteria used to determine goodness of model fit were a Root Mean Square Error of Approximation (RMSEA) < 0.06 with a narrow confidence interval, an RMSEA probability value > 0.5, a Comparitive Fit Index (CFI) > 0.95, a low Akaike’s Information Criterion (AIC), a standardised Root Mean Square Residual (RMR) < 0.05 and a Tucker-Lewis Index > 0.95 (Byrne, 2001).

Scores were found to be skewed towards the more positive responses in many items and did not show a normal distribution. For this reason, the effect of transforming scores to binary such that scores less than the median were assigned a value of 0 and those equal or greater than the median a value of 1, was investigated.

The reliability of structural equation modelling is reduced by an excessively large number of variables. It was therefore determined whether parcellation of items to produce three measures for each factor affected the outcome, as advocated by Yang et al., (2010), using the procedure of Nasser and Wisenbaker (2003).

2.1.6. Analyses to investigate the relationship of the TEAQ factors with other questionnaire measures

For all analyses to investigate the relationship between the TEAQ factors with other questionnaire factors, the two questionnaire databases were combined. Participants were removed from the analysis if 5% of responses on any of the questionnaires were missing, or 20% on one questionnaire factor was missing, as suggested by Tebachnik and Fidell, (2007). A total of 667 participants were excluded using these criteria, leaving a dataset containing 1308 participant responses.
All questionnaires were scored using Microsoft® Excel according to the instructions given by the questionnaire authors. Pearson’s Correlations were calculated between the TEAQ factor scores and various questionnaire factors to determine relationships between factors. Pearson’s Correlations were used because the data was parametric. In a sample as large as the one used in this investigation, correlations are statistically significant even when explaining a very small amount of the variance. For this reason, only correlations greater than 0.3 (explaining 9 % of the variance), were regarded as of interest.

2.1.6.1. Partial correlations

Partial correlation analysis allows the relationship between two factors to be determined while holding the effects of a third factor constant. This allows the unique variance between two factors to be determined while controlling for an additional factor known to contribute to the variation between the two factors being investigated (Field, 2005).

2.1.6.2. Stepwise multiple regression

Multiple regression analysis is a way of predicting an outcome from more than one variable and was used to investigate which questionnaire factors significantly predicted BSI depression score. Stepwise forward method of factor entry was chosen as no previous data to support the inclusion of any particular factors existed and when using this method, each time a predictor is added to the model, a removal test is carried out to determine whether the least significant predictor is redundant and can be removed. This makes the model produced more accurate than using the forward entry method.

Participants were identified as outliers and removed from the analysis if their standardized residual was greater than 3, their covariance ratio was greater than \((1+(3(\text{average leverage}))\) or less than \(1–(3(\text{average leverage}))\), their leverage value was greater than 3 times the average leverage or their Mahalanobis statistic was greater than 25 (Field, 2005).
2.1.7. Participant categorisation

Participants were categorised as either never depressed, remitted depressed or depressed depending on their responses to the general questions regarding psychiatric history at the beginning of the questionnaire battery and their depression score obtained from the BSI. The normative data provided by Derogatis et al., (1993) shows the mean score + 1 standard deviation was 0.92 for females and 0.54 for males in an adult non-patient sample. In this investigation, never depressed individuals were identified by a BSI depression score less than or equal to 0.92 for females or 0.54 for males, as well as negative responses to all general psychiatric questions at the beginning of the questionnaire battery. Remitted depressed participants in this investigation were defined as indicating that they had been depressed in the past, but were not at present, as determined by responses to the questions at the beginning of the questionnaire battery and a depression score the same as that for never depressed participants. Depressed participants indicated that they had been feeling persistently depressed or in low mood for the past two weeks when asked at the beginning of the questionnaire battery and had a depression score of greater than or equal to 1.9 for females or 1.65 for males. These values were used as they equate to the mean depression scores for psychiatric outpatients in the normative data provided by Derogatis et al., (1993). Participants who did not fulfil these criteria were excluded from further analyses.

2.1.8. One-way ANOVA of depression category against touch score

A one-way ANOVA followed by a Games-Howell post-hoc test was carried out on the touch questionnaire data to determine whether there were any group differences between healthy, remitted depressed and currently depressed individuals. This technique was selected because there were three levels of independent variable; depression category and one dependent variable; touch score. A Games-Howell post-hoc was used as sample sizes for the three depression categories were not equal, so the assumption that population variances of the three depression groups were equivalent could not be made (Field, 2005).
2.1.9. Logistic regression of remitted depressed and control participants

Logistic regression is a multiple regression technique, but is used when the outcome variable is categorical with only two possible categories (Field, 2005). Logistic regression was used to investigate which factors predicted whether an individual had been previously depressed or not.

2.2 Imaging Investigation

2.2.1. How does Magnetic Resonance Imaging (MRI) work?

The following section was based on the account provided by Schild, H.H. (1990) *MRI made easy (…well almost)*. Schering: Berlin.

The nucleus of a hydrogen atom contains only one proton and no neutrons. Hydrogen is abundant throughout the body and hydrogen nuclei give the most intense signal compared to other nuclei, so are used for magnetic resonance imaging. Throughout this section, ‘protons’ refers to hydrogen nuclei. The proton in a hydrogen atom spins constantly around an axis. Protons are positively charged and when they move, this creates a small electrical current. Electrical current induces a magnetic field, which means that every proton has its own magnetic field.

Magnetic resonance imaging involves placing a participant in a strong magnetic field. When this occurs, protons align either parallel or anti-parallel to the external magnetic field. The parallel alignment requires less energy than the anti-parallel alignment, causing slightly more protons to align in the parallel rather than anti-parallel orientation.

When in an external magnetic field, protons move in a specific way, known as precession. The speed at which protons precess is known as its precession frequency and is proportional to the strength of the external magnetic field. Precession frequency can be calculated using the Larmor equation: \[ \omega_0 = \gamma B_0 \] where \( \omega_0 \) is the precession frequency in hertz (Hz or MHz), \( B_0 \) is the strength of the magnetic field in Tesla (T) and \( \gamma \) is the gyro-magnetic ratio (for protons, this is 42.5 MHz/T).
When the magnetic forces of protons are equal and opposite, they cancel each other out. The total magnetic force exerted by protons in the body is parallel to the external magnetic field, as there are more protons in the parallel orientation. This is known as longitudinal magnetisation. The strength of longitudinal magnetisation cannot be determined, as it cannot be differentiated from the external magnetic field.

To allow the magnetic force in a participant to be determined, a radio wave is sent in. This radio wave is known as the radio frequency (RF) pulse. The RF pulse has a short duration and a frequency equal to the precession frequency. The RF pulse causes the protons to gain energy, or resonate. This increases the number of protons with an anti-parallel orientation, thus reducing longitudinal magnetisation. The RF pulse also causes the protons to precess in phase rather than randomly, leading to an increase in magnetisation force at 90° to the external magnetic field, known as transversal magnetisation. The protons precessing in phase causes an electrical current, which is the MRI signal and has the precessing frequency.

When the RF pulse is switched off, the protons lose energy and de-phase causing transversal magnetisation to decrease, known as transversal relaxation, and longitudinal magnetisation to increase, known as longitudinal relaxation. The protons do not return to the parallel orientation at the same time, some take longer than others. This means that longitudinal relaxation increases with time, at a certain rate. Longitudinal relaxation can be represented by an exponential curve, known as the $T_1$ curve. $T_1$ is also known as the longitudinal relaxation time and represents the time it takes for longitudinal magnetisation to return to 63% of its original strength.

Proton de-phasing can occur due to inhomogeneities in the external magnetic field as well as influences on the protons being exerted by the small magnetic fields of neighbouring nuclei. This leads to slight differences in the precession frequencies of the protons, so they no longer precess in-phase. The rate at which transversal relaxation occurs is known as the transversal relaxation time and can be represented as a decreasing exponential curve, known as a $T_2$ curve. $T_2$ is the time it takes for transversal magnetisation to decrease by 63%. If the proton de-phasing occurs due to only internal local magnetic field inhomogeneities, but in the absence of external field inhomogeneities, the curve produced is known as the $T_2$ curve. If, on the other hand, the de-phasing occurs due to both internal and external magnetic field
inhomogeneities, the curve produced is much shorter as de-phasing occurs more rapidly. The curve produced is known as a $T_2^*$-curve.

$T_1$ is usually about 300 – 2000 msec and $T_2$ is usually about 30 to 150 msec. Water and other liquids have a long $T_1$ and $T_2$. Fats have a comparatively shorter $T_1$ and $T_2$. If the time between pulses, the time to repeat (TR), is short enough, different tissues, containing different proportions of water and fat as well as other substances, will have regained different amounts of their longitudinal magnetisation before another RF pulse. The resulting MR signal emitted by each tissue type following the second RF pulse will differ. If the time at which the signal is measured after the RF pulse, known as time to echo (TE), is short, little de-phasing will have occurred, so $T_2$ effects will be small and the image will be $T_1$-weighted. An image is created where contrast between different tissue types is high and watery tissues such as the cerebral-spinal fluid (CSF) is dark and fatty tissues such as the white matter of the brain is light due to a greater signal being emitted from the white matter. If the TR is too long, all tissues regain all of their longitudinal magnetisation causing poor tissue contrast to be produced.

Signal location is possible due to gradient coils which superimpose a second magnetic field onto the external magnetic field. They produce a certain gradient along the z-axis, known as the slice selecting gradient, which is only switched on during the RF pulse. The frequency of the RF pulse administered can be selected to resonate a specific slice of interest. By altering either the magnetisation gradient or the frequency range of the RF pulse, slice thickness can be modified.

Location of a signal within a slice is determined by applying another gradient along the x-axis after the RF pulse, called the frequency encoding gradient, which increases across the slice causing protons across the slice to precess at different frequencies. A gradient along the y-axis is also applied after the RF pulse for a short time and is known as the phase encoding gradient. It causes protons to precess at different rates along the gradient, so when the gradient is switched off, the protons precess at the same frequency again, but are out of phase with each other. Protons in different locations in the slice thus emit signals at different frequencies and phases, which are analysed by fourier transformation. The result is a 2D
image of the slice of the body selected. Images of multiple slices along the z-axis are produced and then collated to produce a 3D image (Schild, 1990).

2.2.2. Functional MRI (fMRI)

fMRI is a technique used to image brain activity. Although other methods, mainly perfusion MRI can be used to do this, blood oxygenation level dependent (BOLD) fMRI is most commonly used due to its high sensitivity. BOLD fMRI is possible due to differences in the magnetic properties of deoxygenated compared to oxygenated haemoglobin. Deoxyhaemoglobin is paramagnetic; the external magnetic field is attracted towards it, causing an increase in magnetic flux. Oxyhaemoglobin is diamagnetic; the external magnetic field is repelled by it, reducing magnetic flux.

Relative to the surrounding tissues, deoxyhaemoglobin increases the magnetic susceptibility of the vessels, leading to an increased local field gradient between the vessels and surrounding tissue water. The result is a decreased $T_2^*$ and a reduced signal is recorded at the time of signal measurement. The opposite is true for oxyhaemoglobin with a resultant relative increase in signal strength.

In this investigation, the fMRI signal was measured 35 ms after administration of the RF pulse. This time to echo (TE) was selected as the difference between $T_2^*$ for deoxyhaemoglobin and oxyhaemoglobin at this time is large, allowing high contrast between activated and deactivated brain regions.

When a brain region becomes activated, a series of events known as the haemodynamic response occurs. During the first second of activation, a small decrease in signal occurs due to rapid deoxygenation of surrounding capillary blood, due to the increased synaptic activity leading to increased oxygen consumption. This is followed by a gradual increase in signal over the next 2-4 seconds due to increased blood flow to the activated region, leading to increased blood oxygenation which is proportionally greater than the increased oxygen consumption. Providing no physiological habituation occurs in response to stimulation, the signal remains at a constant level until the stimulus is removed. Following stimulation, the
signal decreases over the next few seconds to a level below baseline. The signal then slowly returns to baseline over the next few seconds. For a brief stimulus, the duration of the haemodynamic response is approximately 12-18 seconds.

The haemodynamic response can affect blood flow over quite a large area relative to the region of cortex activated, causing spatial resolution to be quite poor. To improve spatial resolution, brain imaging data is analysed using contrasts where brain activations during one condition are subtracted from those occurring during another. This allows areas of activation unique to a certain condition to be identified.

In this investigation, gradient echo-planar imaging was used. This method of imaging allows high-speed imaging as the signal from all locations in one brain slice can be measured following one RF pulse. This is particularly useful when using functional MRI, as it allows the fMRI signal of the whole brain to be sampled rapidly and regularly, increasing the accuracy of the data obtained by maximising statistical significance (Jezzard et al., 2001).

2.2.3. Imaging Investigation Methods

2.2.3.1. Participants

Full ethical approval was obtained from the North Manchester Research ethics committee. 30 healthy female volunteers (mean ± s.d. age = 23.7 ± 5.18 years) participated in this study. Participants from the touch questionnaire study were invited to participate in the imaging study if they met the following criteria:

- Consent had been given for future contact about further research volunteering opportunities.
- Female
- No psychiatric history
- Aged 18 – 45

Only female participants were used in this study because it was thought that gender could be a potential confounding variable. Females were chosen over males as depression is twice
as prevalent in females than males (Hamet and Tremblay, 2005). Participants who indicated they had no psychiatric history in response to some general questions at the beginning of the touch questionnaire battery and had a Brief Symptom Inventory (BSI) depression score of less than 0.92 were thought likely to have no psychiatric history and were invited to take part in the study. A depression score of 0.92 was chosen, as the normative data provided by Derogatis et al., (1993) shows the mean depression score + 1 standard deviation was 0.92 for female adult non-patients. Participants were emailed a participant information sheet when invited to participate.

2.2.3.2. Screening

Informed consent was obtained during the screening session. When possible, screening took place two days before scanning. During this time the structured clinical interview to diagnose DSM-IV-TR Axis I disorders (SCID) (First et al., 2002), was carried out. Any participant found to have a previous psychiatric history was excluded from the study. This led to the exclusion of 3 participants. During the screening session, participants completed the Brief Symptom Inventory (BSI) (Derogatis, 1993), so that a depression score could be obtained for the previous week. Participants were also asked a series of questions to ensure suitability for undergoing an fMRI scan. Participants with excessive alcohol consumption or who had taken street drugs recently were excluded from the study, as were potentially pregnant participants. Participants were asked to follow a low-protein diet the day before the scan and were provided with an example diet which they could follow.

2.2.3.3. Receiving touch paradigm – outside the scanner

During the screening session participants were asked to carry out the receiving touch paradigm outside the scanner and rate the pleasantness, smoothness and soothingness of the stimuli being presented. Participants were stroked on either their central left ventral forearm over a distance of 18 cm in the proximal to distal direction, or the ventral side of the left fingers proximal to distal over a distance of 5 cm, ending at the end of the fingertips.
These distances were measured and marks were drawn on the skin to indicate where the beginning and end of the strokes should be. The interval between strokes was 1 second. Stimuli were applied in 20 second blocks preceded by a 20 second rest block. A task was written in e-prime to allow accurate stimulus application during the task. For the rest block the task consisted of a screen displaying the stimulus to be presented, where the stimulus would be presented and a timer counting down 20 seconds from 20 to 1. An example of this can be seen in figure 8.

![Figure 8: example of the receiving touch task written using e-prime. This is an example of what would be displayed during a rest block.](image)

At the end of the rest block, the task was written so that a line would appear at the bottom of the screen. This line was programmed to decrease in size from the right end of the line at a speed proportional to the speed at which the stimulus should be presented. This meant the investigator could follow this line disappearing, allowing the correct velocity to be applied. An example screen from a stimulation block can be seen in figure 9.

![Figure 9: example of the receiving touch task during a stimulation block.](image)
Eight stimuli were used in this task and are described in table 2. Stimuli were selected following a pilot study involving 5 brushes and 9 materials. From the ratings the pilot participants gave, the fur and pleasant brush were selected as the most pleasant stimuli, the sacking and neutral brush as the most neutral and the scourer and unpleasant brush as the most unpleasant without being painful stimuli.

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fur</td>
<td>Artificial fur, pile ~1.5 cm, attached to MTS.</td>
</tr>
<tr>
<td>Sacking</td>
<td>Sacking attached to MTS</td>
</tr>
<tr>
<td>Scourer</td>
<td>Scouring pad (SPAR) attached to MTS</td>
</tr>
<tr>
<td>Pleasant (P) Brush</td>
<td>Pleasant brush (Daler-Rowney, 44 mm, Goat Hair, S155, flat)</td>
</tr>
<tr>
<td>Neutral (N) Brush</td>
<td>Neutral Brush (Hog Bristle, Daler-Rowney Georgian Brush, G36, Short Flat, no.18)</td>
</tr>
<tr>
<td>Unpleasant (UP) Brush</td>
<td>Unpleasant brush, made by the investigator (plastic bristles (obtained from a B&amp;Q shed brush) 44 mm flat brush)</td>
</tr>
<tr>
<td>Finger</td>
<td>The investigator’s index fingertip of the right hand.</td>
</tr>
<tr>
<td>Glove</td>
<td>The researcher’s index fingertip covered with the index finger of a nitrile glove.</td>
</tr>
</tbody>
</table>

Table 2: description of the stimuli used for the receiving touch task.

The materials were all applied using a manual tactile stimulator (MTS) (Dancer Designs, Unilever). This allowed a constant force of 0.22 N to be used when applying the stimuli. The brushes, finger and glove were also applied at a force of ~0.22 N. The investigator practised applying these stimuli at the correct force by stroking a top-pan balance with sufficient pressure to give a reading of 22 grams. Images of all the stimuli used, excluding the finger and glove, are presented in figure 10.
The MTS was modified by adding two pieces of 1 mm thick sponge to each end. Each piece of sponge was 44 mm wide to match the width of the brushes. Adding the sponge also made the end of the MTS softer. The materials were affixed to the end of the MTS using Velcro and all pieces of material were 44 mm wide. A new piece of each material was cut for each participant, but from the same piece of material where possible and from the same supplier, to ensure that the stimuli were the same for each participant.

During the receiving touch task, participants were blindfolded. Their forearm was placed on a VacFix® cushion (Qados) of size 25 cm x 50 cm and the air removed using an Ambu® twin pump to enable the arm to be kept in position and the participant to feel comfortable. The task was then carried out. During the task each stimulus was applied to the forearm and fingers once, but in a randomised order determined by the e-prime task. During each 20 second rest block, participants were asked to lift their blindfold and complete three paper based visual analogue scales (VAS) to describe the stimulus which had just been presented.

![Figure 10: images of stimuli used in the receiving touch task.](image-url)
The VAS were also randomised. Each VAS was 10 cm long with a scale of -10 to +10 and 0 in the middle. The VAS used gave an indication of pleasantness, roughness and soothingness. Figure 11 shows the VAS which were completed by each participant after the presentation of each stimulus.

![Figure 11: the visual analogue scales (VAS) completed by each participant after each stimulus presentation.](image)

If any participants rated materials very differently to the pilot participants, these participants were excluded. This only occurred once when a participant found the fur to be very unpleasant. This would have made analysis of data difficult, so this participant was excluded.
2.2.3.4. Touching materials paradigm – outside the scanner

The stimuli used in this task were the same materials as those used in the receiving touch task. A piece of sacking and scourer of dimensions 7.5 x 10 cm and a piece of artificial fur of dimensions 15 x 10 cm, which was then folded in half so that it was the same size as the sacking and scourer were used. A new piece of material was cut for each participant, but all material was cut from the same piece of material where possible and the same supplier, to ensure the stimulus was the same for each participant. For the touching materials paradigm, the participant was blindfolded and their arm placed on a VacFix cushion as described in section 2.2.3.3. The same VAS as used in the receiving touch task and as shown in figure 11 were given to each participant for this task. The participant was asked to complete the VAS during the rest block proceeding each stimulation block, as they were for the receiving touch task. Each piece of material was placed in the participants' left hand and the participant was instructed to rub the material between their thumb and fingers. After 20 seconds, the stimulus was removed and the participant was instructed to complete the VAS. After that 20 second rest block, the next stimulus was applied and so on. An e-prime task was written to enable accurate timing of each block. A screen from the rest block of the task is displayed in figure 12.

During the rest block, the programme instructs the investigator to get the stimulus ready to give to the participant. It also tells the experimenter which stimulus to apply and displays a
count-down timer from 20 to 1 second, so that the experimenter knows when to give the stimulus to the participant. After 20 seconds, the screen then changes to the stimulation screen, an example of which can be seen in figure 13. During this task each of the participants received all three stimuli, with the order randomised by e-prime.

![Figure 13: Example screen from the stimulation block of the touching materials block.](image)

### 2.2.3.5. Scanning

Seventy percent of participants were using a hormonal contraceptive and were scanned at any time, except for participants taking the combined pill who were scanned on pill-taking days only. All remaining participants were scanned during their follicular phase when they were not menstruating apart from two who were scanned on day 14 of their cycle and may have been in their ovulatory phase.

### 2.2.3.6. Pre amino acid drink

Before administration of the amino acid drink, participants were asked to complete the profile of mood states (POMS) (McNair et al., 1971) and the Fawcett-Clark Pleasure Scale (FCPS) (Fawcett et al., 1983) to determine participants’ mood before administration of the amino acid drink. Blood glucose was measured using an OneTouch® Ultra®2 blood glucose meter (LifeScan, Inc.) and blood pressure was measured using an electronic meter (Microlife®). These measurements allow a baseline recording of blood pressure and glucose,
so that if any marked change in these parameters occurred during the investigation, the investigator could respond accordingly. A 3 ml blood sample was also taken from each volunteer before administration of the drink to allow baseline plasma tryptophan to be determined and to enable genetic analysis.

2.2.3.7. Administration of the amino acid drink

Participants were randomly assigned to receive either the balanced or tryptophan depleted amino acid drink. The drinks were administered double-blind. The content of the amino acid drink was the same as that described by Benkelfat et al., (1994), except that 80% of each quantity was used instead, to account for the lower average body weight of females compared to males (Hood et al., 2005). By giving an 80% drink, this reduces the risk of side-effects such as vomiting. If a participant vomited less than 3.5 hours after administration of the drink, this participant would be excluded from the study. It was important to prevent vomiting for this reason. Throughout this investigation, no participants were excluded due to vomiting.

The contents of the amino acid drinks are shown in table 3. Immediately before administration of the drink, the amino acids were placed into a blender with 150 ml water and some chocolate flavoured ice-cream syrup. The mixture was then blended until fully mixed. It was then poured into a bottle and well shaken before being given to the participants in a cup. Participants were asked to consume the drink within 15 minutes and were provided with sugar-free mints, chewing gum, water and a straw to help them achieve this.
<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Grams per 80 % tryptophan depleted drink</th>
<th>Grams per 80 % balanced drink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Arginine</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Cysteine</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Glycine</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Histidine</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Leucine</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Lysine</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Methionine</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Proline</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Serine</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Threonine</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Tryptophan</strong></td>
<td>-----------</td>
<td><strong>1.8</strong></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Valine</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>82.1</strong></td>
<td><strong>83.9</strong></td>
</tr>
</tbody>
</table>

Table 3: contents of the amino acid drinks used in this investigation.

2.2.3.8 Post Amino Acid Drink

Immediately after administration of the amino acid drink, participants were asked to complete the 57 item TEAQ, the sociotropy-autonomy questionnaire (Beck et al., 1983), the impulsiveness questionnaire from the Impulsiveness Venturesome Empathy (IVE) questionnaire (Beck et al., 1983) and the Schizotypal Personality Questionnaire (SPQ-B) (Raine and Benishay, 1995). They were also asked to complete three neuropsychological tasks which were the n-back task, the faces task and the stop task. It was ensured that all participants had completed all of the questionnaires and tasks within an hour after consumption of the amino acid drink so that the amino acid drink did not have any effect on the data obtained. The data from these questionnaires and tasks apart from the touch questionnaire were used for a different larger ongoing investigation carried out by the...
department and is not reported here. The data was collected at this time as logistically it was
not possible for all of these ratings and tasks to be carried out before the administration of
the drink, so due to time constraints these tasks were carried out after administration of the
drink. After completion of all of the questionnaires and tasks, participants were asked to rest
and only do things which they found emotionally neutral.

2.2.3.9. Scanning

Four hours after consumption of the amino acid drink, participants completed another
POMS and FCPS to determine whether or not there had been any change in their mood.
Participants also had another 3 ml blood sample taken so that change in plasma tryptophan
levels between levels before the amino acid drink and levels immediately prior to scanning
could be determined. Blood glucose and blood pressure levels were measured to check that
these parameters had not changed considerably compared to before the amino acid drink.
This was important as the participant shouldn’t feel unwell during the scan, both for the
safety of the participant and also to ensure the results were as accurate as possible.

Following this, participants were asked to remove any metal they were wearing and to
empty their pockets. The radiographers ensured that there were no reasons why the
participant should not enter the scanner. The participant was then placed in the scanner. A
projection system was set up so that the receiving touch and touching materials tasks which
were written in e-prime (see sections 2.2.3.3. and 2.2.3.4. respectively) could be projected
onto a side wall, so that the investigator, but not the participant, could see the task.

Scanning was carried out using a 3 Tesla (T), Philips Achieva magnetic resonance imaging
(MRI) scanner. T2* weighted images were obtained to investigate changes in blood oxygen
level dependent (BOLD) signal throughout the scan. Single shot gradient echo-planar
scanning was carried out. Whole brain scans of 34 slices, each 3 mm thick with a 0.5 mm slice
gap were obtained. The repetition time (TR) used was 2000 ms, with a time to echo (TE) of 35
ms. The field of view (FOV) was 230 mm with an acquisition matrix of 128 x 128. Voxel size
was 1.8 x 1.8 x 3.0 mm.
A T₁ weighted whole brain image of 160 slices, each 1.8 mm thick with no slice gap was obtained to co-register the T₂* images to. A TR of 8.4 ms and a TE of 3.8 ms was used. FOV was 240 mm with an acquisition matrix of 256 x 256. Voxel size was 0.9 x 0.9 x 1.8 mm.

The scanning session consisted of a 5 minute resting state scan where participants simply lay in the scanner with their eyes closed. This was followed by the receiving touch task, which was carried out as described in section 2.2.3.3. Participants were not blindfolded, but participants reported that they could not see the stimulus being presented. Participants did not complete VAS during the task when in the scanner. Participants were asked to simply lie in the scanner and concentrate on how the stimulus being applied felt.

After this task, the touching materials task was administered in a similar way to that described in section 2.2.3.4. The only differences were participants were not blindfolded and the task was repeated three times, with stimulus order randomised during each repetition. Verbal communication was difficult between investigator and participant during task administration, so to signal to the participant to stop rubbing the material, the investigator tapped each participant lightly on the wrist once at the end of each stimulation block.

Following completion of the touching materials task, the receiving touch task was administered again. A structural brain scan was then carried out to obtain the T₁-weighted image. This was followed by the administration of the receiving touch task again, so that during each scan, each participant received each stimulus on both the arm and fingers three times. After this, the participant was removed from the scanner.

2.2.3.10. Post scanning

After the participants had been removed from the scanner, they were asked to carry out the receiving touch and touching materials tasks as described in sections 2.2.3.3. and 2.2.3.4. respectively. This provided an indication of how the participants perceived the stimuli in the scanner. Following this, participants’ blood pressure and glucose were measured to check it had not been lowered as a side-effect of the amino acid drink. Participants were advised who to contact if they experienced any side-effects after leaving the unit and given a tryptophan
containing meal to reverse the effects of the amino acid drink. Once they had consumed their meal, participants were allowed to leave if they did not feel unwell.

2.2.3.11. Blood Samples

Blood samples were centrifugated at 10 000 rpm for 5 minutes. Following this, the plasma was removed from the blood sample and stored in an eppendorf tube at -70 °C. The remainder of each blood sample underwent DNA extraction by the salting out method. Total plasma tryptophan levels were determined by Dr Mike Franklin (Oxford Brookes University). Genotyping of the DNA samples was carried out by Hazel Platt (CIGMR, The University of Manchester).

2.2.3.12. Data Analysis

Imaging data was analysed using MATLAB (The MathWorks, Inc.) and Statistical Parametric Mapping (SPM) version 5. Images were re-aligned and the artefact repair toolbox used to correct for movement. Images were co-registered to the T1 weighted image obtained for each participant. Co-registered images were then segmented, and normalized to Montreal Neurological Institute (MNI) space. Images were then smoothed (FWHM 5.4 x 5.4 x 10.5). First level analysis was carried out by subtracting brain activation during the preceeding rest block from that during the stimulation block. Average brain activation during each condition was then averaged per participant. Second level analysis involved averaging brain activation during each condition across each treatment group.

Whole brain analysis as well as a-priori region of interest analysis was carried out on all contrasts. The region of interest used consisted of Brodmann areas 11, 12, 13 and 47, the anterior cingulate, insula, amygdala and postcentral gyrus, all defined using the WFU PickAtlas. A 10 x 7.5 mm box, at 0 -24 -20 was used to include the brainstem raphe nuclei. Parietal operculum (OP) regions 1-4, as defined by the anatomy toolbox were also included in this region of interest analysis. The contrasts were thresholded at p<.005 with a minimum cluster size of 10 voxels.
Analysis of variance was used to identify regions showing main effects of all three brush stimuli (2 levels; touch, rest) and main effect of valence (3 levels; pleasant, neutral, unpleasant). These analyses were carried out separately for arm and finger stroking. It was determined whether the brain regions showing main effects of valence were modified by the site of stimulation from the interaction within those regions between valence and location (2 levels; arm, finger). Similarly, it was determined whether main effects of valence were modified by tryptophan depletion from the interaction term between valence and tryptophan treatment group (2 levels; control and tryptophan depletion).

Visual analogue data was analysed using a mixed design ANOVA with factors for valence and location being the within-subject factors and tryptophan depletion being the between-subject factor.
3. Paper 1

Construction and validation of the Touch Experiences and Attitudes Questionnaire (TEAQ), a self-report measure to determine attitudes to and experiences of positive affective touch.

(Paper 1)

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Abstract

Background: Affective touch may be an important component of social influences on depression. The Touch Experiences and Attitudes Questionnaire (TEAQ), was constructed to provide a measure of individual experience and attitude to various aspects of social and affective touch.

Methods: Statements about touch were generated from clinicians, psychologists and non-professional contacts. They were reduced to 117 statements with a 5-point Likert rating of agreement/disagreement. 618 participants completed the draft TEAQ online together with standard and modified questionnaires about childhood trauma, social support and personality. Principle components analysis was used to identify the factor structure and items were eliminated on the basis of low factor loadings, high inter-correlation and effect on Cronbach’s alpha. The shortened version of the TEAQ and other questionnaires was completed by a new sample of 704 participants. A confirmatory factor analysis was carried out and correlation of factor scores with questionnaire measures of social support and childhood adversity were computed as a preliminary analysis of concurrent validity.

Results: 6-factors explained a total of 56.2 % of the variance in the 117-item draft TEAQ. Cronbach’s alphas for these factors ranged from 0.78 to 0.93, indicating reasonable factor reliability. Confirmatory Factor Analysis on the 57-item TEAQ indicated this 6 factor structure to be a reasonable fit of the data in the second sample. The 6 factors correspond to amount of current social touch, touch with intimates and childhood touch, and positive attitudes to skincare, to touch in intimate relationships and to touch with unfamiliar people. Correlations between childhood touch and childhood trauma and current touch and social support were identified.

Conclusions: The TEAQ factors are reliable and relate to concurrent measures of social contact and satisfaction and to childhood adversity. The questionnaire could aid future investigations into the role of positive affective touch in social influences on depression.
1. Introduction

It is well known that supportive social relationships promote resilience to life stress and the onset of depression (Brown et al., 1986). Similarly, early experience of good parenting is a protective factor against depression. However the psychobiological processes that mediate social influences on risk of depression are unknown. An extensive literature has documented long-term behavioural and neurochemical effects of exposing animals to periods of social isolation in adulthood and of maternal deprivation in development. A number of studies report that returning animals to group housing conditions prevents the development of fearful behaviour after experimental stressors. Various investigators have emphasised the possible importance of touch as a key modality that signals social contact and maintains neurochemical mechanisms of stress resilience such as 5-HT, oxytocin and endorphins (Cochrane, 1990, Deakin et al., 1990, Dunbar, 2010, Meaney and Szyf, 2005). Whether such neurobiological effects of affective contact are an important component of the protective effects of social support in adult or developing humans remains uncertain. This study describes the development and validation of a questionnaire to identify dimensions of variation in touch experiences and attitudes as a first step to investigating their role in social support and depression.

Touch questionnaires have been used in various studies in social psychology. The tactile type (TACTYPE) questionnaire was developed by Deethardt and Hines, (1983) as an introspective measure of tactile tendency for college-age students. This questionnaire has 15 items loading on three factors; attitudes to girl/boyfriend touch, social touch with the opposite sex and consoling touch with the same sex. High and low scorers differed in some of the Cattel 16 personality factor dimensions. The touch avoidance measure (TAM) (Andersen and Leibowitz, 1978) has 18 items loading on negative attitude to touch with the opposite or same sex; males and females were shown to differ in these attitudes. Some of the items appear to probe sexual orientation. The TACTYPE and TAM questionnaires were used together in one study carried out by Jones and Brown, (1996), along with a revised version of Gladney and Barker’s (1979) familial touch orientation scale. It was found that the questionnaire responses did not predict day-to-day touching recorded in a daily log. The TACTYPE and TAM questionnaires do not assess experience of touch and have not been used
in the context of social support or depression. The familial touch orientation scale is a 10 item questionnaire. Two of these items relate to touch between parents. The remaining 8 items relate to touch experienced during childhood, but were specific to certain situations, such as ‘mother/father kissed you before you went to school.’ Although this scale was relevant to childhood touch, it was felt that a less specific and more general measure of childhood touch would be of value for this study.

The role of touch in depression in psychiatric in-patients was investigated using an 8 item questionnaire (Questionnaire on Physical Contact Experience QPCE; Cochrane, (1990)). Six items related to experiences of good, bad and neutral touch currently and in childhood. Two items concerned current and childhood experience of love. Cochrane found a higher incidence of depression in individuals reporting unsatisfactory compared to satisfactory physical contact experience either at present, or during childhood or both. An additive effect of feeling unloved with a lack of satisfactory physical contact experience was found. Takeuchi et al, (2010) found that recollections of peer and parental touch correlated with self-rated depression scores.

Current and childhood experiences of giving and receiving touch together with attitudes to touch were measured since these could be dissociable processes mediating vulnerability to depression. The construction of the Touch Experiences and Attitudes Questionnaire (TEAQ) and tests of reliability of its factor structure and concurrent validation using questionnaire measures of current social support and childhood adversity that are widely used in social psychiatry are described.

Approximately 2 billion per annum is spent on products that are self-applied to the skin such as soaps, exfoliants, creams and ointments. A subsidiary aim of this research was to determine whether use of skin products (skin care) related to attitudes to and experience of touch with others.
2. Methods

2.1 Participants

The study was approved by the University of Manchester ethics committee. Participants completed the TEAQ and other questionnaires anonymously online to create large samples and to minimise the influence of embarrassment, social conformity and pressure to participate. The first sample was for principal components analysis and item selection. A second, replication sample completed the reduced TEAQ and other questionnaires for the confirmatory factor analysis using structural equation modelling. All members of the University of Manchester received an emailed invitation to participate including undergraduates, postgraduates, academics, clerical and general staff, allowing a reasonably diverse age range. The study was also advertised through an online social networking site. A £50 prize draw provided an incentive to participate.

2.2. TEAQ item generation

Questionnaire items were generated and assessed for acceptability by discussion with colleagues and social contacts to cover the range of positive touch experiences including hugs, kisses, skin-skin contact and hair-skin contact in everyday circumstances such as greeting, consoling, intimacy and childhood contact. Items consisted of statements and a 5-point Likert scale of agreement. Statements were written to cover attitude to both giving and receiving touch, as well as questions about attitude to touch in general such as ‘I’m not a very tactile person.’

The terms ‘partner’, ‘boyfriend/girlfriend’, ‘husband/wife’ were avoided and instead any questions about intimate touch referred to ‘someone you are close to’. Questions about childhood touch were limited to the amount of various forms of touch they received and not their attitudes as the latter was considered harder to recall and to interpret. An example question is: ‘my parents regularly cuddled me as a child.’ Items also covered self-touch in cleaning and grooming such as ‘I find taking a shower or bath very enjoyable.’ 117 items were created and presented at random using a random number generator. The TEAQ was then included with others described below on a website for completion online.
2.3. Questionnaires for concurrent validity

Two online questionnaires were used as measures of concurrent validity; the Social Support Questionnaire (SSQ6) (Sarason et al., 1987) and questions derived from the Childhood Trauma Questionnaire (Bernstein et al., 1994). Neither contains items about touch, but a-priori it seemed highly likely that current social support and childhood adversity would correlate with experiences and attitudes to touch. Furthermore, it was hypothesised that touch may be a mediating mechanism that contributes to the influence of these social factors on risk of depression. The first item of the SSQ6: “Whom can you really count on to distract you from your worries when you feel under stress?” was replaced with the more general item from the original version of the SSQ ‘Whom can you really count on to be dependable when you need help?’ The SSQ6 was also simplified by asking participants to rate the number of people who they could depend on in each circumstance as ‘None’ ‘A Few’ or ‘Lots’ rather than asking participants to name the people they could depend on in each circumstance. The SSQ produces two scores - the number of supports (SSQN) and satisfaction with social contacts (SSQS).

The Childhood Adversity Questionnaire (CHA) consists of 4 items loosely based on the 28 item Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994): “When I was growing up... 1. I was happy, 2. I believe that I was abused or neglected, 3. People in my family looked out for each other and 4. My parents/guardians weren’t able to take care of me.” Other items, particularly those regarding sexual abuse, were felt to be too intrusive and potentially upsetting for online use. The CHA has been used in previous investigations and has been reported to strongly predict full CTQ score (Pearson’s R = 0.75, p < 0.001, N = 142) (Juhasz et al., 2011). The CHA and the CTQ use a 5 point likert scale ranging from ‘Never True’ to ‘Very Often True.’ In addition the CHA has two additional items rated yes or no: ‘I lost my mother’ and ‘I lost my father.’
2.4. Statistical analysis

All questionnaires were scored according to the instructions given by the questionnaire authors and was carried out using Microsoft Excel. For all datasets, any participants with greater than 5% of responses missing were removed from the analysis to minimise inaccuracies caused by missing values (Tabachnick and Fidell, 2007).

2.4.1. Principal components analysis and item selection

Principal components analysis with direct Oblimin rotation was carried out using SPSS to allow factors to correlate rather than seeking to identify orthogonal components. Covariance rather than correlations analysis was used because covariance analysis is less influenced by variation in the distribution of scores between items on the 5-point Likert scale (Field et al., 2005, Tinsley and Tinsley, 1987). Missing values were excluded pairwise. Scores for negatively phrased questions were reversed so that scores reflect greater touch experience or positive attitude. The number of factors to extract was determined using Cattell’s scree test (Cattell, 1966).

A correlation matrix was used to exclude redundant items that correlated significantly with more than 80% of the others or with another item at more than $r = 0.8$. Items with measures of sampling adequacy (MSA) values less than 0.6 were also removed. Items with rescaled communalities less than 0.3, indicating these items explained only a small proportion of the shared variance were also removed (Field, 2005). Stevens (1992) suggests that factor loadings greater than 0.4 should be considered of interest. Any items with factor loadings less than 0.4 for all factors were removed, as well as any items which loaded similarly on two factors. Reliability analysis was carried out for each factor. Any items which did not increase Cronbach’s alpha were removed.

2.4.2. Confirmatory factor analysis (CFA)

The replication sample completed the reduced TEAQ online and a confirmatory factor analysis was carried out using structural equation modelling (Amos™ 7; SPSS Inc.). In addition, a hierarchical model was tested. The criteria used to determine goodness of model fit were a Root Mean Square Error of Approximation (RMSEA) < 0.06 with a narrow
confidence interval, an RMSEA probability value > 0.5, a Comparitive Fit Index (CFI) > 0.95, a low Akaike’s Information Criterion (AIC), a standardised Root Mean Square Residual (RMR) < 0.05 and a Tucker-Lewis Index > 0.95 (Byrne, 2001).

The reliability of structural equation modelling is reduced by an excessively large number of variables. It was therefore determined whether parcellation of items to produce three measures for each factor affected the outcome, as advocated by Yang et al., (2010), using the procedure of (Nasser and Wisenbaker, 2003).

Scores were skewed towards the more positive responses in many items and did not show a normal distribution. It was therefore determined the effect of transforming scores to binary such that scores less than the median were assigned a value of 0 and those equal or greater than the median, 1.

A third order model was tested that included second order factors representing the common variance between Current Social Touch (CST) and Current Intimate Touch (CIT) and between Attitude to Intimate Touch (AIT) and Attitude to Unfamiliar Touch (AUT). A third order general ‘touch’ variable representing the common variance between all factors was also included in the model. It was also hypothesised that attitude to intimate touch could affect the amount of current intimate touch experienced and the regression of AIT on CIT was included in the model. The model was tested using the binary parcelled data described above.

2.4.3. Correlation of the TEAQ factors with self-reported social support and childhood adversity

To investigate the concurrent validity of the touch questionnaire, Pearson’s Correlations were calculated between the TEAQ factor scores and the two social support scores SSQN and SSQS, and the CHA score in the two datasets combined. In such a large sample correlations are statistically significant even when explaining a very small amount of the variance, therefore, only correlations greater than 0.3 (explaining 9 % of the variance) were regarded as of interest.
3. Results

3.1 Demographics

The age, sex and socio-economic demographics of the samples were similar and the differences were not statistically significantly (table 1). 52-62 % were students and 25-39 % were in full-time employment. About a third of participants were single and a third married. It is noteworthy that the sample is skewed. The majority of participants are young, female and do not have children.

<table>
<thead>
<tr>
<th></th>
<th>PCA Sample</th>
<th>CFA Sample</th>
<th>Correlations Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>618</td>
<td>704</td>
<td>1308</td>
</tr>
<tr>
<td>Mean age ± s.d.</td>
<td>26.9 ± 9.32</td>
<td>27.4 ± 9.6</td>
<td>27.2 ± 9.5</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28.8</td>
<td>26.3</td>
<td>27.6</td>
</tr>
<tr>
<td>Female</td>
<td>71.2</td>
<td>73.7</td>
<td>72.4</td>
</tr>
<tr>
<td>Employment Status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working F/T</td>
<td>39</td>
<td>25.0</td>
<td>30.2</td>
</tr>
<tr>
<td>Working P/T</td>
<td>5.8</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Student</td>
<td>52.4</td>
<td>62.4</td>
<td>58.3</td>
</tr>
<tr>
<td>Not working</td>
<td>2.7</td>
<td>5.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Marital Status (%)</td>
<td></td>
<td></td>
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<tr>
<td>Single</td>
<td>39.0</td>
<td>36.1</td>
<td>37.3</td>
</tr>
<tr>
<td>In a relationship</td>
<td>32.8</td>
<td>35.2</td>
<td>34.2</td>
</tr>
<tr>
<td>Married/Cohabitating</td>
<td>25.9</td>
<td>25.6</td>
<td>26.0</td>
</tr>
<tr>
<td>Separated/Divorced</td>
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<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Widowed</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Children (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>83.5</td>
<td>80.7</td>
<td>82.0</td>
</tr>
<tr>
<td>1</td>
<td>5.3</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>≥ 2</td>
<td>9.7</td>
<td>11.7</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Table 1: Participant demographics for the Principal Components Analysis (PCA) dataset, the Confirmatory Factor Analysis (CFA) dataset and the correlations analysis dataset.
3.2. Principal components analysis (PCA)

953 participants completed the online touch questionnaire. 249 participants with more than 5% missing values were excluded from the analysis. All participants included in the analysis had less than 1.2% missing data. For the whole dataset, only 0.3% of the data was missing once the 249 participants had been excluded.

Cattell’s scree test identified 6 factors. 60 items failed the criteria for inclusion, 40 had low communality scores, 7 had no loadings on any factor, 6 had low MSA scores and 7 on the other grounds. This left a total of 57 items. The final factor structure and factor loadings of each item are available from the authors. The top, middle and lowest factor loading items are shown in table 2. Cronbach’s Alphas for the factors ranged from 0.92 to 0.78. Items loading on each factor were very consistent suggesting the factor names proposed in table 2.
<table>
<thead>
<tr>
<th>Factor names / number of items</th>
<th>% variance Loading</th>
<th>Factor names / number of items</th>
<th>% variance Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Items with highest, medium and lowest loadings</strong></td>
<td></td>
<td><strong>Items with highest, medium and lowest loadings</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1. Current Social Touch (CST) / 11</strong></td>
<td></td>
<td><strong>4. Attitude to Skin Care (ASkC) / 5</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.2</td>
<td></td>
<td>5.6</td>
</tr>
<tr>
<td>I always greet my friends and family by giving them a hug. (Q30)</td>
<td>0.75</td>
<td>I like to use face masks on my skin. (Q55)</td>
<td>-0.77</td>
</tr>
<tr>
<td>I often make physical contact with my friends and family when I am with them. (Q38)</td>
<td>0.69</td>
<td>I like having a bath with lots of bubble bath. (Q52)</td>
<td>-0.70</td>
</tr>
<tr>
<td>I often put my arm around a close friend as we walk along together. (Q51)</td>
<td>0.58</td>
<td>I like using body lotions. (Q2)</td>
<td>-0.64</td>
</tr>
<tr>
<td><strong>2. Current Intimate Touch (CIT) / 14</strong></td>
<td></td>
<td><strong>5. Attitude to Intimate Touch (AIT) / 13</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>Most days I get a hug or a kiss. (Q36)</td>
<td>-0.79</td>
<td>I like to stroke the skin of someone I know intimately. (Q47)</td>
<td>0.74</td>
</tr>
<tr>
<td>I often have my skin stroked. (Q45)</td>
<td>-0.62</td>
<td>I enjoy being cuddled by someone I am fond of. (Q31)</td>
<td>0.59</td>
</tr>
<tr>
<td>I often hold hands with someone I know intimately. (Q17)</td>
<td>-0.43</td>
<td>I enjoy having sex. (Q26)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>3. Childhood Touch (ChT) / 9</strong></td>
<td></td>
<td><strong>6. Attitude to Unfamiliar Touch (AUT) / 5</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.3</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>As a child my parents would tuck me up in bed every night and give me a hug and a kiss goodnight. (Q22)</td>
<td>-0.80</td>
<td>It makes me feel uncomfortable if someone I don’t know very well touches me in a friendly manner. (Q39)</td>
<td>0.79</td>
</tr>
<tr>
<td>As a child my parents would often hold my hand when I was walking along with them. (Q35)</td>
<td>-0.66</td>
<td>I have to know someone quite well to enjoy a hug from them. (Q3)</td>
<td>0.71</td>
</tr>
<tr>
<td>As a child my mother regularly brushed my hair. (Q42)</td>
<td>-0.53</td>
<td>I dislike people being very physically affectionate towards me. (Q1)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Table 2: % variance explained by each factor and factor loadings for the highest, medium and lowest loading item in each factor. Numbers in brackets indicate item number.
3.2.1. Factor correlations

As shown in table 3, factor scores correlated significantly with each other (p < 0.001). The attitude to skin care factor correlated least with the other factors and the current social touch factor the most. The strongest correlation was between current intimate touch and attitude to intimate touch (r = 0.58) and the weakest correlation was between attitude to skin care and attitude to unfamiliar touch (r = 0.12).

<table>
<thead>
<tr>
<th></th>
<th>CST</th>
<th>CIT</th>
<th>ChT</th>
<th>ASkC</th>
<th>AIT</th>
<th>AUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>1</td>
<td>.50</td>
<td>.52</td>
<td>.51</td>
<td>.36</td>
<td>.51</td>
</tr>
<tr>
<td>CIT</td>
<td>.50</td>
<td>1</td>
<td>.41</td>
<td>.30</td>
<td>.58</td>
<td>.30</td>
</tr>
<tr>
<td>ChT</td>
<td>.52</td>
<td>.41</td>
<td>1</td>
<td>.25</td>
<td>.35</td>
<td>.28</td>
</tr>
<tr>
<td>ASkC</td>
<td>.36</td>
<td>.30</td>
<td>.25</td>
<td>1</td>
<td>.28</td>
<td>.12</td>
</tr>
<tr>
<td>AIT</td>
<td>.51</td>
<td>.58</td>
<td>.35</td>
<td>.28</td>
<td>1</td>
<td>.41</td>
</tr>
<tr>
<td>AUT</td>
<td>.51</td>
<td>.30</td>
<td>.28</td>
<td>.12</td>
<td>.41</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>.82</td>
<td>.81</td>
<td>.68</td>
<td>.49</td>
<td>.76</td>
<td>.55</td>
</tr>
</tbody>
</table>

Table 3: TEAQ factor correlations with each other. All correlations are significant at p<0.001. Abbreviations: CST – current social touch, CIT – current intimate touch, ChT – childhood touch, AIT – attitude to intimate touch, AUT – attitude to unfamiliar touch, ASkC – attitude to skin care, total touch – overall touch score.

3.3. Confirmatory Factor Analysis (CFA)

817 participants completed the questionnaires and the 57-item TEAQ. 113 participants with more than 5% missing values were excluded from the analysis leaving 704 participants. The demographics of the dataset used are presented in table 2 (CFA sample). The 6 factor structure from the principal components analysis provided reasonable fit of the data from the replication sample as shown in the first row of table 4. Binary transformation and parcellation of factor items improved model fit as shown in the second row of table 4. The third order model provided an equally good fit of the data, as shown in the third row of table 4.
### Table 4: model fit indices for the TEAQ models tested using structural equation modelling. Abbreviations: RMSEA, Root Mean Square Error of Approximation. RMSEA p, probability statistic associated with the RMSEA. CFI, Comparative Fit Index. AIC, Akaike’s Information Criterion. Std RMR, Standardised Root Mean Square Residual. TLI, Tucker-Lewis Index.

<table>
<thead>
<tr>
<th>Model</th>
<th>RMSEA</th>
<th>RMSEA p</th>
<th>CFI</th>
<th>AIC</th>
<th>Std RMR</th>
<th>TLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st order model</td>
<td>0.069</td>
<td>&lt;0.001</td>
<td>0.805</td>
<td>6811</td>
<td>0.071</td>
<td>0.796</td>
</tr>
<tr>
<td>Parcelled, binary</td>
<td>0.040</td>
<td>0.994</td>
<td>0.981</td>
<td>355</td>
<td>0.037</td>
<td>0.976</td>
</tr>
<tr>
<td>3rd order model</td>
<td>0.041</td>
<td>0.987</td>
<td>0.979</td>
<td>366</td>
<td>0.043</td>
<td>0.974</td>
</tr>
</tbody>
</table>

3.4. Correlation of the TEAQ factors with self-reported social support and childhood adversity.

1308 participant responses were included in this analysis (see table 2). All correlations greater than 0.3 were significant at $p < 0.001$. As shown in table 5, there was a strong negative correlation between childhood adversity (CHA) score and the childhood touch factor score ($r = -0.58$). Other factor scores correlated less than $r = -0.22$ with CHA. There were significant positive correlations ($r = 0.34-0.37$) between number of social supports (SSQN) and the first three factors of the TEAQ - current social touch, current intimate touch and childhood touch. These TEAQ factors also correlated at greater than $r > 0.3$ with satisfaction with social contacts (SSQS) but the correlation with current intimate touch factor $r = 0.50$ was somewhat greater than with the other two TEAQ factors ($r = 0.34$ and 0.37).
4. Discussion

The purpose of this study was to develop a questionnaire that assesses attitudes to interpersonal touch and the amount given and received, to provide preliminary evidence of its reliability and validity and to identify the main dimensions of variation. The overall aim was to provide an instrument to investigate the role of touch in the psychobiological origins of depression, specifically in the association of early adversity and social isolation with depression.

Principal components analysis found 6 factors that accounted for 56% of the variance in 117 questions related to touch in 618 respondents. The factors had high Cronbach’s alpha values suggesting there is one dimension per factor and that they are internally consistent. 5 factors concerned touch with others and a sixth concerned attitude to self skin care. The largest factor was termed Current Social Touch (CST) because it loaded on items about amount and liking of giving and receiving affectionate touch from family and friends. This appears to be a general factor since it correlated with the other factor scores at $r = 0.50$-$0.52$ except with attitude to skin care where $r = 0.36$. This factor contains both attitudinal and amount measures, but as these all loaded on the same factor, it appears that these measures cannot be separated for this factor. Two factors (2 and 3) concerned amount of touch, respectively in intimate relationships and in childhood, and two (5 and 6) concerned affective

<table>
<thead>
<tr>
<th></th>
<th>SSQN</th>
<th>SSQS</th>
<th>CHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>.34</td>
<td>.34</td>
<td>-.22</td>
</tr>
<tr>
<td>CIT</td>
<td>.37</td>
<td>.50</td>
<td>-.22</td>
</tr>
<tr>
<td>ChT</td>
<td>.34</td>
<td>.37</td>
<td>-.58</td>
</tr>
<tr>
<td>AIT</td>
<td>.23</td>
<td>.24</td>
<td>-.16</td>
</tr>
<tr>
<td>AUT</td>
<td>.29</td>
<td>.21</td>
<td>-.16</td>
</tr>
<tr>
<td>ASkC</td>
<td>.13</td>
<td>.17</td>
<td>-.07</td>
</tr>
<tr>
<td>Total Touch</td>
<td>.42</td>
<td>.47</td>
<td>-.34</td>
</tr>
</tbody>
</table>

Table 5: Pearson’s bivariate correlations of touch versus social circumstances. Abbreviations: CST – current social touch, CIT – current intimate touch, ChT – childhood touch, ASkC – attitude to skin care, AIT – attitude to intimate touch, AUT – attitude to unfamiliar touch, SSQN social support number of people, SSQS – social support satisfaction with number of people, CHA – childhood adversity.
attitude to touch with others, respectively in intimate relationships and unfamiliar touch. The greatest correlation between two factors was between attitude to intimate touch and current intimate touch \((r = 0.58)\). This suggested attitude to intimate touch might determine the amount and this was tested using structural equation modelling, discussed below.

The reliability of the TEAQ factor structure was confirmed using structural equation modelling. The six factor solution provided a good fit on most measures in a second large dataset. Scores on many of the items were skewed towards the more positive responses but parcellation and transformation to binary scores improved the fit somewhat, suggesting that the factor structure and model fitting were not artefacts of the distribution of scores. It was investigated whether a third order model improved fit to the data. Specifically, a model with general factors for affective attitude to touch and for amount of touch, which included regression of current intimate touch on attitude to intimate touch, was tested. However, this model had identical goodness of fit scores to the six factor model. These findings suggest that the TEAQ could be scored as six factors but also that the total score is meaningful. An intermediate simplified scheme would have three interpersonal measures: i) amount of affective touch experienced at present, ii) amount of affective touch experienced during childhood and iii) attitude to (ie. liking of) affective touch.

It was reasoned that the concurrent questionnaire measures of quantity of social support and satisfaction with it ought to correlate with the amount and liking of touch since social support usually involves some degree of physical contact. That the first three TEAQ factors correlated with SSQN and SSQS at greater than \(r = 0.3\) is therefore suggestive of concurrent reliability of the TEAQ. Although correlated, the two domains of social contact and touch are far from completely confounded, each explaining no more than 25 % of the variation in the other. Therefore, the results further suggest that the TEAQ could be used as intended to partial out amount and liking of touch from the influence of social support on risk of depression; in other words to determine the independent contribution of physical touch parameters to vulnerability to depression.

The childhood experience of touch factor also appears to have significant concurrent validity in that scores on this factor correlated strongly \((r = 0.58)\) with scores on the CHA
questionnaire and indeed childhood abuse and neglect ought reasonably to be reflected in reduced experience of affective touch in childhood. It was also expected that the experience of childhood abuse and neglect would quite strongly influence adult current experience of social and intimate touch and with affective attitudes, but these correlations, although statistically significant, were low at $r < 0.22$. Relatively low correlations were also seen between the childhood touch factor scores and factor scores on attitude to intimate and to unfamiliar touch in adulthood ($r=0.35$ and $0.28$ respectively). These findings suggest that other factors may intervene to influence the relationship of childhood adversity and touch experience with adult experiences and attitudes to touch. This could, for example, involve genetic predisposition which is known to modify the relationship between childhood adversity and depression (Caspi et al., 2002). Furthermore, there is evidence that the effect of childhood neglect on risk of depression can be moderated by quality of adult relationships whereas this is not true of sexual abuse (Hill et al. 2001). Because the CHA questionnaire conflates sexual and physical abuse and neglect this may have added unexplained variation to the correlation between CHA and adult touch.

Items on liking and use of skin care products all loaded on the same factor and this factor correlated modestly with the general touch factor ($r = 0.36$), but not greater than 0.3 with the other factors. Concurrent correlations with SSQ and CHA were low ($r < 0.2$). These items were included because we were curious with our industrial co-sponsor to explore whether determinants of interpersonal touch might relate to liking and use of skin care products. The results suggest the skin care dimension is largely independent of the interpersonal touch factors. It might possibly relate to body-image perception and personality. Since there is no hypothesis about self-touch or skin care in mechanisms of depression, these items would not usefully be included in the TEAQ in depression research.

This study has numerous limitations. The majority of participants were members of the University of Manchester. Further investigation is required to determine whether or not this questionnaire is valid for use with in-patients and other non-community-based samples, as well as for older individuals and people from different cultures. Another limitation of the sample used is that the majority of participants were female. The advertisement used to recruit participants for principal components analysis stated affective touch and depression.
were being researched. As depression is twice as prevalent in the female than male population (Hamet and Tremblay, 2005), this may have encouraged female participation. A further limitation is that the majority of participants did not have children. Parenthood may alter touch experiences and attitudes and so further investigation of a sample which includes more parents could be of value.

The incremental validity of this questionnaire compared to the TACTYPE, TAM and QPCE questionnaires described in the introduction would have allowed further validation of the TEAQ. Unfortunately, participants were not asked to complete these questionnaires during this investigation and so this requires a further investigation.

In summary, the TEAQ appears to be a reliable measure of affective touch experienced at present and during childhood, as well as attitude to touch and intrapersonal touch. Construct validity was determined by high Cronbach’s alpha values following principal components analysis, a good fit of the data being obtained from confirmatory factor analysis and significant correlations being identified between the current touch factors and social support and the childhood touch factor and childhood adversity. The results of this investigation suggest the TEAQ to be a valid and reliable measure for use in the investigation of positive affective touch in community-based samples.

Acknowledgements and declaration of interest

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4. Paper 2

Investigation into the role of affective touch in depression. Results from a questionnaire study of a community based population.

(The role of affective touch in depression)

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This manuscript has been prepared for submission to Psychological Medicine
Abstract

**Background:** Past parental neglect and current social isolation increases vulnerability to depression. Lack of affective touch could be an important mediating process. Many experimental investigations have reported detrimental effects of touch deprivation on development, behaviour and neurobiology. However, there is little direct evidence that in humans, affective touch promotes resilience to depression.

**Methods:** 1308 participants completed questionnaires online including a recently developed touch questionnaire (Touch Experiences and Attitudes Questionnaire; TEAQ) together with questionnaires covering factors contributing to the onset of depression; social support, childhood adversity, personality and life events, as well as data regarding psychiatric history. Results were analysed using correlation and regression analysis on current depressive symptoms and previous history of depression in currently well participants.

**Results:** Current experience of touch in intimate relationships, but not in social relationships was found to account for variance in current depressive symptoms in addition to predictive effects of neuroticism, satisfaction with social support, recent stressful life events and childhood adversity. Positive experiences of childhood touch, after allowing for the effects of childhood adversity, had a significant influence on previous vs no history of depression in those with no current symptoms.

**Conclusions:** Current experience of touch in intimate relationships is associated with reduced current symptoms of depression even allowing for known personality and social risk factors for depression. The extent to which direct neurobiological effects of affective touch might contribute to resilience to depression requires further study.
1. Introduction

The importance of affective touch in normal emotional development has been a matter of interest and debate since the work of Bowlby and of Harlow on the effects of maternal deprivation in humans and primates more than half a century ago. Subsequent studies in adult experimental animals have documented various behavioural and neurochemical consequences of isolation housing (Jutapakdeegul et al., 2003, Lapiz et al., 2003). Studies in social psychiatry have long established that childhood neglect and current social isolation are risk factors for depression. This paper aimed to investigate the extent to which these depression risk factors might act through lack of affective touch as assessed by a new touch questionnaire in a large sample of students.

In a famous and influential report to the World Health Organisation, Bowlby (1951) described the adverse effects of separating infants from their mothers among homeless children after the second world war. Harlow attempted to model these effects in infant primates and to identify the key detrimental elements of maternal separation. Neonatal macaque monkeys reared in isolation developed a preferential attachment to a mother surrogate made of wood covered in cloth over a surrogate made of wire even if milk from a bottle was available from the latter (Harlow and Zimmermann, 1959). Harlow concluded that touch was a key element of the attachment. Many experiments since then have reported various effects of skin contact and grooming on physical development, stress and immune function in infant primates (Laudenslager et al., 1993, Suomi et al., 1976). Field and colleagues have made analogous observation on the benefits of touch and massage therapy in human infant development (Field et al., 2010). Many investigations using rat pups have shown that tactile stimulation during the neonatal period can improve rat pup development and reverse the effects of maternal separation on development and fearful behaviour (Imanaka et al., 2008, Plaut et al., 1974).

It is well known that early parental neglect increases vulnerability to adult depression (Hill et al., 2001). Whether this involves lack of affective touch, however, is far from clear. Brown et al., (2007) found that a lack of maternal affection during childhood was a significant predictor of chronicity of depression in adult life for women and this may plausibly be related to physical contact. Studies by Meaney and colleagues provide evidence that maternal touch
and grooming in neonatal rats has important effects on later stress reactivity. Increased maternal licking and grooming of rat pups led to increased 5-HT turnover in the hippocampus, which caused a long-lasting epigenetic increase in hippocampal glucocorticoid receptor expression. This in turn resulted in greater feedback inhibition of the of the hypothalamico-adrenal axis (HPA) stress response (Meaney and Szyf, 2005). Sensitive feedback control of the HPA could protect against exaggerated cortisol responses to stress that have been implicated on the pathogenesis of depression. Indeed in humans, increased HPA reactivity to stress has been reported in association with the experience of early adversity, albeit adversity from abuse rather than neglect (Heim and Nemeroff, 2001).

Current social isolation in humans increases vulnerability to depression following stressful life events (Brown et al., 1990). Isolation housing in adult experimental animals can influence responses to stress. For example, Stranahan et al., (2006) indeed reported that access to a running wheel in group-housed rats promoted adult neurogenesis in the hippocampus but reduced it in individually housed rats. Dourish et al (1989) found that returning rats to group housing after one hour of immobilisation stress prevented the incubation of anxiety-like behaviour in an open-field test 24 hours later, seen in animals returned to isolation housing. Interestingly pre-treatment with an antidepressant or a single dose of the 5-HT$_{1A}$ agonist 8-OH-DPAT after restraint mimicked the effect of group housing in preventing incubation of anxiety seen in individually housed animals (Kennett et al., 1987). On the basis of these and other experiments, Deakin (1996) speculated that median raphe 5-HT projections might be conditioned by social contact, perhaps mediated by affective touch, to respond more strongly to adversity and thus promote resilience to stress. However, there is almost no evidence in humans that the protective effect of current social support might involve neurobiological effects of affective touch.

Two studies have investigated the possible role of lack of affective touch in the pathogenesis of depression. On the basis of a six-item questionnaire, Cochrane, (1990) found 58 % of depressed in-patients reported unsatisfactory physical contact either at present or during childhood or both. He suggested that affective touch may enhance stress-coping mechanisms and this would be consistent with some of the animal studies outlined above. Recently, in a self-report study, Takeuchi (2010) asked students to recollect parental touch
experiences in early and later childhood and current peer touch. They investigated whether these scores predicted current depression directly or indirectly via adult attachment style. They found that early and late parental touch weakly (r ≤ -0.11) correlated with depression. Although early parental touch correlated with a positive ‘other’ attachment style the latter did not predict depression. Attachment style did not appear to mediate effect of touch on depression. These studies suffer from the confound that lack of affective touch is likely to be associated with early adversity and neglect and with lack of current social support; these factors were not assessed in the two touch and depression studies. In the present study an attempt was made to assess the strength of the confound between social contact and touch and to partial it out in order to identify whether experiences of touch independently contribute to risk of depression.

Stressful life events are known to trigger depression. One of the earliest studies showing this causal link was carried out by Brown et al., (1973) who found 42 % of patients suffering from a depressive disorder had experienced at least one markedly severe event in the year before depressive onset, compared to 12 % of the community sample in the year before participating in the study. Brown et al., (1990) proposed a model in which the triggering effects of life events are magnified in those with few confiding relationships and this could in part be explained by lack of comfort touch when adverse life events occur. However, the evidence that social support buffers against adversity has been controversial (Alloway and Bebbington, 1987) and lack of social support may be an independent risk factor for depression. Much evidence suggests that the personality trait of neuroticism, the degree to which emotions are aroused, serves to amplify the triggering effect of life events (Kendler et al., 2004). Genetic variation in the 5-HT transporter and cannabinoid receptor also appear to influence sensitivity to life events and they may act through an influence on neuroticism (Caspi et al., 2003, Juhasz et al., 2009).

The role of affective touch in depression was investigated using the Touch Experiences and Attitudes self-report Questionnaire (TEAQ), the construction and validation of which has been described in a separate paper (Trotter et al., in preparation). The TEAQ has three factors that rate amount of touch – current social touch (CST), touch in intimate relationships (CIT) and past experience of childhood touch (ChT). Three factors assess positive attitudes to
touch - in intimate relationships (AIT), with unfamiliar people (AUT), and attitude to skincare (ASkC) such as bathing and using skincare products. The degree to which these factors correlate with social and personality risk factors for depression and whether they independently predict current depression was assessed. It was expected that current experience of touch might buffer against social adversity. Self-ratings of amount and attitudes to touch could be coloured by state-dependent influences of being depressed. A remitted depressed group who were not currently depressed but who had experienced depression in the past and who therefore have trait vulnerability to depression was identified. It was determined whether touch experiences and attitudes were abnormal in this trait vulnerable group.

2. Methods

2.1. Participants

Ethical approval was obtained through the University of Manchester ethics committee. The study was advertised through the University of Manchester and an online social networking site inviting participation in an online study of depression. Further details regarding participant recruitment for this study are detailed in (Trotter et al., in preparation).

2.2. Online questionnaires

Demographics: gender, age, relationship status, number of children, living arrangements and employment status. Mood and psychiatric history: items covered past professional help for emotional or psychiatric problems, help for depression in the last year, persistent depressed or low mood for the past two weeks, past episode of a month of low mood interfering with work and interests, excluding bereavement, current treatment for depression and a rating of their current health. Brief Symptom Inventory (BSI) (Derogatis, 1993): 26 items covering selected depression, anxiety and obsessional factors. Touch Experiences and Attitudes Questionnaire (TEAQ) (Trotter et al., in preparation): three subscores for amount of current social, intimate and childhood touch, together with ratings of attitude to touch with unfamiliar people and to intimate touch. Social Support Questionnaire (SSQ6) (Sarason et al., 1987): Items assess the number of supportive social contacts and satisfaction with them. Childhood adversity (CHA): 4 items derived from the 28
item Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994) relating to emotional and physical neglect and emotional and physical abuse. It has been found previously that the CHA is a reliable predictor of CTQ score (Juhasz et al., 2011). Big 5 inventory (BFI) (John and Srivastava, 1999): 44 items measuring 5 personality dimensions. List of Life Threatening Experiences (LTE) (Brugha et al., 1985): participants rated whether each life-event had occurred in the last 2 months, 12 months or more than a year ago. They were then asked whether or not they wanted to be entered into the prize draw or be contacted about further studies. Participants were then thanked for their participation.

2.3. Participants

Participants were removed from the analysis if 5% of responses on any of the questionnaires were missing, or 20% on one questionnaire subscale were missing, as suggested by Tebachnik and Fidell, (2007). A total of 667 participants were excluded using these criteria, leaving a dataset containing 1308 participant responses. The mean age ± s.d. of the sample was 27.2 ± 9.5 years. 72.4% of participants were female and 27.6% were male.

2.4. Allocation to healthy control, remitted depressed and depressed subgroups

The normative data provided by Derogatis et al., (1993) shows the mean score ± 1 standard deviation was 0.92 for females and 0.54 for males in an adult non-patient sample, so Never Depressed Controls (NDC) had BSI scores less than 1 s.d. above the mean for the depression factor using published norms (Derogatis, 1993) with no current or past history of depression from the mood and psychiatric history questions. Participants were allocated to the remitted depressed (RD) group if they endorsed depression in the past, but not the current symptoms or treatment items, with range BSI scores in the normal range. Depressed participants indicated they had been feeling persistently depressed or in low mood for the past two weeks and had BSI depression scores of greater than or equal to 1.9 for females or 1.65 for males based on normative data for depression scores for psychiatric outpatients (Derogatis, 1993).

Participants who did not meet the criteria for any of the categories were removed from the analysis leaving a total of 866 participants. The participants removed were those who
showed inconsistency in their responses. For example, stating that they were suffering from depression when asked at the beginning of the questionnaire, but the BSI depression score did not meet depression criteria. Individuals who stated they had received professional help for an emotional or psychiatric problem that was not depression were also removed from the analysis. 76.2% (n = 660) of the included participants were female and 23.8% (n = 206) were male. The never depressed group accounted for 52.5% (n = 455) of the sample, 34.6% (n = 300) had been depressed in the past, but were symptom free when they completed the questionnaire (remitted depressed) and 12.8% (n = 111) were currently depressed. The rate of depression is high compared to the average depression rate in a typical population of 5-10% (Hamet and Tremblay, 2005). This could be due to participants being self-selecting as the advertisement for the study explained depression was being investigated, or it could be that depressive symptoms rather than depressive syndromes were investigated in this study.

2.5. Analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 15.0.

2.5.1. Correlations and partial correlations

Pearson’s correlation coefficients were determined for each of the touch factors against social support, personality, psychiatric symptoms and life events using the data of 1308 participants. Due to the large sample size, coefficients above .06 are significant at p < .05 2-tailed and above .10 at p < .001. However, only correlations greater than .3 (p < .001) are considered as results of interest, as they correspond to a medium effect size (Cohen, 1992) and account for more than 9% of the variance.

2.5.2. Regression analysis on BSI depression score

A multiple regression analysis with stepwise forward entry method was carried out to determine how affective touch experience relates to current depression when variables known to influence depression are taken into account. In this analysis the three touch factors relating to experience of affective touch were included, along with the two personality traits most strongly associated with depression; neuroticism and extraversion and measures of
social support, childhood adversity and recent life events, due to the previously established association of these variables with depression. All 1308 participants were included in this analysis.

The model obtained was examined for goodness of fit according to the criterion of 1% of residuals greater than 2.5, and 0.1% of residuals greater than 3 (Field, 2005). 2.8% of the residuals were greater than 2.5 and 1% of residuals were greater than 3. Therefore participants were removed as outliers if their standardized residual was greater than 3, their covariance ratio was greater than (1+(3(average leverage))) or less than 1−(3(average leverage)), their leverage value was greater than 3 times the average leverage or their Mahalanobis statistic was greater than 25. Exactly 100 participants met the outlier criteria. Re-running the analysis on the remaining 1208 participants produced a model meeting the goodness of fit criteria.

2.5.3. Regression analysis on remitted depressives vs never depressed groups

To determine whether ratings for factors that might be considered antecedent to depression, a logistic regression was carried out on the remitted depressed vs controls. The factors were: two personality factors from the BFI; neuroticism and extraversion, three touch questionnaire factors; childhood touch, attitude to intimate touch and attitude to unfamiliar touch and childhood adversity. The first time this analysis was run, 755 participants were included in the analysis. Participants were removed from the analysis if their standardised residuals were greater than 3 or their leverage value was greater than three times the average leverage, causing a total of 24 participants to be removed from the analysis. The analysis was then re-run on the remaining 731 participants.

2.5.4 Clinical group differences in social, personality and clinical ratings

Depression group differences were determined for the personality measures; extraversion and neuroticism, the social support measures; number of social supports, satisfaction with social supports and childhood adversity and the clinical measures; anxiety
and depression, using one-way ANOVAs with Games-Howell post-hoc tests. This analysis was carried out to determine which of the factors associated with BSI depression showed evidence of trait vulnerability and which of mood state-dependency.

3. Results

3.1 Social, personality and clinical correlates of touch questionnaire (table 1a)

As shown in table 1a, number of social contacts (SSQN) and satisfaction with them (SSQS) correlated with amount of current social touch (CST) and touch in intimate relationships (CIT) as well as with touch experience in childhood (ChT) \(r = .34-.50\). The three touch attitude factors correlated less strongly \(r < .3\) with the social support measures. Self-rated childhood adversity (CHA) strongly correlated with ChT \(r = -0.58\), but weakly with all other touch factors.

Extraversion strongly correlated with CST \(r = .43\) and correlated moderately with CIT and attitude to unfamiliar touch (AUT) \(r = .35\) and .32). Pleasure in touch with intimates (AIT) and skincare (ASKC) was weakly influenced by extraversion.

Neuroticism and anxiety showed less marked associations with all TEAQ factors than extraversion with \(r < ±.3\). Depression negatively correlated with CIT \(r = -.38\), but not at \(≥ .3\) with the other touch factors.

3.2 Intercorrelations between social, personality and clinical variables (table 1b)

Table 1b shows intercorrelations between the social, personality and clinical variables. As expected, neuroticism and depression (BSI score) correlated with each other and with most of the other risk factors for depression. Life events showed no important correlations with the other variables (all <.15).
### 3.3. Partial correlations

The correlation of current intimate touch with depression was -.38 (table 1), but after controlling for satisfaction with social support (SSQS), this correlation is reduced to -.17 (p < 0.001). A partial correlation of SSQS with depression controlling for current intimate touch (CIT) gives a correlation of -.38 (p < 0.001), compared to a correlation of -.49 when CIT is not controlled for. A partial correlation of ChT with depression controlling for CHA gives a correlation of -.12 (p < 0.001) compared to a correlation of -.28 (p < 0.001) when not controlling for CHA. A partial correlation of CHA with depression controlling for ChT gives a correlation of .21 (p < 0.001), compared to a correlation of .33 (p < 0.001) when ChT is not controlled for.

<table>
<thead>
<tr>
<th></th>
<th>SSQN</th>
<th>SSQS</th>
<th>CHA</th>
<th>E</th>
<th>N</th>
<th>LE</th>
<th>Anx</th>
<th>Dep</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>0.34</td>
<td>0.34</td>
<td>-0.22</td>
<td>0.43</td>
<td>-0.20</td>
<td>-0.02</td>
<td>-0.14</td>
<td>-0.21</td>
</tr>
<tr>
<td>CIT</td>
<td>0.37</td>
<td>0.50</td>
<td>-0.22</td>
<td>0.35</td>
<td>-0.24</td>
<td>-0.08</td>
<td>-0.22</td>
<td>-0.38</td>
</tr>
<tr>
<td>ChT</td>
<td>0.34</td>
<td>0.37</td>
<td>-0.58</td>
<td>0.29</td>
<td>-0.23</td>
<td>-0.06</td>
<td>-0.20</td>
<td>-0.28</td>
</tr>
<tr>
<td>AIT</td>
<td>0.23</td>
<td>0.24</td>
<td>-0.16</td>
<td>0.26</td>
<td>-0.14</td>
<td>0.00</td>
<td>-0.16</td>
<td>-0.17</td>
</tr>
<tr>
<td>AUT</td>
<td>0.29</td>
<td>0.21</td>
<td>-0.16</td>
<td>0.32</td>
<td>-0.23</td>
<td>-0.08</td>
<td>-0.16</td>
<td>-0.17</td>
</tr>
<tr>
<td>ASkC</td>
<td>0.13</td>
<td>0.17</td>
<td>-0.07</td>
<td>0.19</td>
<td>0.04</td>
<td>-0.01</td>
<td>-0.02</td>
<td>-0.06</td>
</tr>
<tr>
<td>Total Touch</td>
<td>0.42</td>
<td>0.47</td>
<td>-0.34</td>
<td>0.44</td>
<td>-0.25</td>
<td>-0.06</td>
<td>-0.23</td>
<td>-0.33</td>
</tr>
</tbody>
</table>

### Table 1: Pearson’s bivariate correlations between questionnaire factors of interest. Correlations ≥ ±.3 are highlighted in bold and are significant at p < 0.001.

Abbreviations: TEAQ – touch experiences and attitudes questionnaire, CST – current social touch, CIT – current intimate touch, ChT – childhood touch, AIT attitude to intimate touch, AUT – attitude to unfamiliar touch, ASkC – attitude to skin care, Total Touch – overall touch questionnaire score, SSQN – number of social supports, SSQS – satisfaction with social supports, CHA – childhood adversity, E – extraversion, N – neuroticism, LE – number of life events occurring in the last 2 months, Anx – anxiety, Dep – depression.
3.4. Stepwise multiple regression for BSI depression score

The results of the final multiple regression after excluding outliers (see methods) are shown in table 3. It can be seen that model 5 explains the largest amount of the variance ($R^2 = .469$). In this model neuroticism predicts depression score most strongly, then SSQS, then LE, then CIT and finally CHA. The factors that did not significantly improve the model were CST, ChT, extraversion and SSQN. The results are closely similar to the first run except that CST significantly improved model fit.

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>-0.84</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.49</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(Constant)</td>
<td>0.95</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.36</td>
<td>0.02</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>SSQS</td>
<td>-0.28</td>
<td>0.02</td>
<td>-0.38</td>
</tr>
<tr>
<td>3</td>
<td>(Constant)</td>
<td>0.87</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.35</td>
<td>0.02</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>SSQS</td>
<td>-0.27</td>
<td>0.02</td>
<td>-0.37</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>0.17</td>
<td>0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>(Constant)</td>
<td>0.99</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.35</td>
<td>0.02</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>SSQS</td>
<td>-0.22</td>
<td>0.02</td>
<td>-0.31</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>0.16</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>CIT</td>
<td>-0.10</td>
<td>0.02</td>
<td>-0.12</td>
</tr>
<tr>
<td>5</td>
<td>(Constant)</td>
<td>0.93</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.33</td>
<td>0.02</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>SSQS</td>
<td>-0.21</td>
<td>0.02</td>
<td>-0.30</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>0.16</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>CIT</td>
<td>-0.09</td>
<td>0.02</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td>CHA</td>
<td>0.02</td>
<td>0.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* *p=0.014, **p<0.001

Table 2: results of a stepwise multiple regression analysis to determine whether touch factors relating to experience of affective touch are significant predictors of depression score and how strongly these factors predict depression score in relation to factors known to be associated with depression. Neuroticism, satisfaction with social supports (SSQS), number of life events experienced in the last 2 months (LE), current intimate touch (CIT) and childhood adversity (CHA) were found to significantly predict depression score. Factors excluded from the model were current social touch, touch experienced during childhood, extraversion and number of social supports. All β are significant at p < 0.001 except CHA where p = 0.014.
3.5. Clinical group differences in TEAQ scores (figure 1)

A one-way ANOVA followed by a Games-Howell post-hoc test was carried out on the touch questionnaire data to determine whether there were any group differences between never depressed, remitted depressed and currently depressed individuals. The mean score ± standard error for each touch factor and each depression group is shown in figure 1. The depressed group had significantly lower scores on all factor scores than the never depressed group. The remitted depressed group generally had scores intermediate between the never depressed controls and the depressed group. However, the remitted depressed group were not significantly less positive than the never depressed controls on current social touch experience and attitude to intimate touch and skin care. The remitted depressed group, despite their absence of depressive symptoms, did not differ from the depressed group in having less positive attitudes than controls to unfamiliar touch. They also had significantly less positive attitudes than controls on childhood touch and less current intimate touch experience.
3.6. Clinical group differences in social, personality and clinical ratings (table 3)

All pairwise group comparisons between never, remitted and currently depressed groups on the risk variable for depression were statistically significant because of the large sample size. However in terms of magnitude of effect, abnormalities that were most similar in the remitted and currently depressed groups (trait-like) were childhood adversity and neuroticism. The abnormalities substantially greater in the currently than remitted depressed groups (state-dependent) were satisfaction with social support (SSQS) and extraversion. By definition, the remitted group had non-clinically significant depression scores.
3.7. Logistic regression of antecedent factors on remitted depressed and control participants

The results produced are presented in table 4. It can be seen by looking at step 3, which shows the best fit of the data, that neuroticism predicted history of depression \( (\exp b = 2.968, p < 0.001) \), then CHA \( (\exp b = 1.203, p < 0.001) \), then finally ChT \( (\exp b = 0.793, p = 0.040) \). AIT, AUT and extraversion did not improve model fit.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>E</th>
<th>SSQN</th>
<th>SSQS</th>
<th>CHA</th>
<th>Anx</th>
<th>Dep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never depressed</td>
<td>2.62</td>
<td>3.49</td>
<td>7.50</td>
<td>5.45</td>
<td>1.77</td>
<td>0.27</td>
<td>0.22</td>
</tr>
<tr>
<td>n= 455</td>
<td>(0.03)</td>
<td>(0.04)</td>
<td>(0.09)</td>
<td>(0.03)</td>
<td>(0.09)</td>
<td>(0.02)</td>
<td>(0.01)</td>
</tr>
<tr>
<td>Remitted depressed</td>
<td>3.20</td>
<td>3.29</td>
<td>6.58</td>
<td>5.22</td>
<td>3.08</td>
<td>0.46</td>
<td>0.33</td>
</tr>
<tr>
<td>n= 300</td>
<td>(0.04)</td>
<td>(0.05)</td>
<td>(0.08)</td>
<td>(0.05)</td>
<td>(0.16)</td>
<td>(0.03)</td>
<td>(0.02)</td>
</tr>
<tr>
<td>Currently Depressed</td>
<td>4.07</td>
<td>2.74</td>
<td>5.50</td>
<td>3.88</td>
<td>4.79</td>
<td>1.74</td>
<td>2.62</td>
</tr>
<tr>
<td>n= 111</td>
<td>(0.05)</td>
<td>(0.08)</td>
<td>(0.19)</td>
<td>(0.14)</td>
<td>(0.32)</td>
<td>(0.08)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

Table 3: means and (standard errors) for never depressed, remitted depressed and depressed groups for neuroticism (N), extraversion (E), number of social supports (SSQN), satisfaction with social supports (SSQS), childhood adversity (CHA), anxiety (Anx) and depression (Dep). Main effects of group differences are all significant at \( p \leq 0.003 \), as determined by one-way ANOVAs followed by Games-Howell post-hoc tests.
4. Discussion

The TEAQ factors showed a number of differential correlations with social factors, personality and current and trait vulnerability to depression which suggest different functions and roles for touch experience and attitudes in the pathogenesis of depression. In general, the three attitude factors showed lower correlations with the other variables than did the three factors that assess the amount of positive current or childhood touch experience. The experiential factors are discussed first.

Current social touch consists of items about the amount of physical contact with friends and family and it correlated at >.3 with SSQ6 ratings of number of social supports and satisfaction with them and most strongly of all factors with extraversion (r = .43). However, this factor did not correlate strongly with depression at r = -.21 and did not appear as an independent predictor of current depression self-rating in the regression analysis.

In contrast to social touch, degree of physical contact in intimate relationships was less correlated with extraversion (r = .35), but more related to current depression (r = -.38) and
added a statistically significant amount of explained variance in the regression analysis of BSI symptoms. The regression analysis may under-estimate the contribution of intimate physical contact in mitigating depression. The variables identified by the regression analysis prior to intimate touch, namely neuroticism and satisfaction with social supports, are to some degree state-dependent and so remove much of the unexplained variance because they are indirect measures of the dependent variable itself in the regression ie. BSI depression score.

It is well known that neuroticism is partly state-dependent and increases in periods of low mood and decreases with recovery. This can be seen in the greater neuroticism scores of the depressed compared to remitted depressed sample (table 3). Satisfaction with social supports also seems likely to reflect low mood and was reduced in the depressed group but not in the euthymic remitted depressed group (table 3). In this context it may be significant that the number of social supports (SSQN) did not appear in the regression suggesting it is the satisfaction with, not the number of social supports that accounts for the appearance of SSQS in the model. This raises a second factor which may underestimate the contribution of degree of intimate body contact; the fact that satisfaction with social contacts probably reflects to some degree current intimate touch as suggested by their strong inter-correlation at r = .50 (table 1). Thus, inclusion of SSQS in the model is likely to have removed some of the variation due to CIT. Nevertheless CIT still accounted for additional variance. The results at least suggest that intimate physical contact may be an important source of resilience to depression and the lack of it, a currently unidentified component of the association between poor social support and risk of depression.

In order to study the role of touch in vulnerability to depression removing the possible state-dependent influence of depressed mood on social perception, a group of remitted depressed participants was identified who were not currently depressed but who had demonstrated vulnerability in their history of depression. Intimate touch experience was significantly reduced in the euthymic remitted group compared with controls together with reduced childhood touch suggesting these aspects of touch may reflect in part processes of trait vulnerability. However, these touch factors were markedly reduced in the depressed group suggesting they also reflect a cause or consequence of the depressed state. In the logistic regression on controls vs remitted depressed, childhood touch appeared as a
vulnerability factor even after variance attributable to childhood adversity had been removed. This seems quite a striking finding in view of the high correlation between CHA and ChT ($r = 0.58$). The partial correlations suggest CHA and ChT account for overlapping and specific variance in vulnerability to depression. The correlation between CHA and depression ($r = .33$) remained significant at $r=.21$ after allowing for the correlation of childhood touch with depression. A-priori it would be an extreme position to suggest that all the risk associated with childhood abuse and neglect is mediated by neurobiological effects of lack of affective touch. Nevertheless, the results suggest that as suggested by Brown et al., (2007), lack of affectionate touch is an important component of the influence of neglect on future risk of chronic depression.

The attitude TEAQ factors relate to enjoyment of touch in intimate relationships, with unfamiliar people and in skin care, in distinction from how often it occurs. Pleasure in skin care showed lowest correlations ($r < .2$) with all variables and appears not to be strongly determined by any of the personality, childhood, social or clinical factors studied here. The skin care factor did show evidence of state dependency in that the currently depressed group had lower scores than either the never depressed or the remitted depressed and the remitted depressed had identical scores with the never depressed. Depression involves anhedonia and apathy and it is not surprising that interest and pleasure in skin care such as bathing and use of products diminishes with low mood. The same applies to attitude to intimate touch which rates the pleasure of hugging, kissing and stroking in intimate relationships; AIT showed no trait abnormality (identical in controls and remitted depressed groups) and a reduction in the currently depressed group. Attitude to unfamiliar touch mostly comprises items about negative feelings towards bodily contact with people who are not close or well known although the items are scored in a positive direction. This factor showed an appreciable correlation with extraversion which is a measure of sociability and sociable people might be expected to be more at ease with casual touch involving people who are not well known to them. The remitted depressed group were more negative about such contact than never depressed controls although not as markedly so as the depressed group. This might suggest that vulnerability to depression involves a lack of self-confidence in social interactions with less familiar people.
Current intimate touch, but not childhood touch or current social contact was found to be a significant predictor of depression score. This suggests that current affective touch is more important in preventing depression than a lack of touch experienced during childhood. These findings also suggest that the touch experienced during situations such as greeting a family member or friend with a hug or a kiss does not have a physiological effect on the brain in the same way intimate touch does and so does not protect against depression.

Many emotions can be expressed through touch. Hertenstein et al., (2009) found anger, fear, disgust, love, gratitude, sympathy, happiness and sadness could all be communicated between individuals who were unacquainted, with the receiver of touch being blindfolded and no other forms of communication being allowed. The items relating to intimate touch relate to hugging, kissing and stroking. Hugging and stroking were used by the participants in Hertenstein’s study to communicate love. A study by Hill et al., (2001) found a predictive factor for depression at age 26-39 years to be poor love relationships at age 21-25 years.

In summary, amount of current touch with intimates was found to be a significant predictor of depression score, as determined by a stepwise multiple regression analysis, but childhood touch score was not. Childhood touch was found to be a significant predictor of depressive vulnerability though, so it does appear to have a role in depression, but current intimate touch is a more significant predictor of current depression.

Cochrane, (1990) suggested that affective touch could be a stress coping strategy and that if this is the case then current touch would be more important than childhood touch. The results from this study support this hypothesis as current intimate touch, but not childhood touch was found to predict current depression score. Number of life events occurring in the last two months was also found to predict current depression score, as was satisfaction with social support. From these results it could be hypothesised that following a stressful life event, a lack of social support, in particular a lack of affective touch, could increase the likelihood of a depressive episode. This is further supported by the fact that current intimate touch, but not current social contact was found to predict depression score and two items in the current intimate touch factor relate to consoling following a stressful life event: ‘I can always find somebody to physically comfort me when I am upset’ and ‘when I am upset,
there is usually someone who can comfort me,’ but no items in the current social contact factor of the TEAQ relate to consoling. This hypothesis requires further investigation, but studies into massage therapy have found massage to decrease stress responses, measured as reduced cortisol levels, reduced heart rate and a reduction in perceived stress (Lindgren et al., in press, Listing et al., 2010, Moraska and Chandler, 2009), providing evidence to support this hypothesis.

A major limitation of this study was that participants were not categorized as depressed or remitted depressed based on DSM IV criteria. The categorization method was dependent on data from self-report measures, which is likely to have led to inaccuracies in the data. The use of a diagnostic tool such as the structured clinical interview to diagnose DSM IV disorders (SCID) (First et al., 2002) would have improved the accuracy of the data obtained, but would have made the investigation much more expensive and time consuming and a smaller sample size would have been obtained. A future investigation involving accurate diagnosis of depression would be of benefit to this research area.

A large sample size was used in this study, increasing the power of the results obtained. Age range was reasonable, although quite young with a mean age of 27 years. An attempt was made to include older participants and participants who were not all students, but despite this, 58% of participants were students, so the results obtained may not be representative of a more general population. Unfortunately, nationality was not determined for this study, so it is difficult to know the cultural background of the respondents.

To investigate the role of touch in depression further, the TEAQ could be administered to a wider community based sample rather than one mainly limited to a specific University. An investigation using psychiatric inpatients would highlight the role of affective touch in psychiatric disorders in general, not just in the onset of depression. Further investigation into the physiological mechanism by which touch reduces the risk of depression would also be of great interest.

In conclusion affective touch appears to have a role in protecting against depression with current intimate touch being the most protective touch factor followed by childhood touch.
Current social touch was found not to have a protective effect against depression and neither did attitude to touch or use of grooming products. Further investigation to determine if these findings can be replicated in other populations are required to obtain a clearer understanding of the role of affective touch in the prevention of a depressive episode.

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5. Paper 3

Affective perception of touch neurobiology of pleasant and unpleasant skin sensation and the effect of acute tryptophan depletion

(Affective touch perception and the effect of ATD)

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Abstract

Much evidence attests to the importance of affective or affiliative touch in normal development and the expression of emotional and stress responses. However, little is known about the CNS representation of pleasant touch. This study tested the hypotheses that i) a novel class of C-fibre tactile (CT) afferents found in hairy skin that respond to stroking stimuli, transmit affiliative touch information to the posterior insula, and ii) that affective components of CNS responses to pleasant touch stimuli are mediated by enhanced serotonin release.

Using functional magnetic resonance imaging (fMRI), CNS responses to stroking the hairy skin of the forearm with pleasant, neutral and unpleasant brushes with stroking the fingers, which lack CT afferents, were compared. 30 healthy female participants were studied, half pretreated with a tryptophan depleting oral amino-acid mixture (acute tryptophan depletion, ATD) and half pretreated with a control drink.

All touch stimuli activated contralateral primary somatosensory cortex (SSC) and bilateral secondary SSC. Main effects of valence (pleasant vs neutral vs unpleasant) with positive effects of pleasant stroking were seen in a small region of contralateral SSC following arm stroking and in right and left inferior frontal gyrus following finger stroking. Only the latter was attenuated in the ATD condition. The predicted differential activation of the posterior insula to pleasant stroking of the arm was not observed even with a region of interest analysis. The median raphe nucleus showed the greatest effect of valence (FWE p<.05) with deactivation to pleasant and activation by unpleasant brush stroking. This effect was seen only with arm stroking and was abolished by ATD. Subjective ratings of pleasantness of brush stroking were unaffected by ATD.

The results obtained did not corroborate with previous reports suggesting pleasant brush stroking of the arm specifically engages the posterior insula. ATD modulated the effects of pleasant brush stroking of arm (raphe and anterior cingulate cortex) and finger (IFG). The raphe region was activated by unpleasant brush stroking of the arm and the abolition of this effect by ATD suggests raphe 5-HT neurones are engaged by aversive rather than pleasant tactile stimuli.
1. Introduction

1.1 Affective touch in depression

According to the World Health Organisation (2010), depression is the leading cause of disability worldwide, as measured by years lived with disability. Women have an almost two-fold greater probability of being affected by depression than men (Hamet and Tremblay, 2005). Early parental neglect and current social isolation are major vulnerability factors for the onset of depression after stressful life events (Brown et al., 1986). Lack of affective touch may contribute to the effects of psychosocial risk factors. Brown et al., (2007) investigated this idea and found a lack of maternal affection, in terms of warmth, cuddling and kissing during childhood is a significant predictor of adult chronic depression in women. Although it is known that current social isolation and a lack of maternal affection during childhood are important factors for onset and chronicity of depression, the neurobiological mechanisms are not known. One possibility is that pleasant touch or body contact is a basic modality, common to social mammals including man, which signals the presence of social support and attachment. However, little is known about the central representation of pleasant touch or the neurotransmitters involved.

1.2 Peripheral and central encoding of pleasant touch

Classically, peripheral touch has been viewed as a modality mediated by large Aβ myelinated afferents with small receptive fields projecting to thalamus and somatosensory cortex providing fast information about location of skin contact. C-fibre afferents are typically associated with interoception and pain. However, touch sensitive C-fibre (CT) afferents have been reported in hairy skin. Using peripheral microneuronography, these afferents have been shown to fire maximally when hairy skin is stroked with a soft brush at low force and a velocity of 1 – 10 cm/s with cessation of responding at faster or slower rates of stroking. This pattern of responses is paralleled by psychophysical ratings of pleasantness. It has been proposed that CT or ‘soft brush’ afferents peripherally encode pleasant touch that signals
affiliative social body contact (Loken et al., 2009). However, no studies using brushes with varying degrees of stiffness or pleasantness or unpleasantness have been reported.

The CNS representation of CT afferents is difficult to study because hairy skin also contains several other touch sensitive receptors including Ruffini’s endings (vibration), pacinian corpuscles (skin deformation) and field and hair movement units (Fradette et al., 1995, Johnson et al., 2000, Vallbo et al., 1995). However, a functional magnetic resonance imaging (fMRI) study in two patients with a congenital lack of Aβ fibres and touch sensation, showed brush stimuli activated posterior insula and not somatosensory cortex. These findings are in keeping with the putative affective role of CT afferents since insula cortex is implicated in affective states evoked by pain and pleasure (Craig, 2009).

In this study, fMRI responses evoked by stroking the hairy skin of the forearm with responses from stroking the glabrous skin of the palmar aspect of the fingers were compared. It was predicted that the insula would be preferentially activated by pleasant brush strokes applied to hairy forearm skin. Further predictions were that affective touch responses would be seen in anterior cingulate since it is strongly co-activated with the insula (Craig, 2009), and in orbitofrontal cortex and amygdala which were activated by pleasant and painful stimuli in previous studies of touch to the palm (Francis et al., 1999, Rolls et al., 2003).

1.3. Role of neuropetides and 5-HT in affective touch and depression

Primates spend much time in mutual grooming (allo-grooming) and this is thought to be important in social bonding (Dunbar, 2010). There is much interest in the possible roles of oxytocin, vasopressin, endorphins and 5-HT in the effects of allo-grooming. Nelson and Panksepp (1998) proposed that social bonding involves endorphin mediated addictive-like processes. More recently, Insel and others have emphasized the key role of oxytocin and vasopressin in social animals (Dunbar, 2010, Insel, 2003). Raleigh et al., (1991) found that increasing central synaptic 5-HT content through the administration of either fluoxetine or tryptophan, promoted affiliative behaviours, including allo-grooming, in male vervet
monkeys. This suggests serotonin may have a role in affiliative body contact and social bonding. Much evidence suggests that depression involves deficient 5-HT functioning (Cowen, 2008). Many antidepressants act to enhance 5-HT functioning. One of the key findings is that experimental depletion of circulating tryptophan reinstates symptoms in patients recently recovered on antidepressant drugs (Delgado et al., 1990). On the basis of this and other evidence, Deakin (1996) speculated that early and current experience of affiliative touch is a factor that promotes the development and dynamism of median raphe 5-HT projections to the forebrain which function, he previously suggested, to sustain behavioural and cognitive resilience to stress and adversity. Thus deprivation of affiliative touch, through weakening median raphe 5-HT resilience, might contribute to the association of social isolation with risk of depression.

There is very little direct evidence that touch releases any of the neurotransmitters implicated in affiliative behaviour. Meaney showed important developmental affects of maternal grooming on development of stress reactivity that are mediated through the activation of 5-HT_7 receptors in the hippocampus (Meaney and Szyf, 2005). Some patients with migraine experience cutaneous allodynia (pain in response to touch) when treated with triptans, which are presynaptic 5HT_{1B/1D} agonists that decrease 5-HT release. Linde et al., (2004) reported that systemic administration of sumatriptan to healthy participants and migraine sufferers increased unpleasantness ratings of soft brush strokes to the dorsum of the hand and increased pain ratings in the migraine sufferers. This suggests that 5-HT may modulate the quality of touch perception. In an unpublished pilot study in this department, Blackburn found that acute tryptophan depletion (ATD) reduced pleasantness ratings of controlled tactile stimuli. In the present study the hypothesis that ATD would reduce pleasantness ratings and fMRI responses to pleasant brush stimuli was tested.
1.4. Hypotheses and predictions

The hypotheses investigated during this study were that the central and subjective effects of pleasant touch: 1) involve activation of CT afferents, 2) cause activation of the posterior insula and 3) involve increased serotonin release.

It was predicted that:

1) The pleasant brush applied to the hairy skin of the forearm would activate the posterior insula more than when applied to the glabrous skin of the fingers due to the absence of CT afferents in glabrous skin.
2) Pleasant touch would activate the midbrain raphe and acute tryptophan depletion would attenuate brain activations associated with pleasant brush stroking.

2. Methods

2.1. Participants

Full ethical approval was obtained from the North Manchester Research Ethics Committee. 30 healthy female volunteers (mean ± s.d. age = 23.7 ± 5.18 years) participated in this study. All participants had no psychiatric history and were physically healthy. Seventy percent of participants were using a hormonal contraceptive and were scanned at any time, except for participants taking the combined pill who were scanned on pill-taking days only. All remaining participants were scanned during their follicular phase when they were not menstruating apart from two who were scanned on day 14 of their cycle and may have been in their ovulatory phase.
2.2 Procedure

Participants attended a screening session and an imaging session. In the screening session they carried out the touch task with visual analogue ratings. In the imaging session mood ratings were completed at regular intervals. They were administered the control or tryptophan depleting drink and completed questionnaires and cognitive tasks (not reported). They rested until scanning took place 4 hours later. During scanning the touch task was carried out. After scanning the touch task was repeated, but with visual analogue ratings of the pleasant/unpleasantness of the brush stimuli. After de-briefing, a light snack and final mood ratings, participants went home.

2.3 Screening session

2.3.1 Screening

Informed consent was obtained during the screening session. Participants were screened two days before scanning where possible. The structured clinical interview to diagnose DSM-IV-TR Axis I disorders (SCID) (First et al., 2002) and the Brief Symptom Inventory (BSI) (Derogatis, 1993) was completed during screening to exclude participants with a psychiatric history. Participants with excessive alcohol consumption or who had taken street drugs recently were excluded from the study, as were potentially pregnant participants. Participants were provided with an example low-protein diet during screening which they were asked to follow the day before the scan.

2.3.2. The touch task and subjective ratings

Participants rated the valence of the brushes used in the scanning. Participants were stroked on either their left mid ventral forearm over a distance of 18 cm in the proximal to distal direction, and the ventral side of the left fingers proximal to distal over 5 cm, ending at the end of the fingertips. The interval between strokes was 1 second. Stimuli were applied in
20 second blocks preceded by a 20 second rest block. The experimenter maintained the speed of stroking at 5 cm/s by synchronising the stroke with a moving dot on a monitor. The force of application was guided by the degree of bend in the brush which was previously calibrated to produce 220 mN. The following brushes with same dimensions were used: pleasant- Daler-Rowney, 44 mm, Goat Hair, S155, Flat; neutral - Hog Bristle, Daler-Rowney Georgian Brush, G36, Short Flat, no.18; unpleasant - plastic bristles with split ends mounted in the same flat handle as the other brushes. The brushes were selected on the basis of systematic pilot studies with a variety of brushes and materials. Other materials were also used in this investigation, but these results are not reported here.

During the task, the left forearm of the participant was placed on a small VacFix® cushion for comfortable fixation of the arm. Each brush was applied once to the forearm and once to the fingers, in a randomised order. Participants could not see the touch stimuli. They completed 3 10 cm visual analogue scales (VAS) rating pleasantness, smoothness and soothingness of the brushes. The pleasantness VAS was marked at -10 (extremely unpleasant), -5 (unpleasant), 0 (neutral), 5 (pleasant) and 10 (extremely pleasant). The task was carried out at screening and after scanning with VAS ratings. During scanning no ratings were carried out. One participant with aberrant ratings at screening was excluded from further participation.

2.4 Imaging session

2.4.1 Amino acid drink

Participants were randomly assigned to either the control or the tryptophan depletion group. The experimenter and participant were blind to treatment group. Control participants received the balanced drink with amino acids including tryptophan. Tryptophan depletion participants received the same amino acid drink minus the tryptophan. 80% quantities of the recipe of Benkelfat et al., (1994) were used because of the lighter weight of the female participant group. Immediately after administration of the amino acid drink, participants were asked to complete a touch questionnaire (Trotter et al., in preparation), personality
scales and 3 cognitive tasks whose results are not reported here. Blood glucose and blood pressure was monitored throughout the day. Blood samples for commercial assay of total plasma tryptophan were taken before and 4 hours after the amino-acid drink (Oxford Brookes University). Mood was monitored pre-drink and 4 hours post-drink using the profile of mood states (POMS) (McNair et al., 1971) and the Fawcett-Clark Pleasure Scale (FCPS) (Fawcett et al., 1983).

2.4.2. Scanning parameters

Scanning was carried out using a 3 Tesla (T), Philips achievea magnetic resonance imaging (MRI) scanner. T2* weighted images were obtained to investigate changes in blood oxygen level dependent (BOLD) signal throughout the scan. Single shot gradient echo-planar scanning was carried out. Whole brain scans of 34 slices, each 3 mm thick with a 0.5 mm slice gap were obtained. The repetition time (TR) used was 2000 ms, with an echo time (TE) of 35 ms. The field of view (FOV) was 230 mm with an acquisition matrix of 128 x 128. Voxel size was 1.8 x 1.8 x 3.0 mm. T1 weighted whole brain images were obtained to co-register the T2* images to the T1 weighted images.

2.4.3. Scanning tasks

A 5 minute eyes-closed resting state scan was followed by the 11 minute touch task without VAS ratings. Participants were unable to see the brush or material being used and were asked to simply lie in the scanner and concentrate on how the stimuli felt. After this task, a 6 minute task where participants were asked to rub different materials between their fingers and thumb was carried out, the results of which are not shown here. This task was followed by a repetition of the touch task. A 6 min structural brain scan was then carried out. This was followed by a third repetition of the touch task. Each participant thus experienced three 20 second blocks of stroking with each stimulus on both the arm and the fingers.
2.4.4. Post scanning

The touch task was repeated outside the scanner but with VAS ratings of each stimulus block. Participants were then given a tryptophan containing meal to reverse the effects of the amino acid drink. Participants were given discharge advice and allowed home when they met discharge criteria.

2.5. Data Analysis

Imaging data was analysed using MATLAB (The MathWorks, Inc.) and Statistical Parametric Mapping (SPM) version 5. Images were re-aligned and the artefact repair toolbox used to correct for movement. Images were co-registered to the T1 weighted image obtained for each participant. Co-registered images were then segmented, and normalized to Montreal Neurological Institute (MNI) space. Images were then smoothed (FWHM 5.4 x 5.4 x 10.5). First level analysis was carried out by subtracting brain activation during the rest block from that during the stimulation block. Brain activation during each condition was then averaged per participant. Second level analysis involved averaging stimulus activation across each treatment group.

A-priori region of interest analysis was carried out on all contrasts. The region used consisted of Brodmann areas 11, 12, 13 and 47, the anterior cingulate, insula, amygdala and postcentral gyrus, all defined using the WFU PickAtlas. A 10 x 7.5 mm box, at 0 -24 -20 was used to include the brainstem raphe nuclei. Parietal operculum (OP) regions 1-4, as defined by the anatomy toolbox were also included in this region of interest analysis. The contrasts were thresholded at p < .005 with a minimum cluster size of 10 voxels. Statistical effects at p < .001 uncorrected are reported.

Analysis of variance was used to identify regions showing main effects of all three brush stimuli (2 levels; touch, rest) and main effect of valence (3 levels; pleasant, neutral, unpleasant). These analyses were carried out separately for arm and finger stroking. It was determined whether the brain regions showing main effects of valence were modified by the
site of stimulation from the interaction within those regions between valence and location (2 levels; arm, finger). Similarly, it was determined whether main effects of valence were modified by tryptophan depletion from the interaction term between valence and tryptophan treatment group (2 levels; control and tryptophan depletion).

Visual analogue data were analysed using analysis of variance with factors for valence, location and tryptophan depletion. POMS and FCPS data was also analysed using analysis of variance to look at the effect of treatment and whether there were any differences between scores before and after the amino acid drink. Change in plasma tryptophan levels during the control and depletion conditions were compared using analysis of variance with factors for before and after amino acid drink and treatment group.

3. Results

In the tryptophan depleted group, plasma tryptophan levels were reduced by a mean ± s.e. of 74 ± 1.3 %. In the control group, plasma tryptophan levels were increased by a mean ± s.e. of 284 ± 17.6 %. An analysis of variance found a significant effect of plasma tryptophan levels before and after the amino acid drink (p < 0.001) and a significant interaction with treatment group (p < 0.001).

Analysis of the POMS and FCPS data revealed no significant interaction between mood scores before and 4 hours after administration of the amino acid drinks and no significant interaction with treatment group.

3.1. Visual analogue scale (VAS) ratings

VAS ratings of pleasantness and soothingness for each condition were found to correlate strongly (Pearson’s r ≥ .74, p < 0.001). Correlations between pleasantness and soothingness with smoothness were lower, but still significant (r ≥ .39, p ≤ .032). Due to the significant correlations between pleasantness, smoothness and soothingness and to aid simplicity, only
the results from pleasantness VAS will be reported here, as this is the measure of particular interest.

Following analysis of pleasantness ratings, a significant main effect of valence was found \( F(2,27) = 91.10, p < 0.001 \) with significant pairwise comparisons between neutral vs pleasant and unpleasant brushes whether applied to arm or finger. There was no significant effect of location but the location by valence interaction was significant such that neutral and unpleasant brushes were rated as less pleasant in the arm than in the finger with less difference in pleasantness ratings between arm and finger for the pleasant brush. The contrast for arm vs finger with the pleasant vs neutral brush was significant \( (p < 0.001) \), but was not significant for the neutral vs unpleasant brush. ATD condition showed no main effects or interactions with valence or location.

No habituation to touch over time was noted. This is likely due to the 20 second rest block which preceded each stimulation block. Stimulus order was also randomised so that if there was any habituation to touch over time, this effect was removed due to stimulus order being different for every participant and every trial.

3.2. Main effect of touch

Figure 1 shows the main effect of touch when applied to the forearm and fingers. Whole brain analysis found all these regions to be significant at \( p < 0.001 \) uncorrected. Contralateral primary somatosensory cortex was strongly activated when stimuli were applied to the fingers but weakly activated when stimuli were applied to the arm. A region of the secondary somatosensory cortex, region 4 of the parietal operculum (OP4) was strongly activated when stimuli were applied to the arm, but was not activated by stimulation of the fingers but the difference was not statistically significant. A region of the inferior parietal cortex (IPC) known as the inferior parietal area (PFop), was bilaterally activated by stimulation of both the arm and the fingers. Ipsilateral (left) Brodmann area 47 of the orbitofrontal cortex was significantly activated by stimulation of the arm but was just subthreshold \( (p < .002 \text{ unc}) \) for the fingers and the difference was not statistically significant.
Figure 1: glass brains showing the overall positive activations produced by stimulating the forearm (images on the left) or fingers (images on the right) with either a pleasant, unpleasant or neutral brush. Abbreviations: SSC – somatosensory cortex, OP4 – parietal operculum region 4, OFC – orbitofrontal cortex, IPC – inferior parietal cortex. Image thresholded at p≤0.001, uncorrected.
3.3. Main effect of valence

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Main effect of valence</th>
<th>Interaction Arm x Fingers</th>
<th>Interaction valence x ATD</th>
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<tbody>
<tr>
<td></td>
<td>x y z Z-score</td>
<td>x y z Z-score</td>
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<tr>
<td>Arm</td>
<td>MRN 5 -20 -18 4.82</td>
<td>5 -20 -18 3.64</td>
<td>5 -20 -18 3.28</td>
</tr>
<tr>
<td></td>
<td>SSC 22 -43 70 3.83</td>
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<td></td>
<td>Insula -36 18 4 3.36</td>
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<td></td>
<td>ACC 5 34 25 3.30</td>
<td>7 36 21 3.83</td>
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<tr>
<td>Fingers</td>
<td>IFG (L) -50 23 4 4.52</td>
<td>-49 25 4 5.30</td>
<td>-50 22 4 3.39</td>
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<tr>
<td></td>
<td>IFG (R) 52 27 -4 3.80</td>
<td>52 27 -4 4.24</td>
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<td></td>
<td>BA 4 -14 -34 63 4.00</td>
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<td></td>
<td>BA 4 -20 -29 56 3.35</td>
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<td>BA 38 34 7 -18 3.20</td>
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Table 1: MNI coordinates and Z-scores of areas of activation for the main effect of valence of stimuli applied to the arm (top left) and fingers (bottom left). The areas activated in the main effect of valence contrasts and also activated in a contrast looking at the interaction between location and valence are shown in the middle two columns. The areas activated in the main effect of valence contrasts and in the interaction between valence and treatment group (control or ATD) are shown in the final two columns. Abbreviations: MRN – median raphe nucleus, SSC – somatosensory cortex, ACC – anterior cingulate cortex, IFG – inferior frontal gyrus, BA – Brodmann area, OP – parietal operculum.

3.3.1. Main effect of valence following stimulus application to the forearm of control participants

Table 1 shows regions with a main effect of valence when stimuli were applied to the arm or the fingers. All regions were significant following whole brain analysis at $p < 0.001$ uncorrected with the median raphe nucleus surviving familywise error correction (FWE $p = 0.043$). When stimuli were applied to the arm, a significant differential activation occurred in the median raphe nucleus, the somatosensory cortex, the anterior insula and the anterior cingulate, dependant on the stimulus used. The raphe showed a graded response to valence with deactivation to the pleasant brush and activation by the unpleasant brush (Figure 2). In contrast somatosensory cortex (BA 3) was activated by the pleasant brush whereas the neutral and unpleasant brushes produced no effect. Anterior insula was not activated by the pleasant brush, was activated by the neutral brush and was deactivated compared to rest by
the unpleasant brush. Anterior cingulate cortex was deactivated by the pleasant brush with weak activation by the neutral and unpleasant brush (Figure 2).

3.3.2. Main effect of valence following stimulus application to the fingers of control participants

As shown in table 1, bilateral inferior frontal gyrus, Brodmann areas 4 and 38 showed differential activation by the pleasant, neutral and unpleasant brushes applied to the fingers. All were activated by the pleasant brush with lesser and variable effects of the neutral and unpleasant brushes. The effect of valence in inferior frontal gyrus can be seen in figure 3. All brain regions were found to be significant following whole brain analysis with p < 0.001 uncorrected.

3.4. Location by valence interaction

No valence effects were common to arm and finger. Furthermore, the significant effect of valence in the raphe and anterior cingulate to arm stimulation was significantly greater than the absent effect of valence to finger stimulation as demonstrated by the significant location by valence interactions. Similarly, valence effects to finger stimulation were significantly greater than to arm stimulation for bilateral inferior frontal gyrus. All of these regions were significant following whole brain analysis at p < 0.001 uncorrected, with the activation of the ipsilateral inferior frontal gyrus surviving family wise error correction (FWE p = 0.005) and activation of the contralateral inferior frontal gyrus surviving false discovery rate correction (FDR p = 0.021).
3.5. Valence by treatment interaction

The graded response of the raphe to valence of stimuli applied to the arm was absent in the tryptophan depletion group producing a significant valence by ATD interaction (Figure 2). The median raphe is located in the midline and extends from the caudal midbrain into the rostral pons. Caudally, there is no well-defined limit of the median raphe, but the rostral extent of the median raphe is determined by decussation of the superior cerebellar peduncles. The median raphe is found posterior to the cerebral aqueduct (Paxinos, 1990). It was concluded that the region of the brainstem shown to be activated in figure 2 is the median raphe nucleus as its location matches this description and also matches the location depicted in Törk’s diagram of the serotonergic system (Törk, 1990). A reversal of the valence effect on the anterior cingulate was seen after tryptophan depletion (Figure 2). For valence effects of finger stimulation, only the response in the left inferior frontal gyrus was reduced by tryptophan depletion (Figure 3). All of these brain activations were found to be significant following whole brain analysis at p < 0.001 uncorrected.
Figure 2: interaction of valence by ATD. A significant valence by ATD interaction was produced in the raphe nucleus and anterior cingulate when stimuli were applied to the forearm. Images on the left show the interaction of valence in the control condition. Images on the right show the interaction of treatment by valence. The histograms show the interaction of treatment by valence with the control activations shown on the left of the histogram and the ATD interactions shown on the right. Abbreviations: ATD – acute tryptophan depletion, P – pleasant brush, N – neutral brush, UP – unpleasant brush. Images thresholded at p≤0.001, uncorrected.
3.6. Response of the posterior insula to touch

Figure 4 shows the average activation of the posterior insula, determined by region of interest analysis. When the arm of control treated participants was stimulated, only the unpleasant brush significantly activated the posterior insula compared to the rest condition (p = 0.003, 2-tailed). The pleasant and neutral brushes did not cause significant activation of the posterior insula compared to the rest condition. When the stimuli were applied to the fingers, none caused a significant activation of the posterior insula compared to rest.
4. Discussion

4.1. Main effects of touch

Touch to the fingers and arm caused the expected activations in the contralateral dorsal somatosensory cortex and this was more extensive and significantly greater for finger stimuli. This probably reflects the greater density of mechanoreceptors in the finger than the arm and the greater cortical representation of the fingers. The inferior parietal operculum contains somatotopically organised secondary somatosensory cortex and this was activated bilaterally by stimuli applied to the arm or to the fingers. A region of the secondary somatosensory cortex, known as the inferior parietal area (PFop), was also activated more strongly by stroking of the fingers than of the forearm. These results are broadly in keeping with other studies involving a variety of stimuli (tactile, pain, thermal and vibration) mostly applied to the hand (Eickhoff et al., 2006). All touch stimuli caused significant focal activation
at the border of left inferior frontal cortex and lateral OFC (BA47) whether applied to the arm or finger. The functional significance of this activation is uncertain.

4.2. Pleasant touch and the CT-insula pathway

CT fibres are present in hairy, but not glabrous skin and respond maximally to stroking with a soft brush at low force and low velocity. Since the dependency of the discharge rate on velocity of soft brush stroking parallels velocity dependent ratings of pleasantness it was suggested CT afferents peripherally encode pleasant touch (Loken et al., 2009). The evidence from individuals lacking Aβ fibres that CT afferents project via thalamus to posterior insula, but not to somatosensory cortex, further suggested these afferents encode the affective rather than discriminative aspects of touch (Olausson et al., 2008). Olausson (2002) found that soft brush stimulation to the arm but not the finger evoked additional activation in posterior insula which was attributed to the CT fibre innervation of the arm but not the finger.

Following the above rationale, responses evoked by stroking the arm and finger to identify the CNS representation of peripheral CT fibre activation were compared. The additional controls of stroking with brushes rated as affectively neutral and unpleasant were employed. A main effect of valence in the insula to brush stroking of the arm was found but it was a) ipsilateral to the stimulus, b) in anterior insula and c) driven by the combination of activation to the neutral brush, deactivation to the unpleasant brush with no response to the pleasant brush. Furthermore, the effect of valence was not statistically significantly different from the pattern of response seen following finger stimulation. It was also checked whether insula responses were seen to the soft brush compared to rest in a whole brain analysis at an uncorrected threshold of p<.001 but none was observed (data not shown). It is worthy of note that in the investigation by Bjornsdotter et al., (2009), no insula activation was seen in a whole brain analysis but was revealed in a directed search of the posterior insula. A region of interest analysis averaged over the posterior insula was carried out, but the pleasant brush had no significant effect. Indeed, the unpleasant brush caused a significant activation in contralateral posterior insula but not ipsilateral.
The discrepancy in the present results with those from previous studies could be due to the greater force used in the previous investigations (0.8 N compared to 0.22 N) and also the greater number of repetitions of the stimulation carried out in the previous investigations. It is clear that pleasantness of soft brush stroking can be detected in the finger and the VAS ratings of its pleasantness did not differ between arm and finger. It may be that the experiences are based on different peripheral and central mechanisms which subserve different functions to do with affiliative vs perceptual processing. However, there is little evidence in the present study that the pleasantness of soft brush stroking of the arm is encoded in the insula.

4.3. Positive valence effects

Pleasant brush stroking to the arm evoked activation in one region, in part of the contralateral somatosensory cortex and no response was seen to neutral or unpleasant brush strokes. Whether this is mediated by CT afferents is uncertain. First the valence effect was not significantly different from the lack of valence effects with finger stimulation in this brain region. Second, soft brush stroking in patients lacking Aβ fibres not only evokes activation in posterior insula, but also inhibited primary somatosensory cortex in contrast to the activation seen here (Olausson et al., 2008). However, this is not a strong argument against a role for CT afferents in the somatosensory response to pleasant touch since the absence of Aβ fibres could have marked effects on mechanisms of central touch encoding by CT afferents at any stage from the dorsal horn to cortex.

When stimuli were applied to the fingers, all the regions in table 1 showed significant positive valence effects accompanied by opposite or absent changes to neutral and unpleasant brushes. Most notably left and right inferior frontal gyrus showed activations to pleasant brushes applied to the fingers relative to the other brushes and this pattern was significantly different from that seen in these regions after stimulation of the arms where there was no significant effect of valence. It was expected that responses to pleasant touch would be seen in medial orbitofrontal cortex from fMRI activations reported by Rolls et al.,
(2003) and other evidence implicating this region in reward mechanisms, but ventrolateral prefrontal cortex also has important although as yet ill-defined roles in processing of affective information (Elliott et al., 2011).

4.4. Role of 5-HT in affective touch

It was predicted that ATD would attenuate responses to pleasant tactile stimuli. However, there was no evidence that ATD had any effect on subjective ratings of any valence of touch. Some evidence of a differential CNS response to the pleasant brush applied to the fingers was observed notably in left ventrolateral prefrontal cortex in which activations to pleasant brush and deactivation to unpleasant were observed. This pattern was abolished by tryptophan depletion (Figure 3). It seems unlikely that the hypothesised pleasant touch-evoked activation of raphe 5-HT projections could have mediated the response to touch in inferior frontal cortex; ATD not only attenuated the activation to pleasant brush it also lessened the deactivation associated with the unpleasant brush. It might be that 5-HT exerts a permissive effect on touch responses in frontal cortex. However, ATD could be removing an influence of 5-HT at a site far removed from frontal cortex. For example, 5-HT has important modulatory effects in the dorsal horn which might be permissive or otherwise influence the normal balance between Aβ and CT synaptic function.

The idea that pleasant touch activates raphe forebrain projections is falsified by the most striking and significant effect of valence seen in this experiment; that unpleasant brush strokes to the arm, rather than pleasant, increased raphe BOLD signal. That this did not occur for the finger stimulation raises the possibility that CT fibres are somehow involved. If they encode pleasant touch this might inhibit the raphe but the ability of unpleasant brush to activate the raphe selectively when applied to the arm cannot be explained in this way. Microneurographic single fibre recordings are needed to determine whether unpleasant brushes can also activate CT fibres. The results are compatible with the idea that forebrain 5-HT systems are activated by aversive stimuli and inhibited by pleasant (Deakin and Graeff, 1991).
Anterior cingulate cortex showed a similar valence pattern to the raphe. Activation of the anterior cingulate by the unpleasant brush is compatible with evidence from many studies that this structure is part of an attentional network at the interface between cognition and emotion which is engaged when affective contingencies change. It is often activated in paradigms involving competing response tendencies and behavioural restraint or by errors in tasks (di Pellegrino et al., 2007, Ridderinkhof et al., 2004). The de-activation of the anterior cingulate by the pleasant brush might suggest a resting level of vigilance was reduced by the pleasantness of the soft brush. The valence effect in anterior cingulate and the raphe was selective for arm stimuli suggesting CT afferents may be involved. That the raphe and anterior cingulate showed the same valence effect raises the possibility that the valence effect in one location may be driving it in the other especially since the cingulate receives a rich 5-HT innervation and the cingulate projects directly to the raphe.

Tryptophan depletion did not simply abolish the valence effect in the cingulate, it reversed it. This is very reminiscent of the finding of Roiser et al., (2009) that in controls, cingulate activation to emotional distractor words in an affective go/no-go task became a de-activation after tryptophan depletion. The mechanism of this reversal is not clear. Another possibility is that ATD affected interactions between Aβ, nociceptive C-fibre and CT afferents in the dorsal horn. Recent evidence indicates that allodynia following peripheral nerve injury involves a change in the sensation conveyed by CT afferents from pleasant touch to pain (Craig, 2010, Seal et al., 2009). As noted earlier, sumatriptan can cause allodynia (Linde et al., 2004). ATD did not affect subjective ratings but its effects on 5-HT function may be more subtle and more general than those of sumatriptan, a direct specific receptor agonist. Effects of ATD in the dorsal horn would thus appear to be a possible mechanism of the reversal of affective polarity in the response of the cingulate to touch.

In the raphe, tryptophan depletion simply abolished rather than reversed the valence effect and this generally suggests the raphe BOLD response reflects altered neuronal activity in 5-HT containing cells. The specific mechanism might be that reduced raphe 5-HT lessens the well-known local autoreceptor control of 5-HT neural firing and that disinhibited 5-HT neuronal firing prevented modulation by valence.
Conclusions

In conclusion, little evidence was found to support the hypothesis that pleasant brush stroking activates the posterior insula. Evidence to support greater affective processing of touch following arm compared to finger stimulation was found, possibly due to CT afferent activation. This affective processing response was altered by tryptophan depletion suggesting a possible role for serotonin in the encoding of affective touch.

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6. General Discussion

This thesis consisted of a questionnaire study which investigated the role of affective touch in depression and an fMRI study using acute tryptophan depletion to investigate the neurobiological mechanisms of affective touch and whether or not these mechanisms are altered by lowered serotonin levels, a condition thought to occur in depression.

The overarching hypothesis of this investigation was that affective touch promotes resilience to depression through enhancing central serotonin function. The questionnaire study reported in this thesis was designed to investigate the initial part of this hypothesis, that affective touch promotes resilience to depression. A regression analysis of factors identified as potentially contributing to depression identified current intimate touch, but not current social contact or childhood touch as predictors to depression. This supports the existence of a role for affective touch in depression, but it seems that the type of touch is important, or alternatively it is the person from whom the touch is received that is important.

Affective touch has been investigated before, but mainly in terms of tactile communication (Andersen and Leibowitz, 1978, Deethardt and Hines, 1983, Hertenstein et al., 2009). This is an important use of touch and research has shown touch to convey emotions without any additional verbal or visual communication, even between strangers. Intimate touch between partners conveys the emotion of love (Hertenstein et al., 2009). Cochrane (1990) in his study found an additive effect of feeling loved and receiving adequate affective touch in the prevention of depression. This suggests feeling loved as well as affective touch reduces vulnerability to depression and could explain why it was that only the current intimate and not the current social contact factor that reduced vulnerability to depression.

fMRI was used to investigate the neurobiological mechanisms of affective touch in healthy volunteers. Half the volunteers were tryptophan depleted to determine the involvement of serotonin in affective touch perception. Tryptophan depletion was found to affect median raphe and anterior cingulate response following arm stimulation and to affect
inferior frontal gyrus response to finger stimulation. These regions, in particular the anterior cingulate, are involved in affective processing and suggest serotonin to be involved in affective touch processing. Changes in touch perception were subtle though as touch ratings were not significantly different between the control and tryptophan depleted participants. These results suggest serotonin to be involved in affective touch processing, but other neurotransmitters are also likely to be involved, otherwise a greater difference in pleasantness ratings between control and tryptophan depleted participants would be expected. A likely candidate would be dopamine due to its role in reward processing. These results suggest serotonin may have a modulatory effect on affective processing, rather than affective touch being specifically encoded by serotonin.

Unexpectedly, it was the unpleasant rather than pleasant brush that activated the median raphe, posterior insula and anterior cingulate in the control condition. The posterior insula in particular was expected to be activated by the pleasant brush due to previous literature having reported this (Bjornsdotter et al., 2009, Olausson et al., 2002, Olausson et al., 2008). This discrepancy could be explained by the lower force used in this investigation, or the lower number of repetitions per stimulus made.

6.1. Paper 1

The initial stage of this investigation into the role of affective touch in depression involved the construction and validation of the Touch Experiences and Attitudes Questionnaire (TEAQ). A six factor structure was identified following principal components analysis (appendix 2). The six factors were Current Social Touch (CST), Current Intimate Touch (CIT), Childhood Touch (ChT), Attitude to Intimate Touch (AIT), Attitude to Unfamiliar Touch (AUT) and Attitude to Skin Care (ASkC). The largest factor, Current Social Touch (CST) correlated highly with all other factors apart from the ASkC, which it correlated moderately with, suggesting this factor to be a general touch factor. This factor structure was confirmed in a second population using structural equation modelling. A third order factor structure of the TEAQ (appendix 3) was investigated in which the two factors regarding attitude to touch were combined into a second order factor and the two factors regarding amount of touch
were combined to a second order factor. The regression of AIT on CIT was also included. This model was a comparable fit of the data to the original model suggesting an alternative, simplified scoring method using these combined second order factors to give three measures of interpersonal affective touch rather than 5.

Social support often involves some form of physical contact. For this reason, the questionnaire measure of social support was expected to correlate with the TEAQ measures of current touch experienced. A significant correlation was found, although this explained only 25% of the variance at most, showing that the factors measuring amount of touch were not simply measuring social support using a different method, but are in fact measuring a separate construct of amount of physical contact received. For this reason, it was felt that this questionnaire could be used to determine the independent contribution of affective touch received at present to vulnerability to depression.

As predicted, the childhood touch factor from the TEAQ was found to strongly correlate with the childhood adversity questionnaire used in this investigation. Although the correlation was strong ($r = .58$), only 34% of the variance was explained by this correlation, which meant that the childhood touch factor was not simply an alternative measure of childhood adversity, but was independent of this, supporting the use of this measure to determine the contribution of physical contact experienced during childhood to the onset of depression in later life. The childhood touch factor strongly correlated with the Current Social Touch factor and moderately with the Current Intimate Touch factor and Attitude to Intimate touch factor. These findings are compatible with the proposal (see figure 7, introduction) that the affective touch system develops during childhood but then has to be maintained during adulthood in order to be effective.

The imperfect correlation between childhood adversity and rating of childhood touch is hardly surprising since the CHA questionnaire not only rates neglect but also abuse. Thus individuals with high CHA scores may still have received average amounts of parental affective touch, but abusive contact from others. The CHA is a fairly crude measure of childhood adversity as it contains only 6 items and relies on self-report. For the purposes of this investigation, it was felt that the use of this questionnaire was sufficient, as it has a
strong correlation with the CTQ (r = 0.75) and gives a reasonable indication of the amount of childhood adversity experienced. To further investigate the relationship between childhood adversity and affective touch experienced during childhood, an evidence-based measure of childhood adversity which does not rely on self-rating, such as the Childhood Experience of Care and Abuse (CECA), a semi-structured interview, would provide a more accurate indication of childhood adversity and distinguish between neglect and abuse. However, this method is extremely labour intensive and time consuming for both the investigator and participant, so was not possible for this investigation. A recent study by Brown et al., (2007) did use the CECA and found a lack of maternal affection to be a contributing factor to later depression in a study of depression in women. Their definition of maternal affection in terms of ‘cuddling, kissing and warmth of expression and interaction’ clearly implies physical contact but covers other aspects of affection too.

The high Cronbach’s alpha values obtained following Principal Components Analysis, the good fit of the data obtained from confirmatory factor analysis and significant correlations being identified between the childhood touch factor and the childhood adversity questionnaire scores and between the current touch factors and the social support questionnaire scores, led us to conclude that the TEAQ was a valid and reliable measure for use in the investigation of positive affective touch in community-based samples.

6.2. Paper 2

The second stage of the questionnaire study was to use the validated TEAQ to investigate the role of affective touch in depression. The TEAQ was included in a questionnaire battery that also included questions to obtain demographic data, questions relating to previous psychiatric history, and questionnaires to obtain measures of childhood adversity, social support, current psychiatric symptoms, personality and life events.

Data were analysed to determine whether touch scores differed between never depressed, remitted depressed and currently depressed individuals. It was found that all scores for all touch factors were significantly lower for currently depressed individuals.
remitted depressed individuals, current intimate touch, childhood touch, attitude to unfamiliar touch and total touch scores were significantly lower, but current social contact, attitude to skin care and attitude to intimate touch scores were not significantly different to healthy volunteers. This indicated that for individuals vulnerable to depression it was not that these people disliked intimate touch and so avoided this type of contact, but more that they tended to receive less intimate touch. This could be because they actually received less touch, or because they responded to the touch less and therefore reported receiving less touch. The questions in the TEAQ were open to interpretation as they do not specifically quantify amount of touch. For example: ‘I often have my skin stroked.’ Responses depend on an individual’s perception of ‘often.’ It could be that depressed and remitted depressed people report that they have less touch than others even though they actually receive a comparable amount compared to healthy controls. This could be due to the encoding of touch being less strong for those vulnerable to depression or due to the negative cognitive biases associated with a depressive personality type which leads to the amount of touch reported being lower.

An alternative explanation as to why those with depressive vulnerability receive less intimate touch could be that individuals with depressive personality types may have poorer relationships than those never depressed. A one-way ANOVA of relationship status against depression group found no significant difference between the relationship status of healthy, remitted depressed and currently depressed individuals (p = 0.104). This suggests that in the sample used in this investigation, relationship status did not affect depression status, but it could be that depressed and remitted depressed individuals have poorer quality relationships and therefore receive less affective touch. This would require further investigation. If it was found that those vulnerable to depression did have poorer quality relationships, a longitudinal study would be required to determine whether poorer quality relationships were the cause or effect of depressive vulnerability.

An analysis to determine the contribution of affective touch in relation to factors already established for depression was carried out. A stepwise multiple regression analysis found neuroticism, satisfaction with social support, number of life events experienced in the past 2 months, current intimate touch and childhood adversity to be predictors of current
depression. It is interesting to note that current intimate touch, but not childhood touch or current social contact were predictors of current depressive symptoms. The number of people reported to be available to a participant to provide social support was found not to be a predictor of depression, despite satisfaction with social support being a predictive factor. This suggests again that it is the quality of the relationships an individual has that is most important rather than the size of an individual’s social circle. Another possible explanation would be that those vulnerable to depression perceive themselves as having little social support when in fact the support they have is comparable to healthy individuals. This could be due to negative cognitive biases associated with depressive tendencies leading to a self-report of less social support, or it could be due to those vulnerable to depression requiring more social support than average and so report unsatisfactory social support. Further investigation would be required to determine this.

A logistic regression analysis found childhood touch, childhood adversity and neuroticism to be predictors of whether someone had been depressed in the past or not, but not extraversion, attitude to intimate touch or attitude to unfamiliar touch. These results conflict with those above that suggested that childhood touch does not predict current depression. It appears a lack of childhood touch increases vulnerability to depression, but does not significantly contribute to current level of depression. This could be due to some of the participants having been successfully treated for depression in the past which may have involved an intervention such as counselling which ablated the impact of a lack of touch during childhood on their current level of depression. This is supported by Hill et al., (2001) which found the effect of childhood neglect on risk of depression is moderated by quality of adult relationships, but this is not the case for childhood sexual and physical abuse. Childhood touch appears to increase vulnerability, but if other factors such as a current supportive relationship are present, the effect of childhood touch on current depression is reduced.
6.3. Paper 3

An fMRI investigation using the technique of acute tryptophan depletion to investigate the role of serotonin in affective touch processing was carried out. Brain response to application of touch to the glabrous skin of the fingers compared to the hairy skin of the forearm was determined.

The hypotheses investigated were that the central and subjective effects of pleasant touch: 1) involve activation of CT afferents, 2) cause activation of the posterior insula, 3) involve increased serotonin release.

Significant activations for the main effect of brush stroking applied to the arm and finger are tabulated in appendix 4. As expected, all touch stimuli activated contralateral somatosensory (SSC) cortex with greater activation produced following finger compared to arm stimulation. Both arm and finger stimulation caused secondary SSC activation bilaterally. Brodmann area 47 of the orbitofrontal cortex was significantly activated following arm stimulation and was just subthreshold for finger stimulation, but this difference was not found to be statistically significant.

CT afferents are thought to encode the affective rather than discriminatory aspects of touch and to specifically encode pleasant touch (Loken et al., 2009, Olausson et al., 2008). Due to the presence of CT afferents in hairy, but not glabrous skin, it was expected that a main effect of valence with positive activation following pleasant brush stroking would be seen in brain regions associated with affective processing. The only main effect of valence following arm stimulation in which stroking with the pleasant brush caused a positive activation, was in a small region of contralateral SSC, responsible for discriminative, but not affective encoding of touch. Conversely, a main effect of valence with positive activation following stroking with the pleasant brush was seen in the inferior frontal gyrus bilaterally, a brain region involved in affective processing (Elliott et al., 2011), following finger stimulation.

Small fibre tracts are thought to project to the posterior insula rather than the somatosensory cortex and encode the affective properties of touch. C-fibre nociceptors which encode pain, as well as CT afferents project to the posterior insula through this
pathway. The results of this investigation did not agree with previous investigations reporting hairy skin stimulation with a soft brush causes posterior insula activation (Bjornsdotter et al., 2009, Olausson et al., 2002, Olausson et al., 2008). One explanation could be discrepancies in the methodology used, particularly the force of 0.22 N used in this investigation compared to 0.8 N used in the other two investigations. A region of interest analysis specifically investigating posterior insula found the unpleasant, but not the pleasant or neutral brush, to significantly activate the posterior insula. Previous research has suggested the role of these afferents to be the encoding of pleasant touch. The results from this study do not support this finding. It could be that the increased roughness of the unpleasant brush led to increased posterior insula activation. An alternative theory would be that the unpleasant brush activated nociceptive afferents. The unpleasant brush is not perceived as painful, more irritating, but nociceptive afferents may still have been activated, as they have been reported to respond to forces as low as 0.01 – 0.08 N (Vallbo et al., 1999).

The effect of tryptophan depletion on brain response to affective touch was seen in three brain regions; the raphe nucleus and anterior cingulate in response to arm stimulation and inferior frontal gyrus in response to finger stimulation. In the control condition, the raphe was deactivated by the pleasant brush and activated by the unpleasant brush. These results are supported by the idea proposed by Deakin and Graeff (1991) that forebrain 5-HT systems are activated by aversive stimuli and inhibited by pleasant ones. Tryptophan depletion abolished this effect. As this response of the raphe was seen following arm, but not finger stimulation, this suggests CT afferents may possibly be involved.

In conclusion, little evidence was found to support previous reports suggesting pleasant brush stroking of the arm specifically engages the posterior insula and CT afferents. ATD modulated the effects of pleasant brush stroking of arm (raphe and anterior cingulate cortex) and finger (IFG). The raphe region was activated by unpleasant brush stroking of the arm and the abolition of this effect by ATD suggests raphe 5-HT neurones are engaged by aversive rather than pleasant tactile stimuli.

It is interesting to note that stroking with materials produced a similar pattern of brain activation to stroking with brushes for the main effect of touch to the arm and fingers.
(appendix 5), but main effects of valence results differed. No main effects of valence were seen for the arm. Following finger stimulation, a main effect of valence was seen in the amygdala only. The materials and brushes had similar VAS ratings. It appears aspects of touch other than force, velocity and affective ratings may be important in affective responses to touch and further investigation into brain response to stimuli with different psychophysical properties would be of benefit.

During the touching materials paradigm, participants rubbed the materials between their fingers and thumb, so touch was active rather than passive. The main effect of valence in this paradigm when using the same mask as used for the other results reported showed only one region of activation, in the precentral gyrus, BA43 (Z = 3.39), but not in regions attributed to affective processing. It could be that affective touch processing is altered during active rather than passive touch, but the results from this investigation are limited, so further investigation is required.

Total touch score was added as a covariate to the analysis described in paper 3 for control participants. Total touch score was found not to covary either positively or negatively to brain response to arm stimulation. In response to finger stimulation, no positive covariance was seen, but brain response was found to negatively covary with touch score in the secondary somatosensory cortex and pre- and post-central gyri (Appendix 6). This suggests a relationship between TEAQ score and brain response to affective touch may exist, although no covariance with brain regions associated with affective processing was seen. Further investigation into the relationship between TEAQ score and affective responses to touch is required.

6.4. Limitations

The studies described during this thesis had many limitations. In the questionnaire study, the first sample used for exploratory factor analysis was obtained from the same population as the sample used for the structural equation modelling, so it is unclear how generalisable the factor structure of the questionnaire is until the questionnaire is completed by other
populations, such as people from different cultural backgrounds and people who are older. Other limitations of the questionnaire study were that the method used to classify people as depressed, remitted depressed or never depressed relied on self-rating and was not very detailed. A more accurate method of grouping individuals would have been to use an interview technique such as using the structured clinical interview to diagnose DSM-IV-TR Axis I disorders (SCID) (First et al., 2002). A smaller sample size would then have been obtained though due to the additional time and expense involved, which would have decreased the power of the analysis and would have increased the probability of a type II error occurring where a hypothesis is rejected as no significant result is found, but this is due to too little power rather than the hypothesis being incorrect.

Further limitations are that the sample obtained in the questionnaire study was predominantly female and the imaging sample was entirely female. It could be that the role of affective touch differs between the sexes.

6.5. Model of the role of affective touch in depression

This thesis set out to test a model of the role of affective touch in depression proposed in the introduction and displayed below.
From the questionnaire study, evidence was found to suggest early touch deprivation increases vulnerability to depression. Factors such as a strong current love relationship can ablate this effect (Hill et al., 2001). The questionnaire data supported the hypothesis that social isolation and lack of childhood affiliative touch can contribute to vulnerability to depression, but no evidence was found to indicate a relationship between social isolation and a less positive attitude to touch with intimates or to skin care. However, amount of current intimate contact had a significant protective influence independently of other risk factors on current symptoms of depression. The role of serotonin in the effects of early or current affiliative touch on risk of depression remains uncertain. Genotypic data was only obtained from 200 participants during the questionnaire study. This did not provide sufficient power to make any conclusions about whether constitutional variation in serotonin function influences sensitivity to pleasant touch as depicted in figure 14 above. Similarly, the sample size from the fMRI study did not provide sufficient power to allow conclusions into differences in brain responses to affective touch between genotypic groups. In the fMRI investigation, ATD did not lessen the perceived pleasantness of touch as was predicted.

Figure 14: proposed model of the role of affective touch in depression.

Blue boxes represent factors to be investigated during the questionnaire study. Red boxes represent factors to be investigated during the fMRI study.
Although CNS effects of pleasant touch to the fingers in inferior frontal gyrus were lessened by ATD, it is implausible to suggest that this indicates a mediating role for serotonin in the CNS effects of pleasant touch when serotonin cells themselves in the raphe were activated by unpleasant rather than pleasant touch stimuli. It would appear that current affiliative touch does not improve resilience to depression by enhancing serotonin release. The responsiveness of the raphe to unpleasant touch is compatible with the idea that aversive events activate median raphe projections and promote resilience to stress and depression.

In conclusion, this thesis provides evidence that affiliative touch in childhood and in adulthood may play distinct but overlapping roles in the pathogenesis of depression and that this needs to be factored into future studies. The role of direct neurobiological effects of skin contact remains uncertain. There was little evidence to suggest there is a specific skin-sensation modality encoding affiliative touch with a specific CNS representation or that serotonin mediates such effects. However, a novel activation of the raphe by aversive skin sensation was discovered. Some further studies to clarify the neurobiology and role of affiliative touch in depression are outlined in the final section.

6.6. Further studies

Future studies to be carried out would be to give the touch questionnaire to a variety of sample populations including patients with depression or in remission. Structural equation modelling could then be carried out on this data to determine whether the TEAQ factor structure is the same across these different populations. The data could also be used to carry out exploratory factor analysis to determine whether the TEAQ can be further reduced in length. The questionnaire could be completed with the TACTYPE, TAM and QPCE to determine its incremental validity.

The imaging study was carried out in healthy females and, as has been noted, ATD has little effect in those without vulnerability to depression. It would therefore be interesting to repeat the study in a remitted depressed sample and in depressives. This would determine whether the hypothesised insensitivity to affective touch is a feature of trait vulnerability or
the state of depression and whether ATD has an effect on touch processing in those with vulnerable 5-HT function. The effect of early neglect within a remitted depressed sample could also home in on whether this factor affects touch sensitivity.

Due to the existing literature regarding the release of oxytocin, vasopressin and endorphins in social bonding, it would be interesting to carry out a similar imaging investigation to the one carried out here, but manipulating oxytocin, vasopressin or endorphin levels rather than serotonin.
References


Appendices

Appendix 1 – Touch Experiences and Attitudes Questionnaire (TEAQ)

Please select a number from one to five next to each statement to show how much you agree or disagree with each statement. One represents disagree strongly and five represents agree strongly.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Disagree strongly</th>
<th>Disagree a little</th>
<th>Neither agree nor disagree</th>
<th>Agree a little</th>
<th>Agree Strongly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I dislike people being very physically affectionate towards me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. I like using body lotions.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I have to know someone quite well to enjoy a hug from them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I find it natural to greet my friends and family with a kiss on the cheek.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. There was a lot of physical affection during my childhood.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. As a child I would often hug family members.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. I like to use bath essence when having a bath.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. I find stroking the hair of a person I am fond of very pleasurable.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. My parents were not very physically affectionate towards me during my childhood.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. I like to fall asleep in the arms of someone I am close to.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. I often snuggle up on the sofa with someone.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. I enjoy the physical intimacy of sexual foreplay.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. I like to link arms with my friends and family as I walk along.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. I usually hug my family and friends when I am saying goodbye.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. As a child I found a hug from my parents when I was upset made me feel much happier.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. It’s nice when friends and family members greet me with a kiss.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. I often hold hands with someone I know intimately.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Disagree strongly</td>
<td>Disagree a little</td>
<td>Neither agree nor disagree</td>
<td>Agree a little</td>
<td>Agree Strongly</td>
</tr>
<tr>
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</tr>
<tr>
<td>18. When I am upset, there is usually someone who can comfort me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. Kissing is a great way of expressing physical attraction.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. It feels really good when someone I am fond of runs their fingers through my hair.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. I regularly hug people I am close to.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. As a child my parents would tuck me up in bed every night and give me a hug and a kiss goodnight.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. My life lacks physical affection.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. I enjoy having my skin stroked.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>25. I often take a shower or bath with someone.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>26. I enjoy having sex.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>27. I often have sex.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>28. I am put off by physical familiarity.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>29. I can always find somebody to physically comfort me when I am upset.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>30. I always greet my friends and family by giving them a hug.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>31. I enjoy being cuddled by someone I am fond of.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>32. My mother regularly bathed me as a child.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>33. As a child my parents always comforted me when I was upset.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>34. I enjoy the feeling of my skin against someone else’s if I know them intimately</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>35. As a child my parents would often hold my hand when I was walking along with them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>36. Most days I get a hug or a kiss.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>37. If someone I don’t know very well puts a friendly hand on my arm it makes me feel uncomfortable.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>38. I often make physical contact with my friends and family when I am with them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>39. It makes me feel uncomfortable if someone I don’t know very well touches me in a friendly manner.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Question</td>
<td>Disagree strongly</td>
<td>Disagree a little</td>
<td>Neither agree nor disagree</td>
<td>Agree a little</td>
<td>Agree Strongly</td>
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<td>---------------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>40. I enjoy holding hands with someone I am fond of.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>41. I often share a romantic kiss.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>42. As a child my mother regularly brushed my hair.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>43. I like exfoliating my skin.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>44. Kissing is an enjoyable part of expressing romantic feeling.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>45. I often have my skin stroked.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>46. I often hold hands with someone I am fond of.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>47. I like to stroke the skin of someone I know intimately.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>48. I am on huggable terms with quite a few people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>49. I often fall asleep while holding someone I am close to.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>50. Snuggling up on the sofa with someone is great.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>51. I often put my arm around a close friend as we walk along together.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>52. I like having a bath with lots of bubble bath.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>53. I don't get many hugs these days.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>54. I am often given a shoulder massage.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>55. I like to use face masks on my skin</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>56. I like it when my friends and family greet me by giving me a hug.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>57. I often link arms with my friends and family as I walk along.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
## Appendix 2 – TEAQ factor structure

<table>
<thead>
<tr>
<th>Item</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I always greet my friends and family by giving them a hug (Q30).</td>
<td>0.75</td>
</tr>
<tr>
<td>I often link arms with my friends and family as I walk along (Q57).</td>
<td>0.74</td>
</tr>
<tr>
<td>I like to link arms with my friends and family as I walk along (Q13).</td>
<td>0.71</td>
</tr>
<tr>
<td>I usually hug my family and friends when I am saying goodbye (Q14).</td>
<td>0.70</td>
</tr>
<tr>
<td>I find it natural to greet my friends and family with a kiss on the cheek (Q4).</td>
<td>0.70</td>
</tr>
<tr>
<td>I often make physical contact with my friends and family when I am with them (Q38).</td>
<td>0.69</td>
</tr>
<tr>
<td>It’s nice when friends and family members greet me with a kiss (Q16).</td>
<td>0.64</td>
</tr>
<tr>
<td>I am on huggable terms with quite a few people (Q48).</td>
<td>0.63</td>
</tr>
<tr>
<td>I regularly hug people I am close to (Q21).</td>
<td>0.62</td>
</tr>
<tr>
<td>I like it when my friends and family greet me by giving me a hug (Q56).</td>
<td>0.61</td>
</tr>
<tr>
<td>I often put my arm around a close friend as we walk along together (Q51).</td>
<td>0.58</td>
</tr>
<tr>
<td>Most days I get a hug or a kiss (Q36).</td>
<td>-0.79</td>
</tr>
<tr>
<td>I often share a romantic kiss (Q41).</td>
<td>-0.79</td>
</tr>
<tr>
<td>I often have sex (Q27).</td>
<td>-0.75</td>
</tr>
<tr>
<td>I don’t get many hugs these days (Q53 R).</td>
<td>-0.75</td>
</tr>
<tr>
<td>My life lacks physical affection (Q23 R).</td>
<td>-0.75</td>
</tr>
<tr>
<td>I often hold hands with someone I am fond of (Q46).</td>
<td>-0.68</td>
</tr>
<tr>
<td>I often fall asleep while holding someone I am close to (Q49).</td>
<td>-0.67</td>
</tr>
<tr>
<td>I often have my skin stroked (Q45).</td>
<td>-0.62</td>
</tr>
<tr>
<td>I often snuggle up on the sofa with someone (Q11).</td>
<td>-0.60</td>
</tr>
<tr>
<td>I can always find somebody to physically comfort me when I am upset (Q29).</td>
<td>-0.58</td>
</tr>
<tr>
<td>I often take a shower or bath with someone (Q25).</td>
<td>-0.56</td>
</tr>
<tr>
<td>I am often given a shoulder massage (Q54).</td>
<td>-0.55</td>
</tr>
<tr>
<td>When I am upset, there is usually someone who can comfort me (Q18).</td>
<td>-0.51</td>
</tr>
<tr>
<td>I often hold hands with someone I know intimately (Q17).</td>
<td>-0.43</td>
</tr>
<tr>
<td>As a child my parents would tuck me up in bed every night and give me a hug and a kiss goodnight (Q22).</td>
<td>-0.80</td>
</tr>
<tr>
<td>My parents were not very physically affectionate towards me during my childhood (Q9 R).</td>
<td>-0.80</td>
</tr>
<tr>
<td>Factor</td>
<td>1</td>
</tr>
<tr>
<td>--------</td>
<td>----</td>
</tr>
<tr>
<td>There was a lot of physical affection during my childhood (Q5).</td>
<td></td>
</tr>
<tr>
<td>As a child my parents always comforted me when I was upset (Q33).</td>
<td></td>
</tr>
<tr>
<td>As a child I would often hug family members (Q6).</td>
<td></td>
</tr>
<tr>
<td>As a child my parents would often hold my hand when I was walking along with them (Q35).</td>
<td></td>
</tr>
<tr>
<td>As a child I found a hug from my parents when I was upset made me feel much happier (Q15).</td>
<td></td>
</tr>
<tr>
<td>My mother regularly bathed me as a child (Q32).</td>
<td></td>
</tr>
<tr>
<td>As a child my mother regularly brushed my hair (Q42).</td>
<td></td>
</tr>
<tr>
<td>I like to use face masks on my skin (Q55).</td>
<td></td>
</tr>
<tr>
<td>I like to use bath essence when having a bath (Q7).</td>
<td></td>
</tr>
<tr>
<td>I like having a bath with lots of bubble bath (Q52).</td>
<td></td>
</tr>
<tr>
<td>I like exfoliating my skin (Q43).</td>
<td></td>
</tr>
<tr>
<td>I like using body lotions (Q2).</td>
<td></td>
</tr>
<tr>
<td>I like to stroke the skin of someone I know intimately (Q47).</td>
<td></td>
</tr>
<tr>
<td>I enjoy the feeling of my skin against someone else's if I know them intimately (Q34).</td>
<td></td>
</tr>
<tr>
<td>It's feels really good when someone I am fond of runs their fingers through my hair (Q20).</td>
<td></td>
</tr>
<tr>
<td>I find stroking the hair of a person I am fond of very pleasurable (Q8).</td>
<td></td>
</tr>
<tr>
<td>I enjoy having my skin stroked (Q24).</td>
<td></td>
</tr>
<tr>
<td>Snuggling up on the sofa with someone is great (Q50).</td>
<td></td>
</tr>
<tr>
<td>I enjoy being cuddled by someone I am fond of (Q31).</td>
<td></td>
</tr>
<tr>
<td>I enjoy holding hands with someone I am fond of (Q40).</td>
<td></td>
</tr>
<tr>
<td>I like to fall asleep in the arms of someone I am close to (Q10).</td>
<td></td>
</tr>
<tr>
<td>Kissing is an enjoyable part of expressing romantic feeling (Q44).</td>
<td></td>
</tr>
<tr>
<td>I enjoy the physical intimacy of sexual foreplay (Q12).</td>
<td></td>
</tr>
<tr>
<td>Kissing is a great way of expressing physical attraction (Q19).</td>
<td></td>
</tr>
<tr>
<td>I enjoy having sex (Q26).</td>
<td></td>
</tr>
<tr>
<td>It makes me feel uncomfortable if someone I don't know very well touches me in a friendly manner (Q39 R).</td>
<td></td>
</tr>
<tr>
<td>If someone I don't know very well puts a friendly hand on my arm it makes me feel uncomfortable (Q37 R).</td>
<td></td>
</tr>
<tr>
<td>I have to know someone quite well to enjoy a hug from them (Q3 R).</td>
<td></td>
</tr>
<tr>
<td>I am put off by physical familiarity (Q28 R).</td>
<td></td>
</tr>
</tbody>
</table>
I dislike people being very physically affectionate towards me (Q1 R).

Factor structure of the 57 item Touch Experience and Attitudes Questionnaire (TEAQ). The final factor structure and the factor loading of each item are shown. Item numbers are shown in brackets, with an R where appropriate to denote items reverse scored items. Factor loadings less than 0.4 are not shown to increase clarity. Factor 1: Current Social Touch (CST), Factor 2: Current Intimate Touch (CIT), Factor 3: Childhood Touch (ChT), Factor 4: Attitude to Skin Care (ASKC), Factor 5: Attitude to Intimate Touch (AIT), Factor 6: Attitude to Unfamiliar Touch (AUT).
Appendix 3: Third order factor structure of the TEAQ

Third order factor structure of the TEAQ with parcelled items. Circles – latent variables, rectangles – observed variables (parcelled for this model), long arrows – regressions, short arrows - error variances. Abbreviations: CST – current social touch, CIT – current intimate touch, AIT – attitude to intimate touch, AUT – attitude to unfamiliar touch, ChT – childhood touch, ASkC – Attitude to Skin Care. For details of the items included in each parcel, see table below.
<table>
<thead>
<tr>
<th>Parcel number (P)</th>
<th>Item numbers (see table 1) included in parcel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>30, 51, 57</td>
</tr>
<tr>
<td>1b</td>
<td>13, 14, 21, 56</td>
</tr>
<tr>
<td>1c</td>
<td>4, 16, 38, 48</td>
</tr>
<tr>
<td>2a</td>
<td>17, 18, 36, 41, 54</td>
</tr>
<tr>
<td>2b</td>
<td>11, 25, 27, 29, 53</td>
</tr>
<tr>
<td>2c</td>
<td>23, 45, 46, 49</td>
</tr>
<tr>
<td>3a</td>
<td>19, 26, 34, 47</td>
</tr>
<tr>
<td>3b</td>
<td>8, 12, 20, 44</td>
</tr>
<tr>
<td>3c</td>
<td>10, 24, 31, 40, 50</td>
</tr>
<tr>
<td>4a</td>
<td>39</td>
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<td>4b</td>
<td>1, 37</td>
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<tr>
<td>4c</td>
<td>3, 28</td>
</tr>
<tr>
<td>5a</td>
<td>9, 22, 42</td>
</tr>
<tr>
<td>5b</td>
<td>5, 15, 32</td>
</tr>
<tr>
<td>5c</td>
<td>6, 33, 35</td>
</tr>
<tr>
<td>6a</td>
<td>55</td>
</tr>
<tr>
<td>6b</td>
<td>2, 7</td>
</tr>
<tr>
<td>6c</td>
<td>43, 52</td>
</tr>
</tbody>
</table>

Table of items included in each parcel.
### Appendix 4 – Main effect of touch with brush stimuli

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Size (voxels)</th>
<th>Z-score</th>
<th>P uncorrected</th>
<th>MNI coords x,y,z (mm)</th>
<th>Brain region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>207</td>
<td>4.59</td>
<td>&lt;0.001</td>
<td>63 -16 18</td>
<td>Postcentral Gyrus, BA43 (OP4)</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>4.34</td>
<td>&lt;0.001</td>
<td>54 -2 4</td>
<td>Superior Temporal Gyrus, BA22 (OP4)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>4.18</td>
<td>&lt;0.001</td>
<td>-56 4 4</td>
<td>Superior Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td>266</td>
<td>4.06</td>
<td>&lt;0.001</td>
<td>-59 -16 25</td>
<td>Postcentral Gyrus, BA3</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>4</td>
<td>&lt;0.001</td>
<td>-47 38 -4</td>
<td>Middle Frontal Gyrus, BA47</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>3.55</td>
<td>&lt;0.001</td>
<td>25 -40 53</td>
<td>Sub-Gyral, BA40</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>3.08</td>
<td>&lt;0.001</td>
<td>47 -32 46</td>
<td>Postcentral Gyrus, BA2</td>
</tr>
<tr>
<td><strong>Fingers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1025</td>
<td>7.5</td>
<td>&lt;0.001</td>
<td>47 -31 53</td>
<td>Postcentral Gyrus, BA 2</td>
</tr>
<tr>
<td></td>
<td>512</td>
<td>5.58</td>
<td>&lt;0.001</td>
<td>-59 -22 18</td>
<td>Postcentral Gyrus, BA40, (IPC)</td>
</tr>
</tbody>
</table>

Table of significant activations for the main effect of brush stroking applied to forearm and fingers. Abbreviations: BA – Brodmann Area, OP – parietal operculum.
Appendix 5 – Brain activations following stroking with materials

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>Z-score</th>
<th>P uncorrected</th>
<th>MNI coords x,y,z {mm}</th>
<th>Brain region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>4.38</td>
<td>&lt;0.001</td>
<td>36 -16 14</td>
<td>OP2</td>
</tr>
<tr>
<td>211</td>
<td>4.37</td>
<td>&lt;0.001</td>
<td>65 -14 21</td>
<td>Postcentral Gyrus, BA43, (OP4)</td>
</tr>
<tr>
<td>122</td>
<td>3.89</td>
<td>&lt;0.001</td>
<td>-56 -18 14</td>
<td>Transverse Temporal Gyrus, BA41, (OP1)</td>
</tr>
<tr>
<td>61</td>
<td>3.65</td>
<td>&lt;0.001</td>
<td>-36 40 -11</td>
<td>Middle Frontal Gyrus, BA11</td>
</tr>
<tr>
<td>18</td>
<td>3.65</td>
<td>&lt;0.001</td>
<td>23 -4 -21</td>
<td>Amygdala</td>
</tr>
<tr>
<td>35</td>
<td>3.34</td>
<td>&lt;0.001</td>
<td>40 31 -11</td>
<td>Inferior Frontal Gyrus, BA47</td>
</tr>
<tr>
<td>11</td>
<td>3.31</td>
<td>&lt;0.001</td>
<td>59 4 4</td>
<td>Superior Temporal Gyrus, BA22</td>
</tr>
<tr>
<td>12</td>
<td>3.1</td>
<td>0.001</td>
<td>52 18 4</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>Fingers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>536</td>
<td>6.42</td>
<td>&lt;0.001</td>
<td>-59 -22 21</td>
<td>Postcentral Gyrus, BA40 (IPC)</td>
</tr>
<tr>
<td>1004</td>
<td>6.08</td>
<td>&lt;0.001</td>
<td>41 -34 60</td>
<td>Postcentral Gyrus, BA3</td>
</tr>
<tr>
<td>10</td>
<td>3.23</td>
<td>0.001</td>
<td>54 -2 4</td>
<td>Superior Temporal Gyrus, BA22, OP4</td>
</tr>
<tr>
<td>17</td>
<td>3.2</td>
<td>0.001</td>
<td>56 4 4</td>
<td>Superior Temporal Gyrus</td>
</tr>
<tr>
<td>Main effect of valence fingers</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>3.4</td>
<td>&lt;0.001</td>
<td>-29 -5 -21</td>
<td>Amygdala</td>
</tr>
</tbody>
</table>

Table of significant activations for the main effect of material stroking applied to forearm and fingers and the main effect of valence following finger stimulation. Abbreviations: BA – Brodmann Area, OP – parietal operculum, IPC – inferior parietal cortex. The method of analysis was the same as that for stroking with brushes.

Appendix 6 – covariance of touch score with brain response to brush stroking

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>Z-score</th>
<th>P uncorrected</th>
<th>MNI coords x,y,z {mm}</th>
<th>Brain region</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3.81</td>
<td>&lt;0.001</td>
<td>-29 -22 18</td>
<td>OP2</td>
</tr>
<tr>
<td>54</td>
<td>3.54</td>
<td>&lt;0.001</td>
<td>-41 -31 18</td>
<td>OP1</td>
</tr>
<tr>
<td>45</td>
<td>3.38</td>
<td>&lt;0.001</td>
<td>-49 -18 39</td>
<td>Precentral Gyrus, BA4</td>
</tr>
<tr>
<td>80</td>
<td>3.35</td>
<td>&lt;0.001</td>
<td>-38 -27 39</td>
<td>Postcentral Gyrus, BA2</td>
</tr>
</tbody>
</table>

Table of brain activations found to negatively covary with total touch score following finger stimulation with brushes.