SEROTONIN, BRIGHT LIGHT, AND THE REGULATION OF HUMAN SOCIAL INTERACTION AND MOOD

by

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Dedicated to my grandparents

Wijnandus Hubertus Hendriks
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CONTRIBUTIONS OF AUTHORS

Marije aan het Rot conceived of all three studies presented in this Doctoral Thesis, acquired and analyzed all data, and wrote and reviewed the manuscripts. Dr. Moskowitz was involved in the conception and data analysis of Studies 1 and 3 and helped write and review the corresponding manuscripts. Dr. Pinard was involved in the data acquisition of Study 1 and critically reviewed the corresponding manuscript. Dr. Benkelfat was involved in the conception of Study 2 and critically reviewed the corresponding manuscript. Dr. Boivin was involved in the conception and data acquisition of Study 2 and helped write and review the corresponding manuscript. Dr. Young conceived of all three studies and helped write and review the manuscripts. All contributors gave final approval for publication of the manuscripts in which they were involved.[1-3]

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ABSTRACT

The three studies described in this Doctoral Thesis pertain to the neurotransmitter serotonin, the environmental factor light, and their role in the regulation of human mood as well as behavioural and perceptual aspects of daily social interaction. Participants were healthy at the time of the study but considered at risk for mood disorders in the future. In Study 1, the serotonin system was manipulated by administering tryptophan. This resulted in a decrease in quarrelsome behaviours, an increase in agreeable behaviours, and improved mood. Changes in perceptions of others were also seen. In Study 2, acute tryptophan depletion was used in conjunction with dim or bright light exposure during test days. A worsening of mood was seen under dim but not bright light conditions, which suggests that bright light was able to regulate mood by interacting with the brain serotonin system. In Study 3, this idea was explored further by investigating the links between light exposure levels and mood, as well as social behaviours and social perceptions, in everyday life. Higher levels of natural bright light exposure were associated with less quarrelsomeness, more agreeableness, and better mood. In conclusion, serotonin appears to mediate aspects of human social interaction that have been linked to a variety of mental and physical health issues. Bright light may regulate mood in part by altering the activity of the brain serotonin system. An increase in bright light exposure may have effects on mood and social interaction similar to a pharmacological manipulation of the brain serotonin system. The findings of the three studies presented here may have implications for the development of a non-pharmacological approach to the prevention of mental as well as physical disease. The various processes underlying factors that modulate social inclusion and acceptance deserve more attention in psychiatry and human neuroscience.

ABRÉGÉ

Les trois études de cette thèse doctorale portent sur un neurotransmetteur, la sérotonine, un facteur environnemental, la lumière, et leurs rôles dans la régularisation de l'humeur et des aspects comportementaux et perceptifs des interactions sociales quotidiennes. Les participants et participantes de ces études étaient en bonne santé, mais étaient à risque élevé pour développer des troubles de l'humeur. Dans la 1^{iere} étude, le niveau de la sérotonine fut manipulé en administrant du tryptophane. Ceci a résulté une baisse des comportements querelleurs, une augmentation des comportements affables, et une amélioration au niveau de la bonne humeur. Il y a aussi eu des changements au niveau de la perception des autres personnes. Dans la 2^{ieme} étude, l'épuisement du tryptophane fut utilisé en conjonction avec de la lumière faible ou forte pendant les journées de l'étude. Ce qu'a engendré une baisse de l'humeur, mais seulement avec la lumière faible. Ce qui indique que la lumière forte peut régulariser l'humeur en interagissant avec le système sérotoninergique. Dans la 3^{ieme} étude, cette idée fut explorée plus profondément en recherchant les liens entre l'intensité de la lumière et l'humeur, ainsi que les comportements sociaux et les perceptions sociales, dans la vie quotidienne. Un niveau élevé de la lumière naturelle forte fut associé avec une baisse de comportements querelleurs, une hausse de comportements affables, et plus de bonne humeur. On peut conclure que la sérotonine influence les aspects des interactions sociales humaines liés avec plusieurs problèmes mentaux et physiques. La lumière forte peut régulariser l'humeur en changeant l'activité du système sérotoninergique. Une augmentation d'exposition à la lumière forte peut améliorer l'humeur et les interactions sociales, comme une manipulation pharmacologique du système sérotoninergique. Les résultats, des trois études présentées ici, ont d'importantes implications pour le développement d'une approche non pharmacologique pour la prévention des maladies mentales et physiques. Les processus portant sur l'intégration et l'acceptation sociale méritent plus d'attention dans la psychiatrie et la neuroscience humaine.

Chapter 1
INTRODUCTION

Understanding how the human brain performs its social functions is important for public health issues relating to mental disease. Psychopathology is often characterized by social impairments. Yet data on the neural factors involved in human social interaction are lacking. Only a few years ago did the United States National Institute of Mental Health acknowledge the need for more research linking human neuroscience and social psychology.[306] Thus far this interdisciplinary field has mainly focused on social cognition and its anatomical, physiological and developmental underpinnings. This focus can be illustrated by the books edited by Cacioppo and colleagues,[57-59] special issues on social neuroscience in the *Journal of Personality and Social Psychology* and in *NeuroImage*,[177,256] and the 2006 launch of two journals on the topic, *Social Neuroscience* and *Social Cognitive and Affective Neuroscience*.

Two observations can easily be made when examining these writings. Firstly, very few studies have looked at the role of neurochemical factors in the regulation of human social interaction. Several animal models are available and suggest the involvement of a variety of neurotransmitters and neuropeptides.[65,89,199,202,281] However, these have rarely been translated into experimental work in humans. Secondly, the majority of human studies have focused on social cognition using standardized paradigms tested in laboratory settings without exploring the actual social interactions that occur in everyday life. This is especially surprising because people's behaviours and feelings will likely differ depending on for example the location and the characteristics of their interaction partner.[290] In sum, the identification of neurochemical factors involved in social interactions, given that these form an essential part of every human's life, should also take place outside the unnatural environment that defines a laboratory.

To date most human studies on the neurochemistry of social interaction-related processes have focused on the role of serotonin in aggressive behaviours and feelings. Psychiatric disorders often associated with aggression include mood

disorders, intermittent explosive disorder, cluster B personality disorders and alcoholism. The idea that serotonergic activity controls (impulsive) aggressiveness is based not only on studies in patients with a history of aggression and in healthy volunteers, but also on studies in various other animal species. Unfortunately, however, the effects of serotonergic manipulations on aggressive behaviours and feelings in individuals without psychiatric disorders have mostly been measured with standardized laboratory tests. This may limit extrapolation of the proposed inverse relationship between serotonin and aggression to everyday life.

Impulsive-aggressive behaviours are rare, and usually limited to extreme situations. Nonetheless, certain aspects of personality are known predisposing factors. These include irritability, hostility and affective reactivity.[62,305,397,417] The behaviours and feelings associated with these traits can be measured reliably over a period of several weeks using strategies developed in social psychology. For example, in the method developed by Moskowitz (1994), social behaviours are measured by asking people to sample information about their social interactions as they happen.[291] Using this event-contingent recording method across a wide variety of situations, Moskowitz and Coté found that people with hostile and neurotic traits display more quarrelsome as well as less agreeable behaviours in everyday life.[85,293] The measurement of quarrelsome and agreeable behaviours by means of event-contingent recording may provide further insight into the neurochemical factors involved in the aetiology and prevention of psychopathology.

The three studies described in this Doctoral Thesis evaluated the role of serotonin in mood and everyday social interactions in people who were healthy at the time of study participation but nonetheless, due to certain traits, considered at risk for developing a mood disorder. Studies 1 and 3 used the event-contingent recording method developed by Moskowitz (1994).[291] Study 1 looked at the effects of tryptophan administration on social behaviour and mood in quarrelsome individuals. Tryptophan is the amino acid precursor of serotonin. Study 3 looked at the effects of bright light exposure on social behaviour and mood in mildly seasonal individuals. The idea that bright light can be an effective alternative to a pharmacological manipulation of the serotonin system in improving everyday mood

is largely based on indirect evidence. Therefore, Study 2 was designed to provide evidence for a direct relation between bright light, changes in brain serotonin function, and mood. This laboratory-based study used acute tryptophan depletion to transiently reduce serotonin synthesis, a method known to lower mood in populations vulnerable to mood disorders.[30,454]

Chapters 2-4 first provide reviews on the topic of serotonin, human social interaction, and mood disorders from the neurochemical, social psychological, and psychiatric perspectives. Chapter 5 outlines the rationale and specific hypotheses for each of the three studies. Chapters 6-10 contain the reports from the three studies that have been submitted for publication, separated by brief intermezzos that provide a summary of the preceding chapter and an introduction to the following chapter. Chapter 11 provides a brief summary and includes a discussion of the studies' findings. Finally, Chapter 12 discusses the implications of the results and provides some ideas for future studies.

Chapter 2
SEROTONIN

2.1 Synthesis

Serotonin is derived from the essential amino acid, L-tryptophan. In cells containing the enzyme tryptophan hydroxylase, tryptophan is converted into 5-hydroxy-tryptophan. This is then rapidly converted into 5-hydroxy-tryptamine, or serotonin, using a second enzyme called aromatic L-amino acid decarboxylase.[140] Serotonergic cells are found almost exclusively in the intestines; only a small percentage is present in the raphe nuclei in the brain stem. Under physiological conditions, the speed of serotonin synthesis is limited in part by the degree of saturation of tryptophan hydroxylase with tryptophan. Since this is normally around 50%, a change in tryptophan availability will usually directly influence the synthesis of serotonin.

Levels of tryptophan in the brain are affected by its uptake from the periphery using an active transport system.[326] Tryptophan competes with other large neutral amino acids for transport. Consequently, brain levels of tryptophan depend on plasma levels of tryptophan relative to its competing amino acids. Moreover, this means that ingestion of an amino acid source (*i.e.* protein) will generally not result in an increase in brain tryptophan levels.[135] In fact since tryptophan is one of the least abundant amino acids in most sources of protein, its levels in brain usually decrease slightly following ingestion of protein. However, brain levels of tryptophan can rise by selectively increasing tryptophan intake.[452,453] Further, experimental amino acid mixtures devoid of tryptophan have been used to study the effects of short-term reductions in brain levels of tryptophan on a variety of human brain functions.[453,454] Human brain imaging studies of tryptophan hydroxylase activity have confirmed that this method, known as acute tryptophan depletion (ATD), transiently reduces brain serotonin synthesis, especially in women.[316]

Serotonin is an ancient neurotransmitter, as indicated by its presence in most if not all life forms. Bacteria produce serotonin using homologs of mammalian tryptophan hydroxylase and aromatic amino acid decarboxylase.[87,126,203,249,458] They

also express serotonin transporters and channel-type serotonin receptors on their cell surface.[12,322] This allows for rapid interaction with the environment, *e.g.* by phagocytosis, by regulating cilial motility, and by growth.[87,126] G-protein-coupled serotonin receptors seem to have evolved later than the channel-type serotonin receptors.[331] Moreover, evolution has seen an increase in the number of G-protein-coupled serotonin receptors yet only one channel-type serotonin receptor has been identified.[331] This reflects the change in function of serotonin, from being a simple intercellular signal into a hormone and a neuromodulator with a multitude of complex functions.[187,410]

2.2 Light

Given its presence throughout evolution, it is perhaps not surprising that tryptophan and serotonin have been linked to circadian and seasonal changes in light exposure. For example, tryptophan residues in bacterial light receptors play a role in changing their sensitivity to light during night/day transitions.[283] The tryptophan derivative indole-3-acetic acid plays a role in plant growth toward a light source.[19,300] In vertebrates, retinal amacrine cells are innervated by serotonergic cells such that these raphe-to-retina projections modulate perception of brightness.[257] In addition to a pathway from the raphe to the retina, there may also be a direct pathway going from the retina to the raphe, at least in some mammals.[138,144,345,374] The existence of such a pathway would help explain findings of increased cell discharge rates, serotonin content, and c-Fos expression in raphe in response to light in these mammals.[60,289,299] It is unknown if a direct retina-to-raphe projection exists in humans.

In humans an effect of light on the brain serotonin system is largely inferred from findings of circadian and seasonal rhythms in serotonin function that correspond with diurnal and annual variations in light levels. For example, Carlsson *et al.* (1980) found that post-mortem brain serotonin levels are lower in individuals who died during the night than in those who died during the day, and they are lower in individuals who died in winter than in those who died in summer.[63] Other studies on circadian rhythms have found changes in serotonin uptake in blood platelets and

in tryptophan levels in plasma and cerebrospinal fluid (CSF) that are indicative of reduced brain serotonin activity in the night, at least in healthy volunteers.[127,201,214,262,445] Conflicting results do exist but may be explained for example by methodological issues and by small sample sizes. Similarly, several though not all studies on seasonal rhythms have found changes in peripheral serotonin transporter binding, receptor binding and uptake, in the cortisol responses to meta-chlorophenylpiperazine (m-CPP), in plasma tryptophan levels, and in brain serotonin transporter availability.[120,137,151,221,260,308,384] Lambert *et al.* (2002) reported seasonal changes in whole brain serotonin turnover. Overall, these findings are indicative of reduced brain serotonin function in the dark half of the year.

Data suggesting a direct, time- and season-independent, influence of light exposure on human serotonin function are virtually non-existent. Visible light has the potential to directly increase serotonin synthesis and metabolism in humans, at least in human leukocytes in vitro.[137] In the study by Lambert *et al.* (2002), whole brain serotonin turnover measured in the morning correlated with higher sunlight levels on the day of the study.[236] In contrast, no such correlation was found with sunlight levels on the day before, nor were there associations between sunlight and the catecholamines.

2.3 Social behaviour in animals

Unicellular organisms sometimes group together to promote reproduction of some, at the expense of death to others.[86,274] Thus, while the price to individual cells may be high, the net outcome for the group does benefit the continued existence of the species. Intra-species interaction has been vital throughout evolution. Animals display a variety of social behaviours that may influence access to food (for survival) and mates (for reproduction). Due to individual differences, some animals within a group will have better access than others, thus resulting in a social hierarchy. In lower species such as crustaceans, fishes and lizards, hierarchy relationships are mainly determined by the amount of aggressive behaviour displayed during agonistic encounters.[200,324,439] Primates, however, have developed additional and more cost-effective means to acquire dominant status. Dominance is primarily obtained and

maintained through grooming, greeting, sharing and other behaviours that convey social affiliation, cooperation, and support.[94,95,129,341] Not surprisingly, dominant chimpanzees are more likely to have a personality high in extraversion and low in neuroticism.[425]

When aggression increases an animal's position in a social hierarchy, thereby improving access to resources required for ensuring the existence of future generations, it is usually considered an adaptive behaviour. Primates do occasionally use restrained aggression to ascertain their social position.[94] However, they are species living in large groups with complex social hierarchies, and, when displayed in an inappropriate social context, a display of aggression can also lead to a decrement of status.[56,95,340] This type of aggression is often impulsive, and generally considered maladaptive. Indeed, monkeys that display impulsive-aggressive behaviours and few affiliative behaviours are usually ranked lower in the group.[129,341] Not surprisingly, they gain less access to food, have fewer sexual opportunities during the mating season, are more likely to sustain injuries, and even die younger.[47,190,277]

Low brain serotonin has long been considered a marker and predictor of impulsive aggression.[74,358] Accordingly, serotonin has been described as a neurotransmitter involved in behavioural constraint.[104,383] This function of serotonin can be observed across animal species. Administering serotonin or its precursors to ants decreases their aggressiveness towards beetles.[226] Administering serotonergic drugs to rats will reduce their aggressiveness towards mice.[106,285] Administering tryptophan-supplemented diets to dogs may result in fewer displays of territorial aggression.[100] Serotonergic drugs also reduce aggressive acts in monkeys, which in the absence of the highest-ranking alpha male may in fact contribute to their attainment of dominance.[342]

Indeed the role of the serotonin system in establishing group hierarchies within species seems to be to stimulate rank-promoting behaviours. Paradoxically, these behaviours often do include aggression, especially in lower species. Serotonin and related drugs increase intraspecies aggressive behaviour in ants, agonistic encounters between pairs of crayfish and lobsters, dominance displays in

lizards, competitiveness in mice, and dominance aggression in dogs.[23,100,200,226,263] Importantly, however, in this case aggressive behaviour is considered instrumental and proactive rather than impulsive and reactive. This is illustrated by a study in monkeys in which 8-week tryptophan treatment resulted in an overall decrease in aggression, despite the fact that treated monkeys did become more aggressive toward their competitors near the end of the sequence of behavioural changes involved in dominance acquisition.[342] They were only able to do so with support from loyal others, who were more likely to show their cooperation after having received affiliative gestures, such as grooming and shared resources. Rather than simply controlling impulsive aggression, serotonin thus seems to influence social interaction in a more complex way, by regulating different types of behaviour that together may help with attaining a higher status over time. In monkeys this may be evident from observed links between brain serotonin function, affiliation, and rank,[189,276,340,343] but even in other species this might explain findings of links between brain serotonin and rank that cannot be explained by aggression alone.[238,373] Clearly serotonin plays an important role in the adaptive regulation of social interaction.

Chapter 3
HUMAN SOCIAL INTERACTION

3.1 Circumplex theory

The theory of human social interaction has its roots in personality research. Personality not only explains people's own behavioural patterns, but also elicits predictable behaviours from others in interpersonal events. Leary (1957) was the first to arrange social relations along a circle defined by two orthogonal main axes.[241] These two axes or domains have been referred to as "affiliation", "communion", "love", or "warmth", and "agency", "control", "power", or "status".[142,216,241,432] The communal domain conveys social attachment and the need to be interconnected with others, by means of group alliances, intimacy and trust. At the social interaction level it includes behaviours ranging from warm, friendly, and agreeable to cold, hostile, and quarrelsome. The agentic domain conveys social competition and the need for individual autonomy or superiority, by means of having influence and control over tasks and others. At the social interaction level it includes behaviours ranging from dominant, assertive, and active to submissive, hesitant, and passive.

Using this circumplex model, individual social behaviours can be defined by any combination of communion and agency. The two domains are independent such that people can behave in, for example, either a quarrelsome-dominant way or an agreeable-dominant way. Behaviours of one domain can be used to change the nature of a social relation on the other domain, for example both quarrelsome and agreeable behaviours may be used to become more dominant. According to Leary (1957), social adjustment is maximal when interpersonal behaviour is accurate and appropriate in response to an event, and flexible across events.[241] People usually behave in an agreeable-dominant way, a pattern often described as engaging, but in some interpersonal contexts other behavioural patterns may be more adaptive. Humans, unlike most other animals, occupy multiple hierarchical positions characterized by different goals that require different kinds of social relations.

The principle of complementarity posits that people, when interacting with others, define their social relations along the two domains defining the interpersonal

circumplex.[64,216] Quarrelsome behaviours tend to evoke quarrelsome or hostile relations and agreeable behaviours tend to evoke agreeable or friendly relations. In contrast, dominant behaviours often invite subordination and submissive behaviours invite domination. Most social interactions are recurring events with significant others. Therefore interpersonal behaviours and perceptions of others often influence each other in a cyclic manner. An individual's perceptions of others are usually considered adaptive when they are in agreement with those of the social group to which the individual belongs.[241]

3.2 Measurement

Social functioning is often assessed only globally, especially by those outside the field of social psychology. DSM-IV-based psychiatric diagnosis of a mental disorder, apart from the requirement that symptoms must cause impairment in daily life, includes a Global Assessment of Functioning scale on which social, psychological, and occupational functioning are rated together using a number between 1 and 100. Similarly, coding of socioeconomic and psychosocial circumstances according to the ICD-10 is based on an overall indication only. Patient perspectives of social functioning, and the effect of antidepressant medication, have been assessed using the Social Adaptation Self-evaluation Scale and other self-report measures,[41,42,426] but again these questionnaires are limited to general questions about motivation and behaviour in social settings.

Other approaches used in the measurement of social motivation and behaviour, in patients as well as in healthy populations, include a variety of personality questionnaires and standardized laboratory tests. Many originated from research on aggression. For example, the Buss-Durkee Hostility Inventory (BDHI)[54] and the Buss-Perry Aggression Questionnaire [55] were designed to measure aspects of aggressive disposition. The Competitive Reaction Time Task and the Point Subtraction Aggression Paradigm are laboratory tests designed to measure aggressive reactions to provocation.[69,397] Questionnaires that assess social aspects of personality more broadly are more recent and include for example the Inventory of Interpersonal Problems and the Interpersonal Adjective Scales (which are based on

Leary's circumplex model).[198,433] More recent laboratory-based social skills tests include facial emotion recognition as a measure of social perception and mixed-motive games as a measure of social bonding.[223,407]

The measurement of specific aspects of human social interactions in daily life has long been limited by their inherent characteristics. Behaviours, perceptions, and cognitions are likely to vary depending on the gender, age, and role of the other(s), the time and location of the social interaction, et cetera. A person's mood at the time of the social interaction, which itself might be influenced by the interaction as well as by a variety of other stimuli, may constitute an additional factor. Laboratory measures include standardized questionnaires and psychological skills tests. Questionnaires are limited to processes of which respondents are aware, tend to focus only on how people interact with others in general, and are likely to elicit biased responses due to the cognitive processes that are known to distort information recalled from memory. This latter limitation also applies to diary studies. In laboratory skills tests the variable of interest is often studied under highly controlled conditions in a limited number of possible situations such that it may have limited face validity. Only with multiple and frequent momentary recordings in naturalistic settings can conclusions be drawn about how people interact in daily life.

Ecological momentary assessment (EMA), also known as experience sampling, fulfils these requirements.[88,270,291,390,431] EMA allows for the collection of repeated measurements as they occur in people's own environments. Since these measurements are not made retrospectively, the bias in self-report that is often seen when people recollect past experiences can be minimized. Moreover, given that data collection occurs under natural circumstances, EMA is thought to represent the dynamic individual better than laboratory testing would.[390] This is especially true for events in which he or she could be affected by the environment. EMA involves prompting participants to record the variables of interest at certain predetermined times during the day, as opposed to times selected by the participants (who might be likely to favour certain times over others and thereby render the recordings unrepresentative).[88]

Variations of EMA include time-contingent, signal-contingent and event-contingent recording.[431] In time-contingent recording studies, the prompts that inform participants to record information are pre-determined clock times. In signal-contingent recording studies, the prompts are external signals, usually delivered to the participants by means of a paging device. In event-contingent studies, the prompts are the repeated occurrences of the event of interest. An advantage of signal-contingent recording and event-contingent recording over time-contingent recording is that time intervals can be irregular and even random. An additional advantage of event-contingent recording over signal-contingent recording is that retrospective bias can be avoided altogether. This is especially useful if the event of interest occurs with long and irregular intervals. Also, it may be somewhat less intrusive, which is important especially since EMA usually involves a substantial number of repeated events to ensure more reliable samples of the variable of interest.

Despite its advantages over more traditional methods, EMA in general and event-contingent recording in particular have the disadvantage of generating data that require advanced statistical analysis.[390] In event-contingent recording, not only are data collected across unequally spaced time intervals across multiple days, but also the number of records is likely to vary per day and per person. Analysis at the person-level (*i.e.* based on aggregated means) is useful for descriptive purposes but results in significant loss of information. Similarly, the use of general linear modeling for analysing event-level effects (*i.e.* based on individual social interactions) would necessitate the exclusion of large amounts of data. In contrast, hierarchical linear modeling, also known as mixed or multilevel modeling, allows for the unbiased assessment of between-people differences, of within-people differences among events that are similar across people, and of between-people variations of within-people differences, all at the level of the event. This is important because the impact of the event on the person is variable.[391] EMA is useful for investigating complex natural phenomena, but the associated analytic complexities must be taken into account before deciding to use this approach.

3.3 Event-contingent recording

To sample human social interactions from everyday life, Studies 1 and 3 of this Doctoral Thesis used the event-contingent recording method developed by Moskowitz and collaborators.[51,85,291,294,297] It allows for the examination of social interactions outside the laboratory, in different contexts, on multiple occasions, and over prolonged periods of time. The method is sensitive to psychopharmacological intervention.[294] The previously demonstrated reliability and validity of this method make it an ideal measure for the concurrent measurement of different aspects of social interactions that are typical of everyday life.

The method focused on behaviours, affect, and perceptions of others in the context of social interactions as they occurred during the day. Behaviours were measured using the Social Behaviour Inventory (SBI), which consists of a list of quarrelsome, agreeable, dominant and submissive behaviours.[291] The SBI has been tested for construct validity of the four scales, for inter-item reliability and for stability of scale scores across days and across situations. Factors that reliably predicted levels of behaviour in past event-contingent recording studies have included personality traits, gender, social role of the other, time of the day, and day of the week.[51,85,291,292,295]

Within the same interpersonal context, affect valence was measured using a list of positive and negative affect items.[108] While positive and negative affect are correlated on single occasions of measurement, the two poles are generally independent when measurements are aggregated over long time periods,[108,239,293,422] both within and between situations.[161] Indeed, positive and negative affect can change independently from each other in response to pharmacological treatments.[147] Factors that reliably predict levels of positive affect include extraverted personality, trait-congruent behaviours, and home settings. Factors that reliably predict levels of negative affect include neurotic personality, trait-incongruent behaviours, and work settings.[85,293]

Affect was also measured using an Affect Grid, designed after the work of Russell (1980) to provide a simple yet effective instrument to summarize current mood on multiple occasions using a circumplex structure.[361] It assesses affect on

two orthogonal dimensions, valence and arousal, with valence measured along a bipolar axis ranging from unpleasant to pleasant, and arousal measured along a bipolar axis ranging from sleepy to alert.[237,362] The Affect Grid has been tested for different components of validity and for stability across time.[217,362] With one exception it has not been used in event-contingent recording studies.[294] Feldman Barrett and Russell (1999) have suggested that a series of scales, each with a different format, should be used when measuring affect.[132] The Affect Grid was included in Studies 1 and 3 because the factors of interest (tryptophan treatment and bright light exposure) were deemed likely to have an impact on arousal that could confound a possible effect on affect as measured using the list of positive and negative affect items alone.

Perceptions of others were measured using an Interpersonal Grid.[297] Based on the circumplex model of social behaviours, it can be used to assess perceptions of others along the two orthogonal dimensions of the model, communion and agency, with communion measured along a bipolar axis ranging from quarrelsome to agreeable, and agency measured along a bipolar axis ranging from submissive to dominant. Preliminary data suggest that levels of perceived communion and agency measured using the Interpersonal Grid are reliable and valid, especially when used for multiple assessments by and of the same person.[297] The measurement of perceptions of others provides a means to assess the interpretation of others' verbal and nonverbal behaviours (including facial expression, voice intonation, posture, and hand movements), signals that people normally use to predict the intentions of others over short as well as longer time periods. Given the obvious evolutionary survival value of accurate social perception skills, it is not surprising that people can rate even strangers with good accuracy.[223,421] People's behaviours are usually influenced by their perceptions of others in a complementary manner.[68]

3.4 The role of serotonin

There is substantial support for the idea that serotonin may modulate aggression in humans as it does in other species (see Chapters 2 and 4). However, this is mostly based on patient data; the number of studies done in healthy individuals is relatively

small. Men who report high levels of hostility and impulsive aggression tend to have lower CSF levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) and blunted fenfluramine responses.[71,265,357] In one study in healthy volunteers of both genders, administration of paroxetine, a selective serotonin reuptake inhibitor (SSRI), resulted in a decrease in subjective hostility scores.[224] Moreover, tryptophan supplementation can decrease aggressive feelings and behaviours in both men and women, whereas ATD may increase these, at least in laboratory settings.[32,38,70,268,440,441]

Beyond aggression, human experimental data on the role of serotonin in social behaviours are scarce. Tranter *et al.* (2002) administered a global social functioning scale in healthy volunteers treated for two weeks with the SSRI, sertraline.[403] Treatment increased scale scores without affecting mood, which suggests that the effects of serotonin on mood and social behaviour can be dissociated. A limited number of studies in healthy volunteers have used laboratory tests to study the effects of SSRI-induced changes in serotonin function on specific social behaviours. One study looked at the effects of four weeks of treatment with another SSRI, paroxetine, on affiliative behaviour expressed during a standardized dyadic puzzle task.[224] Pairs of paroxetine-treated and placebo-treated participants were instructed to solve spatial puzzles together. Treatment increased the frequency of cooperative behaviours in paroxetine-treated participants. In another study, following two weeks of treatment with yet another SSRI, citalopram, participants behaved more cooperatively during a mixed-motive game.[406] If SSRI treatment enhances social cooperation, then it may not be surprising that ATD reduces it.[447]

Other studies have looked at the role of serotonin in the processing of social cues, a crucial element in adaptive social interaction. Facial expressions, for example, provide information concerning the internal emotional states and intentions of interaction partners and are therefore very important in social cognition and communication. An acute reduction in brain serotonin induced by ATD decreases the processing of fearful faces in healthy women.[175] ATD may do so by increasing amygdala activation in response to a fearful face, which then interferes with the

required behavioural response.[82] This effect may be trait-dependent, for example Cools *et al.* (2005) found it to be modulated by individual threat sensitivity (assessed using a personality questionnaire).[82] Based on observations by Hariri *et al.* (2002), one might speculate that the genetic factor underlying this modulation may exist at the level of the serotonin system.[170]

The efficiency with which healthy women detect facial expressions of happiness can be increased by given them an acute dose of either tryptophan or citalopram.[16,171] In other words, an increase in serotonin function may enhance the perception of affiliative signals. It might even introduce a positive perception bias, given that Harmer *et al.* (2004) found that negative facial expressions tended to be misclassified as happy when citalopram was given for multiple days.[176] Indeed, while an acute increase in serotonin enhances the recognition of fearful expressions,[16,171] a more prolonged stimulation of the serotonin system impairs fear and disgust recognition.[176,302] It also reduces the amygdala's response to these threat stimuli.[174] Together, these data obtained by augmenting brain serotonin might be interpreted as reflecting an acute increase in empathic feelings and social attachment towards another, and the facilitation of approach behaviour over time.

While the experimental data summarized here provide useful information about the role of serotonin in some aspects of social interaction, it is clear that their relevance to everyday life can only be discussed by means of extrapolation from the laboratory settings in which they were measured. In a small number of recent studies, indices of serotonin function were associated with daily ratings of mood.[113,141,436] Using a time-contingent recording method for 5 days, positive but not negative mood was associated with whole-blood serotonin levels in both healthy men and healthy postmenopausal women.[113,436] Using a signal-contingent recording method in a large sample of adults of various ages, Flory *et al.* (2004) observed a positive relation between positive mood and the neuroendocrine response to fenfluramine that was independent of personality and a variety of other possible confounders. No such relation was found between negative mood and the fenfluramine response.[141] These studies provide some insight in the role of serotonin in everyday mood. However, despite the existence of EMA and related

methodologies, until recently no data were available on the role of serotonin in other aspects of everyday life, including social interactions. The one exception, which provided an important basis for this Doctoral Thesis, will be discussed in Chapter 5.[294]

Chapter 4
MOOD DISORDERS

4.1 Serotonergic abnormalities

The idea that abnormalities in the brain serotonin system underlie the symptoms associated with mood disorders has its origins in the monoamine theory of depression that emerged in the 1950s following reports of reserpine-induced mood lowering and anxiety.[192] Measurements of serotonergic markers in CSF confirmed that brain serotonin turnover might be reduced, at least some patients.[14,355] Neuroendocrine responses to fenfluramine and to m-CPP were also found to be blunted when compared to those of healthy controls.[72,79,250] Further, abnormalities in serotonergic brain areas indicative of reduced activity during depressed episodes have been reported on the basis of brain imaging studies.[348,364,435]

Impulsive-aggressive behaviour is often seen as a result of mood dysregulation. Not surprisingly, there are similarities between serotonergic abnormalities seen in depressed patients and those in patients with aggression problems. In the latter group, low CSF 5-HIAA levels and blunted neuroendocrine responses to fenfluramine and to m-CPP are also common.[50,74,228,258,298,382,417] Moreover, the serotonergic abnormalities seen with imaging show anatomical overlap with those of depressed patients.[146,254,313,320]

ATD has been used to experimentally induce mood lowering in patients with mood disorders. Individuals with major depressive disorder in remission following antidepressant treatment were found to experience a brief relapse following ATD.[97] This mood response was most likely to occur if the patients had improved with SSRIs.[40,98] In contrast, no effect of ATD on mood was seen in untreated currently depressed patients.[99] Similarly, ATD has been shown to elicit a partial relapse of symptoms in groups of patients with seasonal affective disorder (SAD) in remission but not result in a further worsening of mood in those who were symptomatic.[309-311] These findings have had implications for the serotonin theory of mood disorders because they led some to suggest that changes in brain serotonin may be more closely associated with treatment than with the underlying pathogenesis. On the

other hand, a recent study by Booij *et al.* (2005) has provided evidence for the idea that the serotonin system may constitute a mood regulator which only after a sufficient depletion crosses a threshold and results in depressive symptoms, the magnitude of which is then independent of further depletion.[29,39,97]

4.2 Social impairments

Using a time-contingent daily diary known as the Rochester Interaction Record, Nezlek *et al.* (2000) found that depressed patients reported less enjoyment during their daily social interactions, and felt less close to others, compared to non-depressed individuals.[314] In a recent event-contingent recording study by Russell *et al.* (accepted), patients with borderline personality disorder experienced more unpleasant affect, and more variability in pleasant affect, during social interactions.[363] Abnormal emotional responses to external stimuli, including social situations, are characteristic of mood disorders. Anhedonia and irritability may contribute to inappropriate social behaviours and perceptual and cognitive biases, and these in turn may perpetuate the mood disturbance. The DSM-IV requires the presence of either depressed mood or loss of interest in daily activities as primary qualifying symptoms for a diagnosis of major depression. However, studies on affective symptoms are much more common than studies on behavioural symptoms.

At the social behavioural level, depressed patients avoid eye contact with their interaction partner, they speak slowly and softly, gesticulate little, and have few positive facial expressions, even when interacting with their psychiatrist.[404,455] In one laboratory study, individuals suffering from depression were less likely to cooperate during a mixed-motive game, even though they would have been more likely to receive a positive response if they had been cooperative.[197] Depressed patients, especially those with comorbid borderline personality disorder, consider themselves hostile and report frequent anger attacks.[131,388] The event-contingent recording study by Russell *et al.* (accepted) also found that borderline personality disorder patients report higher levels of quarrelsome and agentic behaviours during social interactions than individuals without any mood disorders.[363] However, similar behavioural studies have not been done in depressed patients.

In terms of social perceptual changes during depression, patients are more likely to report that they receive negative responses in interpersonal situations than healthy controls.[455] Given that patients with mood disorders tend to misinterpret pictures of facial emotions, this may constitute a perceptual bias.[43,172,279] In a recent signal-contingent recording study patients with borderline personality disorder tended to underestimate positive emotions and overestimate negative emotions during retrospective assessment as compared to momentary assessment.[119] These negative perceptions may have been partially a reflection of a perceptual bias,[195] but also partially a reflection of the actual behaviours of others: in a study of students' perceptions of their flatmates' behaviours, when the students were depressed and reported negative perceptions of their flatmates, their flatmates did indeed report higher levels of hostile behaviours towards the depressed students.[196]

Depressed patients also evaluate their own behaviours in social interactions as more negative.[193] These negative cognitions may be related to fear of rejection or exclusion by others and might even explain suicidal ideation, at least in depressed adolescents.[336] Negative thinking styles that persist beyond depressive episodes may be reactivated during acute dysphoria and thereby contribute to relapse.[369] For example, in SAD patients who were studied from before symptom onset until remission, low self-esteem and poor subjective social support in autumn accelerated the onset of depression in winter.[271]

Despite the existence of data in patients with mood problems that are indicative of behavioural, perceptual and cognitive abnormalities in the context of social interactions, these are often based on laboratory-based measures administered on a restricted number of occasions. This limits their generalization across situations and to everyday life. Investigations that take place outside the laboratory have mostly focused on mood alone. However, research on mood disorders must integrate different aspects of human social interaction when exploring their interpersonal origins.

4.3 Social-evolutionary theories of depression

Observations of social behavioural, perceptual, and cognitive impairments in patients with mood disorders are consistent with several theories that explain the possible evolutionary origin of depressed mood (with clinical depression as an extreme) in the context of interpersonal processes. A recent review by Gilbert (2006) summarizes two evolutionary theories of depression in which the loss of control over events in the social environment is central.[157] The first theory focuses on loss in the context of hierarchical relations.[158] Individuals are very motivated to increase their position in society. Social competition is an important process in everyday life. However, conflict situations usually do not escalate because "losers" will voluntarily resign and reconcile with "winners"; this is less costly than persisting in the conflict.[334] Pervasive low mood may be the result of involuntary defeat in conflict situations.[335] This theory may explain why low self-esteem and worthlessness are common in depression and can even predict future depressive episodes.[271,325,372] This may be especially true in men.[5,213] Low self-esteem has also been associated with higher levels of hostility and with suicide risk.[134,230]

The second theory focuses on loss in the context of affiliative relations.[44] People are also very motivated to form interpersonal bonds, and will usually break these bonds only with much difficulty, especially those with romantic partners, relatives, and close friends.[22] The signs of distress that are seen with the loss of a close bond (*e.g.*, crying) will usually elicit comforting behaviours from others. Pervasive low mood may be the result of a lost bond of which the distress that it causes on the individual is not alleviated by their bonds with others.[44,157] Women may be more prone to depression in response to perceived threats to their close bonds with others than men,[5,213] although men are at elevated risk for depression after losing their romantic partner through separation or death.[5,213]

These social competition and social attachment theories of depression are not necessarily mutually exclusive. In both scenarios people feel excluded from their social networks. In reference to Leary's circumplex model of interpersonal relations, they feel threatened in one of the two domains, agency or communion. Their initial response may be to display aggression (or quarrelsomeness). Yet a more adaptive

response to threat may be to show defeat (or submissiveness) or distress (which may evoke agreeableness in others). These signals may be more likely to evoke social inclusion and acceptance.[156,335] Nonetheless, when these behaviours endure, or are not adequately responded to by others, a depressed state may result. The affective, perceptual, and cognitive processes associated with the development of this state may become self-perpetuating, thus adding to the chronicity of the depressed mood.[7,156]

Overall, it may be concluded that social processes play a critical role in the formation of different mood states. If depression is often precipitated by interpersonal events, then the overall improvement of social functioning may prevent depression.[9]

4.4 Pharmacotherapy, phototherapy, and effects on social functioning

The serotonin precursors tryptophan and 5-hydroxytryptophan have been used to treat mild to moderate depression.[83,280] Tryptophan is considered less effective than standard antidepressant medication in more severe cases of depression.[453] Other serotonergic drugs, most notably the SSRIs, tricyclics, and monoamine oxidase inhibitors, are prescribed more often and for a wider variety of mood disorders.[192] Depressed patients treated with a combination of tryptophan and an SSRI may show mood improvement faster than those treated with an SSRI alone.[251]

When treating depression, especially the winter type associated with SAD, bright light is an accepted alternative to antidepressant drugs.[353,396] Its benefit in patients with SAD is comparable to that of pharmacotherapy and at least approaches that of the natural increase in bright light levels associated with the lengthening of days in spring and summer.[155,160,233,333,360,443] Phototherapy is also efficacious in treating non-seasonal depression.[160,412] In addition, it has been used to reduce winter binges in women with bulimia and to treat irritability in women with premenstrual dysphoria.[46,232] In summary, bright light may have mood-regulating potential across a variety of psychiatric disorders.

Treatment efficacy in clinical trials of antidepressant therapies is usually based primarily on standardized clinician-rated mood scales. The use of secondary

patient-rated mood scales is less common. Only occasionally is patients' functioning in everyday life assessed, either through clinician ratings or patient ratings.[181,296] This is surprising given that (1) social impairments are common in patients with mood disorders, (2) subjective improvement may be necessary, in addition to improvement as observed by others, for sustained benefit, and (3) actual social behavioural change is more likely to reflect long-term adaptation to normal everyday life and may help prevent future relapse. In a retrospective study, formerly depressed patients whose mood had improved on SSRIs reported that the treatment had also made them less irritable and ruminative.[11] SSRIs can also reduce feelings of irritability and anger in personality-disordered patients with a history of aggression.[37] These changes may positively affect patients' appreciation of their environment,[112,416] their actions toward other people, and others' reactions toward them. The effects of antidepressant therapy on social functioning, as opposed to their effects on mood alone, may be especially relevant to long-term outcome. Nevertheless, from the above studies it cannot be determined if the changes in social functioning were simply the result of concurrent changes in mood.

4.5 Studies in at-risk populations

An advantage of researching the links between the different factors that may be involved in the aetiology of mood disorders in healthy individuals at risk rather than in patients with a diagnosis is the absence of a mood problem in the former group at the time of study. A variety of biological and psychological traits may predispose certain populations to future illness. For example, it is well-known that people with a family history of mood disorders are more likely to develop a mood disorder than those without such a family history.[134,427] This genetic loading has low diagnostic specificity.[8] There is evidence that a familial risk for mood disorders may be transmitted via the serotonin system. In one fenfluramine challenge study, personality disordered patients were more likely to have a relative with cluster B personality disorder if the neuroendocrine response to fenfluramine was lower.[77] Having a family history of mood and personality disorders also results in a larger mood response following ATD in remitted patients with major depression.[253]

This serotonin-mediated vulnerability has been extended to unaffected relatives of patients with mood disorders. Healthy volunteers are also more vulnerable to ATD-induced mood lowering if a family history of major depression is present.[30,220] In a recent study in healthy women with a family history of depression, the magnitude of the ATD-induced mood effect was correlated with poorer recognition of negative emotions in faces.[415] This may explain why transient low mood may induce more permanent perceptual changes especially in individuals at risk, such that it may be harmful in the long run. In further support of a serotonin-mediated genetic susceptibility, Neumeister *et al.* (2002) found that being heterozygotic for the shorter variant or s-allele of the serotonin transporter length promoter region (5-HTTLPR) predicted the magnitude of the mood response to ATD in women with a family history of depression.[307] The 5-HTTLPR polymorphism is known to affect functional serotonin transporter expression and has repeatedly been associated with individual differences in impulsive-aggressive personality traits, such as neuroticism and angry hostility.[162,165,184,248] These traits may indeed mediate the association between the 5-HTTLPR polymorphism and the risk for mood disorders.[170,301]

Healthy men with higher levels of neuroticism and angry hostility may show a blunted neuroendocrine response to fenfluramine independently of family history.[264] Compared to men without these impulsive-aggressive traits, they are also more prone to show changes in aggressive feelings and behaviours in response to changes in brain serotonin levels induced by tryptophan supplementation or by ATD.[33,70,110,136,440] This has also been found in women.[38,268] Stewart *et al.* (2002) could not confirm that neuroticism might also increase the mood response to ATD, but their sample may have primarily included anxious as opposed to hostile individuals.[389] Both facets are part of the neuroticism trait.

Neurotic individuals are also more likely to report seasonal changes in their mood and behaviour.[124,304] According to a study in twins, the overlap between the two traits, neuroticism and seasonality, is best explained by common genetic factors.[206] If SAD patients are more likely to possess the s-allele of the 5-HTTLPR polymorphism than healthy controls,[350] then this suggests that the genetic variability

underlying individual differences in neuroticism and seasonality may be present at the level of the serotonin system. An association between higher seasonality and having the s-allele of the 5-HTTLPR polymorphism has also been found in people without SAD.[375] If individuals who possess a less active form of the serotonin transporter gene are more sensitive to reductions in brain serotonin synthesis, then this may explain why they show a more pronounced lowering of mood and reduction of social activity in winter.

Chapter 5
RATIONALE

In 2001, Moskowitz *et al.* published a study that described the effect of 12 days of tryptophan administration on social behaviours and affect in healthy working people, measured during the event-contingent recording of everyday social interactions.[294] When participants were taking tryptophan, they reported less quarrelsome behaviours and more dominant behaviours. Mean levels of affect did not change, in other words there was no change in mood.

These findings are in line with studies in monkeys. When tryptophan is supplemented to their diet, monkeys display lower levels of aggression.[67,337] Moreover, tryptophan supplementation has been shown to help monkeys obtain dominant status in unstable group hierarchies.[342] They may do so by means of alliance building, and indeed tryptophan supplementation has been to increase grooming and other affiliative behaviours.[338]

There is one major difference between the observations in monkeys and those obtained by Moskowitz *et al.* (2001) in humans. In the humans studied no active increase in affiliation was seen, in other words levels of agreeable behaviours did not change when participants were taking tryptophan.[294] This was not expected. However, it should be noted that normal healthy people generally display high levels of agreeable behaviours, and so tryptophan might have been unable to increase these even further due to a ceiling effect. It is conceivable that tryptophan might have increased levels of agreeable behaviours had they been lower in the first place. Thus, Study 1 was designed to extend the findings by Moskowitz *et al.* (2001) by selecting participants based on their lower levels of agreeable behaviours at baseline. Individuals with mood disorders may constitute one such group. However, tryptophan administration during an episode of depression might be expected to result in overt mood improvement. Not only would this then likely be responsible for subsequent behavioural changes, but also these behavioural changes might no longer occur outside participants' awareness, as was observed by Moskowitz *et al.* (2001).

An alternative is the study of healthy individuals whose personality may be described as being neurotic, who may be expected to have lower levels of agreeable behaviour in the absence of clinical depression.[85] The neuroticism trait has been described as the tendency to experience intense emotions in ordinary situations, and to interpret these situations as negative. Not surprisingly, neurotic individuals report high levels of unpleasant affect during social interactions.[85] They are often referred to as being irritable and indeed display higher levels of quarrelsome behaviours.[85] While not currently depressed, people high in neuroticism are at risk for a variety of mood disorders, including major depression. The underlying neurobiology is thought to include a role for serotonin.[301] Therefore, Study 1 included a group of healthy but irritable people.

The decrease in quarrelsome behaviours observed by Moskowitz *et al.* (2001) was observed only in participants who received tryptophan during the second half of the study. In other words, there was an effect of treatment order.[294] It appeared that tryptophan had no effect in participants who received tryptophan during the first half of the study. However, it is possible that tryptophan treatment did decrease quarrelsome behaviours in these participants, and that levels then remained low during the subsequent placebo period. Such an explanation is possible if one keeps in mind the interactive cycle that constitutes a series of social interactions. If a person consistently displays lower levels of quarrelsome behaviours as a result of taking tryptophan over multiple days, then the people with whom he or she interacts on a regular basis may ultimately also change their behaviours towards him or her. This may in turn help reduce quarrelsome behaviours even further, and it may provide a basis for long-term changes in social behaviour that would last longer than the actual tryptophan treatment. Study 1 explored this idea by adding a measure of perceptions of others to the social interaction record forms. While this does not provide a measure of actual behavioural changes in others, it might provide some insight as to whether these kinds of changes did occur.

In summary, the following hypotheses were formulated for Study 1:

1.1 Tryptophan administration will decrease levels of quarrelsome behaviours as well as increase levels of agreeable behaviours.

1.2 Tryptophan administration will improve perceptions of others.

1.3 Tryptophan administration will improve mood.

1.4 Tryptophan administration will increase levels of dominant behaviours.

An increase in brain serotonin levels can be induced by tryptophan administration as well as by numerous other psychopharmacological compounds, including for example the SSRIs. On the other hand, relatively little is known about the environmental variables that might affect the brain serotonin system in humans. As described in Chapter 2, one variable thought to have an effect on serotonin is bright light. For example, brain serotonin levels show circadian and circannual rhythms that appear to be related to daily and seasonal variations in light levels. Most representative for explaining the rationale behind Studies 2 and 3 is a recent report in Lancet, which found that human brain serotonin turnover was not only lower in winter compared to summer, but also varied with the level of sunlight reported on test days.[236] This study highlights the idea that light may affect the serotonin system fairly rapidly.

If bright light directly affects brain serotonin levels, as does tryptophan administration, then bright light would be expected to have effects on social behaviour and mood similar to those of tryptophan administration. Moreover, if the effect of bright light on serotonin is indeed relatively quick, then exposure would lead to changes in social interaction over short time periods. Studies in patients with SAD as well as in healthy but mildly seasonal people have confirmed that bright light has a positive effect on mood over long time periods, in the range of days to weeks.[160,246] However, several questions remain. First, does bright light interact directly with the brain serotonin system when regulating mood? Second, can bright light also affect mood over short time periods, such as a couple of hours? Third, do the effects of bright light also include changes in social behaviour? These questions were addressed in Studies 2 and 3.

A role for serotonin in the therapeutic action of bright light has been suggested by two studies in which SAD patients in remission following phototherapy showed a brief worsening of mood during ATD.[235,309] However, in these studies serotonin levels were not manipulated at the time of the bright light exposure, so it remains possible that the alleviation of depression caused by the light therapy did not include serotonergic mechanisms. It would thus be of interest to expose individuals to bright light whilst undergoing the ATD procedure. If bright light does indeed regulate mood by interacting with the brain serotonin system, then an attenuation of ATD-induced mood lowering might be expected when participants are exposed to bright, as opposed to dim, light. Study 2 explored this possibility. Two groups of participants were exposed to either bright light or dim light during test days. Participants were healthy but mildly seasonal and hence considered sensitive to the effects of bright light on mood.[246] People with a (family) history of depression were excluded to insure that any mood change following ATD in dim light could be attributed to the lack of bright light rather than to this depression (family) history. Dependent variables included mood scales as well as side effects ratings to exclude the possibility that side effects commonly seen in ATD studies would be causing the changes in mood.

For Study 2, the following hypotheses were formulated:

2.1 ATD will result in a lowering of mood that will be attenuated in participants exposed to bright light during test days compared to participants exposed to dim light during test days.

2.2 Side effects following ATD will be less pronounced in participants exposed to bright light compared to those exposed to dim light.

Study 2 involved bright light exposure for only a couple of hours during test days in the laboratory. Confirmation of the hypotheses would strengthen the idea that the effects of bright light on mood regulation do indeed occur fairly quickly, presumably through rapid changes in brain serotonin. However, it would also be necessary to confirm these putative effects of short-term bright light exposure on mood in a more naturalistic setting. An event-contingent recording study provides this option, and also permits exploration of bright light's effects on social behaviours

and perceptions of others. This idea was the basis for Study 3. A non-experimental design was employed, in which wrist-worn light meters were used to measure natural bright light levels. An advantage of this approach was that associations between bright light exposure and social interaction variables could be tested over short time periods.

The following hypotheses were formulated for Study 3:

3.1 Bright light exposure, measured over short time periods, will be associated with lower levels of quarrelsomeness and higher levels of agreeableness.

3.2 Bright light exposure, measured over short time periods, will be associated with better mood.

3.3 Bright light exposure, measured over short time periods, will be associated with more positive perceptions of others.

In summary, the rationale behind Studies 1-3 was to provide more insight in the role of serotonin and bright light in the regulation of human social interaction and everyday mood.

Chapter 6

SOCIAL BEHAVIOUR AND MOOD IN EVERYDAY LIFE: THE EFFECTS OF TRYPTOPHAN IN QUARRELSOME INDIVIDUALS (Study 1)

aan het Rot M, Moskowitz DS, Pinard G, Young SN (2006). *J Psychiatry Neurosci* 31, 253-262.

6.1 Abstract

We hypothesized that increasing brain serotonin in healthy individuals with high scores on two self-report measures of trait quarrelsomeness would reduce quarrelsome behaviours and enhance agreeable behaviours when measured ecologically using an event-contingent recording method. We conducted a double-blind crossover study, in which participants took tryptophan (3 gram/day) and placebo for 15 days each and recorded how they behaved, felt and perceived others during everyday social interactions. Tryptophan significantly decreased quarrelsome behaviours and increased agreeable behaviours and perceptions of agreeableness. Men also behaved less dominantly, whereas both men and women perceived others as more dominant. Tryptophan's effects on behaviours and perceptions, while more marked in the men, were generally positive and accompanied by improved affect. Increasing serotonin in quarrelsome people may not only reduce behaviours associated with a predisposition to various mental and physical disorders but also enhance socially constructive behaviours and improve social perceptions.

6.2 Introduction

In monkeys and in humans, levels of various markers of brain serotonin function are negatively associated with impulsive aggression.[49,71,189,191,275] For example, in monkeys low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) predict impulsive-aggressive behaviour and early mortality.[190,429] In humans, this serotonergic marker is associated with aggression, as well as with suicide.[49] Moreover, impulsive-aggressive behaviour can be elicited by decreasing serotonin

experimentally.[38,67,339,378] Conversely, serotonin-enhancing drugs can decrease inappropriate aggression.[67,75,287] Serotonin seems to play a different role in regulating aggression that is used to increase dominance. This is particularly evident in evolutionarily older species such as ants, crayfish and lobsters, in which serotonin-enhancing drugs have been shown to increase aggression during agonistic encounters.[200,226,259] A similar positive relation between serotonin function and dominance-related aggression has been observed in at least one species of monkey.[450] However, in other monkey species, subordinate group members treated with serotonin-enhancing drugs often achieve dominance by first increasing affiliative behaviours toward group members, thereby creating social support, and only then engaging in aggressive encounters with competitors.[342] High serotonin function has been linked to both social status and levels of affiliation.[189,276,340,343] Affiliative behaviour in primates may be a more cost-effective means to establish dominance relationships.

These and other data suggest that the human serotonin system may not only inhibit maladaptive behaviours but also promote socially constructive behaviours. Given the importance of good social functioning for mental well-being and physical health, it is surprising how little information is available concerning the role of serotonin in human social interactions. Only the serotonin-aggression relation has been studied in both patients [75] and healthy individuals.[38,378] A few volunteer studies have looked at the role of serotonin in other social behaviours. The findings are generally in agreement with data from studies of monkeys and show that serotonin may indeed enhance human affiliation and promote social dominance.[224,406] However, measurements were generally limited to standardized social interactions, laboratory settings and single observations. In contrast, Moskowitz *et al.* (2001) used an event-contingent recording method to study the effects of a serotonergic manipulation on people's social behaviours during social interactions in their everyday lives.[294] Twelve days of tryptophan supplementation resulted in a decrease in quarrelsome behaviours and an increase in dominant behaviours. There were no changes in agreeable behaviours, submissive behaviours and experienced affect.

The present research, using the same event-contingent recording method and tryptophan treatment, aimed to confirm that tryptophan can decrease quarrelsome behaviour and to extend these findings in a group of people with high trait levels of quarrelsomeness. Individuals who are quarrelsome during everyday social interactions are not only prone to impulsive-aggressive behaviour in more extreme situations but also are at risk for depression, suicide, hypertension and heart disease.[81,404,437,448] Given that in laboratory settings the effects of changed availability of tryptophan on aggression are more pronounced in people with higher self-reported quarrelsomeness,[33,70,136] we expected that the effects of tryptophan in quarrelsome individuals in everyday life would not only include a decrease in quarrelsomeness and an increase in dominance, but also an increase in agreeableness.

Another goal of this study was to further examine the range of effects of tryptophan. Given the reciprocal nature of social interactions, a behavioural change in one person is likely to elicit a behavioural change in others. In our previous study, tryptophan decreased quarrelsome behaviours in individuals who received tryptophan second, but not in those who received tryptophan first.[294] We then suggested that a decrease in quarrelsomeness in individuals who received tryptophan in the first treatment phase might have carried over into future social interactions in the subsequent placebo phase, if there was also a change in the behaviour of participants' interaction partners. Two steps were taken to provide a more rigorous test of whether the order effect was the result of a pharmacological carryover or of a change in behaviour in response to changed perceptions of others. The washout between the study phases was increased from 2 to 6 days. In addition, participants in the present study also rated the behaviour of their interaction partners to examine whether there was a perceived change in the behaviour of others. Specifically, it was expected that tryptophan would increase perceptions of agreeableness.

6.3 Methods

Participants

The study was approved by the Research Ethics Board of the McGill University Health Centre, Montreal. All participants signed a consent form after the nature of the study had been explained to them. They received monetary compensation for time spent. The study was carried out in accordance with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[61] Participants were recruited via advertisements in local newspapers. Requirements for study participation were the following: working at least 30 hours per week, a high score on two questionnaires related to trait quarrelsomeness (see below), absence of current depression and alcoholism, absence of current major medical illness, and no contraindication for the use of tryptophan as mentioned in the product monograph. In Canada, tryptophan is a prescription drug. Advertisements used to recruit participants included the following statements: Do you have problems with irritability?; Do you repeatedly lose control of your temper?; and Do you get easily agitated? People who telephoned in response to the advertisements were given a brief explanation of the study. Those who were interested in participating were asked about their eligibility. Those who qualified were invited for screening.

In the laboratory, the study was explained in detail. Informed consent was then obtained, and participants completed the Beck Depression Inventory (BDI),[26] the Short Michigan Alcoholism Screening Test (SMAST),[370] the Buss-Durkee Hostility Inventory (BDHI),[54] and an adapted version of the NEO Five-Factor Inventory that included the entire Angry Hostility subscale of the Revised NEO Personality Inventory (NEO-PI-R).[84] Trait quarrelsomeness was based on a person's score on (1) the NEO-PI-R Angry Hostility subscale, which reflects the "tendency to experience anger and related states such as frustration and bitterness," and (2) the BDHI Irritability subscale, which reflects the "readiness to explode with negative affect at the slightest provocation".[54,84] Only those whose score was at least one standard deviation above the population mean on one scale and at least half a standard deviation above the population mean on the other were included.[54,84] Individuals who met the criteria for high trait quarrelsomeness were interviewed by

the collaborating psychiatrist [GP]. Individuals with current depressed mood as indicated by a BDI score higher than 10 and as determined by the psychiatrist were excluded. Those with probable alcoholism as indicated by a SMAST score higher than 2 and as determined by the psychiatrist were also excluded. Finally, eligibility for taking tryptophan was confirmed. Given ties between irritability, aggression and impulsivity,[371] people who entered the study after meeting all criteria also completed the Barratt Impulsiveness Scale, version 11 (BIS-11).[20]

Screening appointments were made by telephone with 151 people. A total of 46 participants did not show up. Two individuals were no longer interested in participating after reading the consent form. The number of excluded individuals was 57 (2 did not have a job, 8 showed signs of depression, 47 scored below the cut-off on trait quarrelsomeness measures). A total of 46 participants started the study. One man and 1 woman dropped out before the beginning of the second treatment phase; both had been on placebo in the first phase. Three men and 2 women were withdrawn from the sample when they stopped fitting the inclusion criteria during the study (*e.g.,* lost job, became ill). The results are described for the 39 participants (20 men, 19 women) who completed the study. There were no gender differences on the baseline measures of Angry Hostility, Irritability and Impulsiveness, or on the baseline BDI scores, but men scored significantly higher on the SMAST (Table 1.1). There were no significant treatment order effects or gender by treatment order effects on the baseline measures.

Treatment

We carried out a double-blind crossover study, in which participants took 1 g of L-tryptophan (Tryptan, ICN Canada, Montreal) or an identical placebo 3 times a day with meals for 15 days each. Treatment order was counterbalanced. A 6-day inter-treatment interval was included to ensure washout and to start each treatment phase on the same day of the week. For all participants, both phases started and finished on a Tuesday.

The daily dose of tryptophan given is considered sufficient to maximize serotonin synthesis.[452] Tryptophan was chosen over other serotonin-enhancing drugs, because it has a relatively specific effect on brain serotonin,[28] it is a dietary

component with few side effects and negligible toxic effects when given as a drug,[451] and in healthy people it has little if any effect on mood.[453]

Event-contingent recording

During both treatment phases, participants reported their social interactions. Data were collected using the event-contingent recording method used by Moskowitz *et al.* (2001).[294] Treatment length was 15 days, because (1) reliability across days asymptotes after 12 days and does not increase with greater aggregation of the number of days,[51] and (2) Moskowitz *et al.* (2001) showed that data from the first 3 days might need to be excluded, because these days may be affected by participants' tendency to provide socially desirable self-ratings upon entry into the study.

Information was recorded using standardized forms. As before, participants provided information about the context in which each interaction occurred, and they indicated how they felt and behaved. The present study also included a rating of the perceived behaviour of interaction partners. Finally, participants were asked to report whether they had ingested alcohol within 1 hour of a social interaction and not to report an interaction when illicit drugs had been consumed in the 3 hours before an interaction. A brief description of the measures taken from the event-contingent method used is provided below. Readers are referred to Moskowitz *et al.* (2001) for more details.[294]

Measurement of affect: Each form included two methods for measuring affect experienced during a social interaction. First, participants rated the following positive and negative affect adjectives on a scale from 0 to 6:[108] worried/anxious, happy, frustrated, pleased, angry/hostile, enjoyment/fun, unhappy, joyful, depressed/blue. Second, participants marked the valence and arousal of their experienced affect on a 9 by 9 affect grid.[362] By placing a single mark, they indicated the extent to which they were feeling unpleasant versus pleasant on the horizontal dimension of the grid and the extent of alertness versus sleepiness on the vertical dimension of the grid. Event-level positive and negative affect scores were constructed by (1) adding up the individual adjective scores corresponding to positive and negative affect and (2) dividing each sum score by the number of

adjectives to provide a mean. The difference between mean positive affect and mean negative affect provided a composite measure of affect. In addition, event-level affect valence and affect arousal scores were coded from the affect grid using a number between 1 and 9. Higher scores on the horizontal dimension indicated more pleasant affect. Higher scores on the vertical dimension indicated greater arousal.

Measurement of social behaviour: Each form listed 12 social behaviours that could be classified according to the interpersonal circumplex model: affiliation on one axis is defined by agreeable and quarrelsome behaviours, and power or status on the other axis is defined by dominant and submissive behaviours.[64,241,291,434] Each form included 3 items of each dimension of behaviour, such as "I exchanged pleasantries" and "I gave information" for agreeableness, "I showed impatience" and "I criticized the other(s)" for quarrelsomeness, "I expressed an opinion" and "I assigned someone to a task" for dominance, and "I gave in" and "I spoke softly" for submissiveness. Participants were asked to check off all behaviours they engaged in during a social interaction. To prevent them from marking the same behaviours for every interaction, the list of behaviours on each form varied in a daily rotation of 4 forms. All behaviours were taken from a list of 46, which has been shown to provide valid and reliable scores of each dimension of social behaviour.[51,291,293,295] The steps required for construction of event-level scale scores for agreeable, quarrelsome, dominant and submissive behaviours were the following: (1) calculation of a score for each scale by computing the mean frequency of behaviours corresponding to the scale, and (2) construction of ipsatized scores by subtracting mean frequency for all behaviours from each scale score. These ipsatized scores thus reflect the frequency with which agreeable, quarrelsome, dominant and submissive behaviours were marked, adjusted for the general rate of behaviour marking (in other words, scaling effects have been removed). Given that people usually mark quarrelsome and submissive behaviours less often, ipsatized scores for quarrelsome and submissive behaviours are on average lower than those for dominant and agreeable behaviours, and are frequently negative.

Measurement of social perception: Each form also included an 11 by 11 interpersonal grid.[297] By placing a single mark, participants indicated to what extent they perceived their social interaction partner as quarrelsome versus agreeable, and dominant versus submissive. When in a group, participants only rated the behaviour of the person with whom they primarily interacted. When a primary interaction partner could not be identified, participants were instructed to leave the grid blank (this was the case for 11% of all interactions recorded). For each event, scores on the two dimensions of the interpersonal grid were coded using a number between 1 and 11. Higher scores on the horizontal dimension indicated greater perceived agreeableness. Higher scores on the vertical dimension indicated greater perceived dominance.

Study overview

A significant social interaction was defined as lasting at least five minutes and involving a spoken conversation between at least two people. Participants were asked to complete a record form as soon as a social interaction ended, using a maximum of ten record forms a day. The completion of record forms was dispersed throughout the day. All participants received packages containing tryptophan or placebo tablets, record forms and pre-addressed, stamped envelopes for each day's forms. On each day, they also recorded the time they took each tablet, and women were asked to indicate if they were menstruating.

Participants received the materials for the first study phase at the end of the screening procedure, and they received another set of materials for the second study phase during a meeting in the laboratory in between the 2 phases. BDI scores were obtained during screening and after each study phase. At the end of the study, participants were asked during which phase they thought they were taking tryptophan.

Data analysis

Data were analyzed after the exclusion of all events sampled within 1 hour of alcohol ingestion (7.0% of over 7000 events). The number of such interactions that took place during tryptophan treatment was not significantly different from the number that took place when participants received placebo. In the primary analyses,

treatment (tryptophan, placebo) was considered a within-subjects factor. Period, a second within-subjects factor, divided each phase into 5 periods of 3 days. Treatment order (tryptophan first, placebo first) and gender (men, women) were the between-subjects factors. Main effects were entered first, followed by their two-way and three-way interactions. All statistical analyses were performed twice. First, analogous to our previous study, the first 3 days of each treatment phase were excluded, and only the data from the final 12 days of each treatment phase were used (periods 2-5). Second, all analyses were repeated with all 15 days included (periods 1-5). The results did not change, but in order to maintain consistency with our previous study only the former analyses are presented below.

Based on the outcome of *F* tests and *t* tests, effect-size calculations were performed for each significant effect of tryptophan.[354] The formula $r^2 = t^2 / (t^2 + df)$ was used, where *r* is the effect-size correlation, *t* is the square root of the *F* test ($F = t^2$) in the case of a main effect or the value of the post hoc *t* test in the case of an interaction effect, and *df* is the number of denominator degrees of freedom in the *F* test or *t* test. Cohen's *d* values were calculated from effect-size correlations using $r^2 = d^2 / (d^2 + 4)$. To examine how much of the behavioural and perceptual changes could be explained by the observed changes in affect valence, secondary covariate analyses were also performed. The analyses for the 4 social behaviour variables and the two social perception variables were repeated using three main effects (treatment, treatment order, gender) and their interactions, with affect valence added as a covariate.

The number of record forms varied per day, per period and per person, thus resulting in different numbers of observations between as well as within individuals. Therefore, we used mixed linear modelling with maximum likelihood estimation (PROC MIXED in SAS 8.2). Treatment differences were calculated for the principal outcome measures with statistical significance set at $p < 0.05$. Tukey corrections were used for multiple comparisons in post hoc tests. Estimated least squares means and standard errors of the mean (SEM) are given for significant treatment differences.

6.4 Results

At the end of the study, participants were asked when they thought they were taking tryptophan. Of the men, 60% guessed correctly. Of the women, 63% did. This was not significantly different from chance, even when treatment order was taken into account.

Effects of tryptophan on affect

For affect arousal and affect valence, positive and negative affect, and the composite affect score, analyses were conducted with four main effects (treatment, order, gender, period) and their two-way and three-way interactions.

Affect arousal: The treatment by order by gender interaction was significant ($F_{1,35} = 5.41$, $p = 0.026$), but none of the post hoc tests were. No other effects were found.

Affect valence: There was a significant period effect ($F_{3,114} = 7.68$, $p < 0.001$): affect valence was significantly lower in period 3 than in periods 4 ($t_{114} = -4.20$, $p < 0.001$) and 5 ($t_{114} = -3.97$, $p < 0.001$). There was a significant treatment effect ($F_{1,38} = 5.38$, $p = 0.026$) and a significant treatment by order interaction ($F_{1,36} = 16.81$, $p < 0.001$). Tryptophan increased the pleasantness of affect in those participants who received tryptophan second (placebo *vs.* tryptophan: 5.75 [SEM 0.14] *vs.* 6.16 [SEM 0.14], $t_{36} = -4.55$, $p < 0.001$), but not in those who received tryptophan first (placebo *vs.* tryptophan: 5.98 [SEM 0.14] *vs.* 5.89 [SEM 0.14], $t_{36} = 1.15$, $p = 0.26$; Figure 1.1). Cohen's *d* for affect valence in those who took tryptophan second was 1.5 (based on an *r* of 0.60), which is indicative of a large treatment effect.

Positive and negative affect and the composite affect score: The analyses for the positive and negative affect variables and for the composite affect measure showed results that were very similar to those for affect valence. Thus, for positive affect, there was a treatment effect ($F_{1,38} = 21.29$, $p < 0.001$) and a treatment by order interaction ($F_{1,36} = 7.35$, $p = 0.010$), as well as an effect of period ($F_{3,114} = 9.88$, $p < 0.001$). Positive affect was lower on placebo than on tryptophan when tryptophan was given second ($t_{36} = -5.12$, $p < 0.001$) but not when tryptophan was given first ($t_{36} = -1.46$, $p = 0.47$), and it was lower in period 3 than in periods 2 ($t_{114} = 3.09$, $p = 0.013$), 4 ($t_{114} = -5.10$, $p < 0.001$) and 5 ($t_{114} = -4.10$, $p < 0.001$). There was

also a significant tryptophan by order by period interaction ($F_{3,108}$ = 2.80, p = 0.044) that showed no significant treatment differences post hoc.

For negative affect, there was again a treatment effect ($F_{1,38}$ = 8.55, p = 0.006) and a treatment by order interaction ($F_{1,36}$ = 21.36, p < 0.001), and an effect of period ($F_{3,114}$ = 7.24, p <0.001). An additional tryptophan by order by period interaction ($F_{3,108}$ = 4.80, p = 0.004) showed that the negative affect-lowering effect of tryptophan in those who received tryptophan second was significant only in period 3 (t_{108} = 3.80, p = 0.021).

For the composite affect score, the main effect of treatment ($F_{1,38}$ = 18.05, p < 0.001), the treatment by order interaction ($F_{1,36}$ = 15.25, p < 0.001), the main effect of period ($F_{3,114}$ = 9.98, p < 0.001) and the tryptophan by order by period interaction ($F_{3,108}$ = 4.32, p = 0.006) were again all significant. Tryptophan improved affect in those who received tryptophan second exclusively in periods 3 (t_{108} = -3.83, p = 0.019) and 4 (t_{108} = -3.60, p = 0.039).

Effects of tryptophan on behaviour

For each behavioural variable, the analyses were first conducted with 4 main effects (treatment, order, gender, period) and their two-way and three-way interactions. Second, given the finding that tryptophan improved affect, covariate analyses were conducted for each variable, with three main effects (treatment, order, gender) and their two-way and three-way interactions, and affect valence as a covariate.

Quarrelsome behaviour: In the primary analyses, there was a significant main effect of treatment ($F_{1,38}$ = 5.22, p = 0.028), and no interaction with gender or with treatment order. Tryptophan decreased quarrelsome behaviours (placebo *vs.* tryptophan: -11.0 [SEM 0.92] *vs.* -12.3 [SEM 0.93]; Figure 1.2a). The r for quarrelsomeness was 0.35, thus yielding a Cohen's d value of 0.74 (medium effect size). In the secondary (covariate) analyses, more positive affect during social interactions was associated with lower levels of quarrelsomeness ($F_{1,5143}$ = 813.42, p < 0.001). The effect of tryptophan was no longer significant when affect valence was controlled for ($F_{1,35}$ = 1.68, p = 0.20).

Agreeable behaviour: Both the main effect of treatment ($F_{1,38}$ = 23.43, p < 0.001) and the treatment by gender interaction ($F_{1,35}$ = 4.28, p = 0.046) were

significant in the primary analyses. Tryptophan increased agreeableness in both men (placebo *vs.* tryptophan: 9.97 [SEM 1.5] *vs.* 14.6 [SEM 1.5]) and women (placebo *vs.* tryptophan: 10.5 [SEM 1.6] *vs.* 12.4 [SEM 1.6]), although the effect was only significant in the men (t_{35} = -4.97, $p < 0.001$ for men; t_{35} = -1.99, $p = 0.21$ for women; Figure 1.2b). The treatment effect size for men was large, based on an r value of 0.64 and a Cohen's d of 1.7. In the secondary analyses, more positive affect was associated with higher levels of agreeableness ($F_{1,5143}$ = 933.05, $p <$ 0.001). Whereas the tryptophan by gender interaction was no longer significant ($F_{1,35}$ = 3.36, $p = 0.08$), a significant main effect of tryptophan remained ($F_{1,35}$ = 15.29, $p < 0.001$). When affect valence was controlled for statistically, levels of agreeable behaviours were higher on tryptophan (13.0 [SEM 1.1]) than on placebo (10.6 [SEM 1.1]) across genders.

Dominant behaviour: The primary analysis revealed a treatment by gender effect ($F_{1,36}$ = 13.62, $p < 0.001$; Figure 1.2c). Tryptophan decreased dominance in the men (placebo *vs.* tryptophan: 4.87 [SEM 1.5] *vs.* 1.46 [SEM 1.5], t_{36} = 3.96, $p =$ 0.002), but there was no significant change in the women (placebo *vs.* tryptophan: 5.98 [SEM 1.6] *vs.* 7.10 [SEM 1.6], t_{36} = -1.27, $p = 0.58$). The treatment effect size for men was large ($r = 0.56$, Cohen's $d = 1.3$). In the secondary analyses, more positive affect was associated with lower levels of dominance ($F_{1,5143}$ = 5.60, $p =$ 0.018). The tryptophan by gender interaction was maintained when controlling for affect valence ($F_{1,35}$ = 12.58, $p = 0.001$), and no other effects were found.

Submissive behaviour: Neither the primary nor the secondary analysis revealed any significant effects.

Effects of tryptophan on perceptions of others

Primary and secondary analyses were identical to those conducted for the behavioural variables.

Perceptions of agreeableness: In the primary analysis, there was a significant period effect ($F_{3,114}$ = 4.95, $p = 0.003$): as was the case for affect valence, perceptions of agreeableness were significantly lower in period 3 than in periods 4 (t_{114} = -2.97, $p = 0.019$) and 5 (t_{114} = -3.17, $p = 0.010$). Both the treatment by order interaction ($F_{1,36}$ = 8.32, $p = 0.007$) and the treatment by order by gender interaction

($F_{1,35}$ = 4.76, p = 0.036; Figure 1.3a) were also significant. Post hoc testing of the three-way interaction indicated that only men who received tryptophan in the second half of the study perceived their interaction partners as more agreeable when on tryptophan (placebo *vs.* tryptophan: 7.69 [SEM 0.32] *vs.* 8.23 [SEM 0.32], t_{35} = -3.61, p = 0.019). There was no such effect in men who received tryptophan first *(*placebo *vs.* tryptophan: 7.79 [SEM 0.32] *vs.* 7.58 [SEM 0.32], t_{35} = 1.45, p = 0.83*)* or in women, whether they received tryptophan first (placebo *vs.* tryptophan: 7.69 [SEM 0.32] *vs.* 7.60 [SEM 0.33], t_{35} = 0.60, p > 0.99) or second (7.81 [SEM 0.34] *vs.* 7.81 [SEM 0.34], t_{35} = -0.05, p > 0.99). Based on an r value of 0.52 and a Cohen's d of 1.2, the treatment effect size for perceptions of agreeableness in men who received tryptophan second was again large. In the secondary analysis, more positive affect was associated with higher perceived agreeableness in others ($F_{1,4582}$ = 3190.90, p < 0.001). Whereas the tryptophan by gender by order interaction was again significant ($F_{1,35}$ = 4.50, p = 0.041), none of the post hoc contrasts were.

Perceptions of dominance: The primary analysis revealed a main effect for treatment ($F_{1,38}$ = 53.16, p < 0.001). Compared with placebo, participants on tryptophan perceived others as more dominant (placebo *vs.* tryptophan: 7.31 (SEM 0.18) *vs.* 7.77 (SEM 0.18); Figure 1.3b). The treatment effect size was large (r value = 0.76, Cohen's d = 2.4). In the secondary analysis, more positive affect was associated with higher perceived dominance in others ($F_{1,4577}$ = 89.31, p < 0.001), and the tryptophan effect was maintained ($F_{1,35}$ = 45.64, p < 0.001).

Influence of menstrual cycle

The results did not change when women's premenstrual days were excluded (data not shown).

6.5 Discussion

Tryptophan treatment significantly decreased quarrelsome behaviours in all participants. Agreeable behaviours were increased and dominant behaviours decreased in the men. When affect valence was controlled for statistically, tryptophan increased agreeable behaviours in both men and women. Others were perceived as more agreeable by the men, and as more dominant by all. Affect was

significantly improved in participants who received tryptophan second and moderated the effects of tryptophan on quarrelsomeness (but none of tryptophan's other effects). Overall, the primary analyses were indicative of medium-to-large treatment effect sizes.

This is the second study to show that tryptophan supplementation may not only reduce aggressive behaviours in experimental laboratory situations [38,378] but also decrease quarrelsome behaviours in daily life.[294] More important, this is the first study to show that tryptophan can also enhance agreeable behaviours in everyday social interactions. Given that participants in the present study, unlike those in our previous study,[294] were selected on the basis of being highly quarrelsome, it is suggested that the extent to which tryptophan may enhance social affiliation depends on who is taking it. Similar to the notion that antidepressants elevate mood in depressed patients but not in euthymic people, and that serotonergic manipulations affect laboratory-measured aggression mostly in aggressive people,[33,70,136] tryptophan may increase everyday agreeableness only in quarrelsome people. In addition, although this is not a direct comparison because the data were obtained from different studies, the treatment effect size for quarrelsomeness in the present study was greater than that in our previous study of unselected people (0.74 this study *vs.* 0.54 previous study).[294] This shift toward more socially constructive behaviours may be especially important for quarrelsome individuals. Participants in the present study (n = 39), who initially reported high levels of anger, hostility and irritability on selection measures, were indeed more quarrelsome and less agreeable than participants in our previous study (n = 98; overall mean level of quarrelsomeness during the placebo phase: -10.6 [SD 6.5] this study *vs.* -15.1 [SD 7.4] previous study, t_{135} = -3.39, $p < 0.001$; overall mean level of agreeableness during the placebo phase: 10.0 [SD 7.8] this study *vs.* 13.9 [SD 6.4] previous study, t_{135} = 3.03, p = 0.003). Quarrelsome people are considered at risk for a variety of mental as well as physical illnesses.[81,404,437,448] An increase in serotonin function that lowers quarrelsomeness and enhances agreeableness may improve social relationships and augment the benefits derived from such relationships that contribute to health.

The apparent ability of serotonin to promote positive social behaviours is also of interest, because the serotonin system has traditionally been thought of as an impulse-control system, inhibiting a wide range of behaviours that may be disadvantageous to an individual's survival.[383,386] Yet the present study shows that serotonin not only inhibits negative behaviours but may also stimulate certain behaviours thought to be beneficial to social functioning and health. There have been a few laboratory studies in healthy volunteers showing similar effects of treatment with SSRIs on a measure of social affiliation: both Knutson *et al.* (1998) and Tse and Bond (2002) observed an increase in cooperative behaviours measured during an experimental task involving dyadic interaction.[224,406] The present study thus adds to a small body of evidence indicating that an increase in serotonin function may result not only in behavioural inhibition but also in facilitation of positive behaviours in response to social stimuli.

In line with the idea that a positive shift in quarrelsomeness-agreeableness may enhance personal well-being, tryptophan also improved affect during social interactions: participants reported more positive and fewer negative emotions when taking tryptophan and rated their interactions as more pleasant. The data from our previous study suggest that a change in mood is not necessary for a change in quarrelsomeness-agreeableness to occur.[294] In the present study, the covariate analyses indicated that the effect of tryptophan on quarrelsomeness could be accounted for by a person's level of affect valence during social interactions. This suggests that tryptophan decreased aspects of affect valence such as irritability along with quarrelsome behaviour, which is what would be expected. The decline in quarrelsomeness may be the result in whole or in part of improved affect or, alternatively, an increase in serotonin may have a direct effect on both the mood and the behaviour. In contrast, the main effect of tryptophan on agreeableness remained significant even after affect valence had been added as a covariate, which suggests that tryptophan enhanced agreeable behaviours independent of its effects on mood. Thus, affect valence alone could not account for the observed changes in agreeable behaviour. It seems plausible that the improvement in mood was at least partially

initiated when participants' behaviours during social interactions became more pro-social, which may have lead to reciprocated agreeable behaviour from others.

In our previous study, tryptophan decreased quarrelsomeness only when tryptophan was given second, that is, when the tryptophan phase followed the placebo phase.[294] We hypothesized that the explanation for this carryover effect was less likely to be pharmacological (tryptophan is metabolized within 8 hours)[457] than psychological: when tryptophan was given first, it may have altered the tone of interactions, which then persisted during the subsequent placebo phase. In the present study, tryptophan decreased quarrelsomeness whether it was given first or second. This could be due either to the longer washout period in this study or to the higher placebo levels of quarrelsomeness for this group. An important addition to the present study was the assessment of perceptions of others' behaviours using the interpersonal grid.[297] There was an interaction between treatment and order and gender for perceptions of agreeableness. Only male participants who received tryptophan second perceived their interaction partners as more agreeable when on tryptophan. The fact that the effect of tryptophan on perceptions of agreeableness was limited to men is consistent with its effect on behaviour. The treatment by order interaction suggests that male participants may have required the contrast of attending to others' agreeableness during placebo to observe the change in others that occurred during subsequent tryptophan treatment. In future treatment studies, this issue could be addressed using an initial placebo-only run-in phase. However, it may also be an indication of a carryover effect similar to that observed for quarrelsomeness in the previous study. Although a visual inspection of the raw data revealed no apparent linear trend over time, as may have been expected if the effects of tryptophan on one day were carried over into the next, time-related treatment effects are likely to have been confounded by the day of the week.[51,292] Whereas weekly cyclicity may have dampened linear trends over time, the present finding on perceptions of agreeableness at least suggests that some effects of tryptophan may persist for days beyond its last administration, possibly because there is a change in both participants and their interaction partners. If this is so, then the order effect should be abolished by increasing the length of time of the washout

period between treatments. Further research is also necessary to examine whether the behavioural changes followed or led the perceptual changes. For example, future study designs could include pairs of frequently interacting participants who would rate both their own and the other's behaviour, while only one of each pair would undergo double-blind placebo-controlled treatment.

In the men, tryptophan also decreased dominance, without increasing submissiveness. Separate influences on dominance and submissiveness have also been found in other domains, such as situational influences.[293] According to the interpersonal circumplex model, the dominant-submissive and quarrelsome-agreeable axes are independent so, for example, individuals can act either in an agreeable-dominant or in an agreeable-submissive way.[64,241,291,434] Within the interpersonal circumplex, tryptophan treatment in the men thus induced a shift away from quarrelsome-dominance toward agreeable-submissiveness. Whereas an agreeable-dominant behavioural pattern is generally considered socially constructive, behaving in a more agreeable-submissive manner can also be adaptive, especially in those who exhibit a high degree of quarrelsomeness. The male participants in the present study (n = 20) were less dominant compared with those in the previous study (n = 51; overall means during the placebo phase: 3.93 [SD 7.2] this study *vs.* 8.88 [SD 6.1] previous study, $t_{69} = 2.92$, $p = 0.005$). On placebo, they were also quarrelsome and disagreeable, which in combination with low dominance may be perceived as being socially withdrawn.[297] A tryptophan-induced move toward agreeable low dominance may be perceived as politely deferring to others and may promote opportunities for social bonding. It remains unclear why tryptophan did not change dominance in the women (n = 19), but their levels of dominant behaviours were not unusually low compared with the previous study (n = 47) as was the case for the men (overall means during the placebo phase: 5.64 [SD 7.3] this study *vs.* 7.02 [SD 6.6] previous study, $t_{64} = 0.74$, $p = 0.46$).

Tryptophan increased ratings of dominant behaviour in others in all participants, yet only the men responded with reduced dominance. Perceptions of dominance may have increased when participants were taking tryptophan, because they were taking more notice of how other people behaved toward them. Further,

there is some evidence that interactions with dominant others that result in less dominance may increase liking of the other more than similar interactions that result in more dominance.[402] The decline in dominance observed in the men may thus have contributed to their enhanced social affiliation. Whatever the mechanism, further research into the role of serotonin in perceptions of others and their influence on the flow of social interactions is warranted, for example, given that distorted social perceptions are common in mental disorders such as depression and social phobia.[43,150,344]

In conclusion, this study has shown that an increase in brain serotonin, induced pharmacologically by means of oral tryptophan supplementation, can lead not only to a decrease in quarrelsome behaviours but also, in individuals with elevated trait levels of quarrelsomeness, to an increase in agreeable behaviours. Changes in dominance may also vary with the characteristics of those taking tryptophan. Further, as the present study has shown that tryptophan can change perceptions of others, it is important to consider the dynamic quality of human social interactions in understanding how serotonin influences behaviour. The observed improvement in affect was associated with the decrease in quarrelsomeness but not with any of the other behavioural and perceptual changes. Overall, tryptophan had a positive effect on social interactions in everyday life. Given that participants initially reported problems during their social interactions, and given the importance of good social functioning for well-being and health, the improvement in both social behaviour and mood is noteworthy.

Chapter 7
INTERMEZZO 1

The purpose of Study 1 was to extend the findings of Moskowitz *et al.* (2001)[294] to a population of healthy but irritable people. Hypothesis 1.4 was not supported. Levels of dominant behaviours were expected to increase when participants were taking tryptophan, yet they decreased in the men and remained unchanged in the women (see Figure 1.2). This will be discussed further in Chapter 11. Hypotheses 1.1-1.3 were supported. When participants were taking tryptophan, they reported lower levels of quarrelsome behaviours and higher levels of agreeable behaviours (Figure 1.2). Furthermore, tryptophan administration improved perceptions of others, at least in the men (Figure 1.3). These behavioural and perceptual changes were accompanied by an increase in pleasant affect (Figure 1.1). Study 1 expanded on the idea, first discussed by Moskowitz *et al.* (2001), that the cyclic nature of social interactions might explain why the tryptophan-induced changes in behaviours, perceptions, and mood may have lasted longer than the actual treatment period.[294] If, over time, more positive social interactions result in better social relations, then the long-term benefit of the changes seen with tryptophan administration could theoretically be substantial, especially in relation to the prevention of future health problems associated with chronic irritability.[368,381] However, continual administration of tryptophan, or any other serotonergic drug, is not feasible in presently healthy populations.

Public health recommendations for disease prevention include most notably a healthy diet and sufficient physical activity. For the treatment of mood disorders, food supplements can be effective especially when they cure a deficiency.[34] Fitness interventions have also shown to be successful.[116,240] In healthy individuals, some evidence of positive mood effects of certain dietary factors and of exercise also exists.[143,272,365] Brown *et al.* (2001) used a multimodal intervention that focused on diet and fitness as well as light exposure in women with sub-clinical depression symptoms and reported that it reduced tension and anger and increased self-control and well-being.[52] In this study, participants were instructed to maximize exposure to

all light sources available in their everyday lives. Unfortunately, the impact of each individual lifestyle change separately (improved diet, better fitness, increased light exposure) could not be determined from this study. However, Leppamaki *et al.* (2002) have found that effect sizes for exercise versus artificial bright light exposure can be similar. Moreover, combining the two in a sample of individuals with sub-clinical SAD was more effective in alleviating anergia, hypersomnia, and hyperphagia (common symptoms in SAD), than exercise alone.[244]

It is indeed surprising that bright light is not recognized at the public health level as being a likely factor involved in the regulation of human well-being and possibly even in preventing disease. Artificial bright light has well-established antidepressant properties.[160,412] and can improve mood even in people who are not depressed.[245,329] Modern lifestyles include many "adaptations" (living and working indoors, using window screens and dim artificial lighting, and wearing dark sunglasses) that have reduced natural bright light exposure to around 1.5 hours per day in summer and only 30 minutes per day in winter.[80,167,182] Most humans spend more than 90% of their lives indoors. Some have hypothesized that the extreme avoidance of one of the most salient stimuli in the environment may have contributed to the rise in a variety of diseases.[423,456] It might explain also why mood disorders often show seasonal variability in symptoms.[128,393]

Bright light is considered to be as effective as serotonergic medication in the treatment of depression.[160,233] The therapeutic effect of bright light in patients with SAD can be reversed by ATD.[235,309] While this is consistent with a role for the brain serotonin system in the mechanism of action of bright light, evidence for a direct effect of bright light on serotonin and human mood is lacking. The discovery of such a link would strengthen the idea that light exposure is an important regulator of well-being, and could have important implications for disease prevention from a public health perspective.

Study 1 confirmed that an increase in brain serotonin induced by tryptophan administration can have a positive impact on everyday mood in healthy but irritable individuals, as well as on other aspects of life. If serotonin has the ability to make people more socially skilled, then it might be useful to identify an environmental

factor with effects on social functioning similar to those seen with tryptophan. Bright light seems to be a good candidate, but its neurochemical effects and subsequent impact on mood have not been researched over short time periods. This issue formed the basis of Study 2. Further, as will be described in more detail in Chapter 9, the findings of Studies 1 and 2 combined provided good rationale for Study 3.

Study 2 was laboratory-based. The advantage of a controlled environment was preferred over that of a natural setting because light and serotonin levels needed to be manipulated concurrently in order to provide evidence of a direct interaction. The study focused mostly on mood although a computerized facial-emotion recognition task was included as a measure of social perception. ATD was used to manipulate brain serotonin. Ceiling-mounted light banks were used to manipulate light exposure in the test rooms. Participants were healthy mildly seasonal women without a personal or family history of mood disorders. Women were chosen because they may be more vulnerable to ATD-induced mood effects.[123] Selecting participants on the basis of their self-reported level of mild seasonality was thought to result in (1) the inclusion of women sensitive to variations in bright light exposure and (2) a sample representative of a large proportion of the (female) population. The absence of a depression (family) history was required in order to exclude two possible confounders.[30,97] If Hypotheses 2.1 and 2.2 were supported, then this would provide the first direct evidence that bright light can acutely mediate the effects of changes in the brain serotonin system on mood.

Chapter 8
BRIGHT LIGHT EXPOSURE DURING ACUTE TRYPTOPHAN DEPLETION PREVENTS A LOWERING OF MOOD IN MILDLY SEASONAL WOMEN (Study 2)

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8.1 Abstract

We investigated the influence of bright light exposure on the mood-lowering effect of acute tryptophan depletion (ATD). Mildly seasonal healthy young women without a personal or family history of psychiatric disorders received either dim or bright light during the two test days. Tryptophan-deficient and nutritionally balanced amino acid mixtures were administered in counterbalanced order. Mood state was assessed using the Profile of Mood States (POMS) and Visual Analogue Scales (VAS). In dim light, ATD decreased POMS scores across most subscales, indicating a worsening of mood. In bright light, mood was unaffected by ATD. Thus, bright light blocked the worsening of mood caused by ATD. This was also observed on the positive mood VAS. These results indicate a direct, immediate interaction between bright light and serotonin function. Bright light might help protect against ATD-induced mood change by increasing serotonin above the threshold level below which there is a lowering of mood.

8.2 Introduction

Seasonal affective disorder (SAD), when it occurs in winter, responds well to treatment with bright artificial light.[353,396] The efficacy of phototherapy is comparable to that of pharmacotherapy [160,233,360] and approaches that of the natural increase in light levels associated with the lengthening of days in spring and summer.[333,443]

Bright light can also affect mood in healthy individuals, an effect generally seen in people with self-reported seasonality or subsyndromal SAD,[208,209,329] but not

always in those without.[208,209] Mood worsening, mainly irritability, has also been reported, but may occur primarily in those with low seasonality.[21,152] Overall, bright light's positive effects may be more marked in individuals who do experience seasonal changes in mood and behaviour.

The mechanism of action underlying bright light's effects on mood is still unknown. A role for serotonin has been proposed but this is largely based on indirect evidence.[205,377,449] Most relevant here are results from several acute tryptophan depletion (ATD) studies carried out in patients with SAD.[231,235,253,309,311] ATD involves the use of a tryptophan-deficient amino acid mixture to decrease brain tryptophan levels and brain serotonin synthesis.[316,454] Short-lasting depressed mood following ATD has been observed in SAD patients in remission after phototherapy.[235,309] A similar effect has been shown in SAD patients who improved in spring and summer during the gradual increase in natural light levels, though not in all studies.[231,253,311] Together these reports suggest that successful mood improvement following bright light exposure can be reversed by decreasing brain serotonin. However, they do not confirm that bright light exerts its mood-regulating effects through serotonergic mechanisms.

Phototherapy efficacy in patients has mostly been studied over time periods in the range from weeks to months.[160] There is some evidence, based on the magnitude of mood change after one week, that the onset of action of bright light may be faster than that of fluoxetine.[233,360] Clinically significant mood changes have indeed been found to occur even after time periods of 2-3 days,[352,353] in the afternoon following morning phototherapy,[227] and after as little as 1 hour.[376] Surprisingly, however, these observations have received little attention.

Several lines of evidence suggest that an acute effect of bright light on the brain may include a rapid increase in brain serotonin. First, Lambert *et al.* (2002) reported that human brain serotonin turnover was positively associated with the number of hours of sunshine on the day of measurement and not on the day before.[236] Assuming that the bright light exposure was responsible for the increase in serotonin, the effect must have been fairly direct. Second, in studies of human circadian rhythms even a few hours of bright light can exert a biological action,[252,347]

and these rhythms do influence mood.[35] Finally, studies in experimental animals have shown interactions between short-term light exposure and serotonin in the suprachiasmatic nucleus (SCN).[159,299,330] Thus far, however, there are no studies on the concurrent interaction of bright light and lowering of serotonin in humans.

Here we describe an experimental study in healthy mildly seasonal young women, a group likely to benefit from the effects of bright light.[208,209] Mood changes in response to ATD were measured in the presence or absence of bright light during test days. We hypothesized that bright light exposure would influence the magnitude of the ATD-induced mood change.

8.3 Methods

Participants

This study was approved by the Institutional Review Board of McGill University's Faculty of Medicine. Healthy mildly seasonal women were recruited through postings that contained the question "Do you feel less energetic in winter than in summer?" and an invitation to contact the laboratory for more information. Following a brief study description and a telephone screening, 83 women were interested and eligible and came in for a laboratory screening. Upon arrival, the study was discussed in detail and candidates provided written informed consent. They completed the 21-item Beck Depression Inventory (BDI)[26] and the Seasonal Pattern Assessment Questionnaire (SPAQ).[349] The SPAQ includes a Global Seasonality Scale (GSS), which assesses the extent of seasonal change in sleep length, social activity, mood, weight, appetite and energy level. Candidates were then interviewed using the Structured Clinical Interview for DSM-IV (Non-Patient Edition, version 2.0)[385] and the family history method described by Andreasen *et al.* (1977).[10] General health was assessed through a standard physical examination, electrocardiography, and routine blood tests.

The main inclusion criterion was a score of at least 6 on the GSS, indicative of at least mild seasonality, with symptom worsening in winter and improvement in summer, both on the phone and in the lab. According to one epidemiological study this includes about 44% of the population.[210] Exclusion criteria were age under 18

or over 40, current or past use of psychotropic medication, recent use of hormonal contraceptives, a BDI score over 15, a personal or first-degree family history of Axis I disorders, presence of a major physical illness, and/or abnormal medical tests precluding exposure to bright light or ATD. We excluded women with a BDI score over 15 and/or a personal or first-degree family history of Axis I disorders because these factors were expected to influence the response to ATD and therefore could confound the results.[30,97] Women who passed the screening (n = 49) were assigned to one of two light groups according to order of study entry.

Of 23 women allocated to the dim condition, 4 were lost to follow-up and 3 dropped out after the first day (2 stated side-effects, 1 stated time constraints). Of 26 women allocated to the bright condition, 8 were lost to follow-up and 4 dropped out after the first test day (2 stated side-effects, 2 stated time constraints). Six of seven dropouts had received the tryptophan-deficient mixture. The study was completed by 30 women (dim: n = 16; bright: n = 14). They averaged 23 years in age (SD 5) and scored 5.2 on the BDI (SD 4) and 9.0 on the GSS (SD 2). The two light groups were comparable on a variety of demographic and psychosocial variables (Table 2.1; $p > 0.21$ for all).

Study Design

Participants were randomized into two groups with different light conditions, bright or dim, and received different amino acid mixtures on two separate test days. The alternative, having participants ingest four mixtures on four separate test days, was deemed not feasible due to the expected high number of dropouts. Neither participants nor experimenters were blind to the light conditions, but amino acid mixtures were administered using a double-blind cross-over design, with order of treatment randomized per light group in blocks of four. Testing was carried out at the McGill Center for Study and Treatment of Circadian Rhythms (Douglas Hospital Research Center, Montreal, Quebec, Canada) during two consecutive winters (November-March). Participant quarters, provided with a bathroom, bed, sofa, desk, chair and standalone TV/VCR combo, were free of time cues, windowless, air-conditioned, temperature-controlled (mean 23.5 °C, SD 2.0 °C), and soundproof. An intercom system allowed for contact with the experimenter in the adjacent control

room. Light was administered by ceiling-mounted banks of cool-white fluorescent lamps (4100 °K, F32T8/TL841, Philips Lighting, Somerset, NJ, and F032/841, Sylvania, Danvers, MA) covered with lenses emitting less than 1% UV energy (Uvalite Plus, KSH, St. Louis, MO). Light intensity was set in the control room using an electronic device with settings ranging from 0 to 10,000 lux as verified with a calibrated light meter (IL1400A, International Light, Newburyport, MA).

Participants were asked to maintain their self-reported normal sleep/wake schedule (Table 2.1) the week before test days. Test days were planned in the follicular phase of the menstrual cycle and at least 3 days apart (mean 16.3 days, SD 19 days). The day before each test day, participants followed a 24-hour low-protein diet [123] and arrived in the lab 1 hour before normal sleep time (Figure 2.1). They handed in all personal devices indicating time, were isolated in their rooms with light intensity set at 150 lux, completed evening baseline questionnaires (see below) and were tested for recent illicit drug use (Triage™ Panel for Drugs of Abuse, Biosite Diagnostics©, San Diego, CA) and pregnancy. Lights were turned off to total darkness (< 0.01 lux) at normal sleep time.

Test days commenced at normal wake time with light set at 10 lux. In the dim condition, participants remained exposed to this light intensity throughout the test days. In the bright condition, light intensity was increased to 3000 lux in three 10-minute steps (150, 380, 3000 lux) and participants remained at this intensity during the test days. Light exposure at eye level was generally 25-30% lower than at ceiling level. At 30-45 minutes after wake time, participants completed morning baseline questionnaires (see below) and had a blood sample taken. They were then given 1 of 2 amino acid mixtures and asked to ingest it as fast as possible (mean duration 28min, SD 12min). In the subsequent 5-hour waiting period, participants were allowed to read, or watch a limited number of movies, but not sleep. Questionnaires were administered in the afternoon at 5, 6, and 7 hours after drinking the amino acid mixture. A second blood sample was taken between 5 and 6 hours, two computer tests were administered between 6 and 7 hours (data are not presented here), and a meal was administered after 7 hours. Participants then returned home. They were followed-up by telephone the next day.

Treatment

Participants received a nutritionally balanced amino acid mixture on one day (87.7 g, B) and a tryptophan-free mixture on the other (85.8 g, T-). Mixture content, based on the 100 g mixtures used with men in the study of Young *et al.* (1985)[454] and adapted for the lower average body weight of women,[123] was identical except for omission of 1.9 g tryptophan in the T- condition. Mixtures were prepared just prior to ingestion, either with water and chocolate syrup or with orange juice, and sweetened with sodium cyclamate. At the end of each test day, participants received a 1-g tryptophan tablet (Tryptan, ICN Canada, Montreal) with their meal, to restore plasma tryptophan levels on the T- day and maintain double-blind conditions on the B day. In the dim group, 7 participants received T- first and 9 B first. In the bright group, 7 participants received T- first and 7 B first.

Test measures

Mood state: The 72-item Profile of Mood States (POMS)[273] assesses non-clinical fluctuations in mood. Its 6 bipolar scales (Agreeable-Hostile, Clearheaded-Confused, Composed-Anxious, Confident-Unsure, Elated-Depressed, Energetic-Tired) each consist of 12 adjectives rated on a 4-point scale. The 2 poles represent the positive and negative aspects of a subscale, respectively. For each subscale, the sum of positive items minus the sum of negative items plus a constant of 18 is transformed into a T-score with a mean (SD) of 50 (10). The Total of the 6 subscale scores is also widely used and a reliable indicator of overall mood state.

A list of Visual Analogue Scales (VAS)[36] included 7 positive mood items (Elated, Enthusiastic, Excited, Happy, Interested, Lively, Satisfied) and 6 negative mood items (Angry, Anxious, Bored, Depressed, Irritated, Restless). Items were rated on unipolar scales ranging from 0 to 100 with increments of 5. Composite Positive Mood and Negative Mood scores were calculated using the average of positive and negative item scores, respectively.

Two baseline measurements of mood state were obtained. First, the BDI, POMS, and VAS were administered 30-60 minutes before normal sleep time the evening before each test day (evening baseline). Second, the POMS and VAS were administered 30 minutes after normal wake time in the morning of each test day

before ingestion of the amino acid mixture (morning baseline). Effects of amino acid mixtures on mood were measured repeatedly in the afternoon of each test day, at 5, 6, and 7 hours after amino acid mixture ingestion. Afternoon mood ratings (POMS, VAS) coincided with the trough in tryptophan levels that occurs following ingestion of the tryptophan-deficient mixture.[438]

Side Effects: Dizziness, headache, nausea have been reported both following amino acid mixture ingestion [219] and with bright light.[321] Therefore, each mood assessment also included three VAS labelled Dizzy, Headache, and Nauseous, with scaling identical to the mood VAS. When vomiting occurred, clock times were recorded. A test day was discontinued if vomiting occurred and less than one hour had passed since mixture ingestion. Mean elapsed time was 3h41min (range 1h00min-6h55min).

Sleep: A post-sleep questionnaire (PSQ) was administered in the morning of each test day. Participants were asked at what time they went to bed, how long it took to fall asleep, how often they woke up during the night, and how many hours they slept. They also rated how deep and how good their sleep was on separate 7-point scales.

Plasma Amino Acid Levels: Venous blood samples were collected 15 minutes before and between 5 and 6 hours after ingestion of the amino acid mixtures. Some could not be obtained (8 morning, 1 afternoon). Samples were centrifuged immediately (10 minutes, 1500 g, 0 °C). Some of the plasma was transferred into a 1ml ultra-filtering unit (Millipore, Bedford, MA) and centrifuged again (30 minutes, 1500 g, 20 °C), while the remainder plus the resulting ultra-filtrate were stored at -80 °C, until further analysis.

Plasma amino acid levels were measured using high-pressure liquid chromatography (HPLC) with fluorometric detection on an Ultrasphere ODS reverse-phase column (Beckman Coulter, Fullerton, CA) with ophtalaldehyde pre-column derivatization and aminoadipic acid as an internal standard. Total and free tryptophan levels were assessed by HPLC with fluorometric detection on a Bondpak® reverse-phase column (Phenomenex, Torrance, CA).

Data analyses

All analyses were performed using SAS 8.02 for Windows (SAS Institute Inc., Cary, NC). Demographic and psychosocial differences between the 2 light groups at screening were examined using T-tests (Table 2.1). Evening and morning baseline differences were investigated using general linear models with the between-subjects factor Light (Bright, Dim) and the within-subjects factor Mixture (T-, B). Each model included Mixture, Light, and the 2-way interaction. POMS Total and subscale scores were considered primary dependent variables and VAS scores secondary dependent variables.

Effects of Mixture and Light on test days were investigated using hierarchical linear models,[166,446] with maximum likelihood estimation and use of the between-within method for computing the denominator degrees of freedom for the tests of fixed effects. For afternoon plasma amino acid levels, models considered Mixture and Light and the 2-way interaction after controlling for morning baseline values. For mood, in addition to Mixture and Light, a third independent variable was identified: Time (3 levels: +5h, +6h, +7h, indicating the time passed since amino acid mixture ingestion). Models considered Mixture, Light, Time, and their interactions, after controlling for morning baseline values. Type III tests were deemed significant if p-values were below 0.05. Significant interaction effects were analyzed post-hoc using simple contrasts that were Tukey-corrected for multiple comparisons. Findings are reported using estimated least-squares means and standard errors of the mean (SEM).

8.4 Results

Baseline Measurements

Test days included an evening baseline and a morning baseline (Figure 2.1). Measurements taken the evening before amino acid administration included the BDI, POMS, and VAS. Measurements taken in the morning just before amino acid administration included the PSQ, POMS, and VAS. BDI scores obtained the evening before test days did not vary significantly according to Mixture and/or Light ($F < 0.77$, $p > 0.38$ for all). Both in the evening before test days and in the morning

before amino acid administration, treatments and/or groups did not reveal any differences in POMS Total and subscale scores ($F < 2.66$, $p > 0.10$ for all), in VAS Positive Mood and Negative Mood ($F < 2.59$, $p > 0.11$ for all) or in nausea ($F < 2.64$, $p > 0.11$ for all). Participants in the dim group tended to experience more headache ($F = 3.99$, $p = 0.05$) and dizziness ($F = 3.53$, $p = 0.07$) in the evening, but this was no longer so in the morning ($F < 1.62$, $p > 0.20$ for all). PSQ scores revealed no differences in sleep ($F < 2.40$, $p > 0.12$ for all). In sum, there were no significant group differences on any of the questionnaires prior to amino acid mixture administration.

Various season-related variables were tested for their possible influence on test days: day of winter (counted from November 1), day of the week (weekend *vs.* weekday), rainfall, snowfall, total precipitation, minimum, maximum and mean temperature (obtained for Montreal from www.theweathernetwork.com), day length (www.sunrisesunset.com), and hours of sunshine (www.criacc.qc.ca). Values on the day before each test day did not vary by Mixture and/or Light ($F < 2.65$, $p > 0.11$ for all). Thus, all of the season-related variables tested could be excluded as possible confounders of observed effects.

Plasma amino acids

For brevity, only the analyses for free tryptophan levels are reported here. The expected effects of Mixture emerged ($F_{1,17} = 82.11$, $p < 0.0001$). There were no effects of Light ($F_{1,24} = 0.28$, $p = 0.60$) or Mixture by Light interactions ($F_{1,17} = 0.16$, $p = 0.69$). Free tryptophan levels increased from 5.9 (SEM 0.6) to 9.6 (SEM 0.5) µM following B and decreased from 6.2 (SEM 0.5) to 1.2 (SEM 0.5) µM following T-. The ATD-induced decline in free tryptophan levels was ≥ 55% in all samples, and not affected by vomiting ($t_{21} = 0.96$, $p = 0.35$). The analyses for total tryptophan levels and for the ratio of free and total tryptophan to plasma levels of other large neutral amino acids produced similar findings (not shown).

Mood following ATD

Outcomes of the *F*-tests used in the hierarchical linear models are summarized in Table 2.2. In the case of significant interaction effects, outcomes of post-hoc Tukey-corrected *t*-tests are provided below.

POMS: Bright light prevented a lowering of mood following ATD on the POMS Total score. There were significant effects of Mixture and Mixture by Light. POMS Total scores were lower following T- (mean 300, SEM 4.4) than following B (mean 308, SEM 4.4), which indicates that ATD resulted in a lowering of mood. However, post-hoc investigation of the Mixture by Light interaction showed that the decrease in POMS Total scores occurred only in the dim group (B: mean 311, SEM 6.0; T-: mean 293, SEM 6.0; $t_{28} = 3.86$, $p = 0.0032$). No change was observed in the bright group (B: mean 306, SEM 6.4; T-: mean 306, SEM 6.4; $t_{28} = 0.05$, $p = 1.0$).

Bright light prevented a lowering of mood following ATD on 5 of the 6 POMS subscales. These effects are summarized in Figure 2.2 and explained in detail here.

Agreeable-Hostile: The Mixture by Light interaction was significant and attributable to a change in mood after ATD in the dim condition (B: mean 49.8, SEM 1.6; T-: mean 46.8, SEM 1.6; $t_{28} = 2.81$, $p = 0.04$), but not in the bright condition (B: mean 48.3, SEM 1.7; T-: mean 48.7, SEM 1.7; $t_{28} = -0.35$, $p = 0.98$). There was also an effect of Time: participants became generally less agreeable/more hostile as the afternoons progressed.

Clearheaded-Confused: There was again a significant Mixture by Light interaction. Scores decreased following ATD in the dim group (B: 52.4, SEM 1.3; T-: mean 48.7, SEM 1.3; $t_{28} = 4.28$, $p = 0.0011$) but not in the bright group (B: mean 51.6, SEM 1.6; T-: mean 52.8, SEM 1.6; $t_{28} = -1.35$, $p = 0.54$).

Composed-Anxious: There was a significant effect of Mixture such that participants were less composed/more anxious following T- (mean 56.8, SEM 0.98) than following B (mean 58.4, SEM 0.98). However, the Mixture by Light interaction was also nearly significant ($p = 0.059$) and post-hoc analyses showed that ATD significantly decreased scores in the dim group (B: mean 59.6, SEM 1.3; T-: mean 56.6, SEM 1.3; $t_{28} = 3.10$, $p = 0.02$) while there was no effect in the bright group (B: mean 57.2, SEM 1.4; T-: mean 57.0, SEM 1.4; $t_{28} = 0.20$, $p = 1.0$).

Confident-Unsure: Again the main effect of Mixture was significant, as was the Mixture by Light interaction. Scores were lower after T- (mean 49.9, SEM 0.85) than after B (mean 51.6, SEM 0.85), but this effect was restricted to the dim group only (B: mean 52.6, SEM 1.2; T-: mean 49.0, SEM 1.2; $t_{28} = 4.24$, $p = 0.0012$); there

was no effect in the bright group (B: mean 50.6, SEM 1.2; T-: mean 50.8, SEM 1.2; t_{28} = -0.25, p = 0.99).

Elated-Depressed: The Mixture by Light interaction again approached significance (p = 0.0998) so the post-hoc contrasts were also investigated. ATD tended to decrease Elated-Depressed scores in the dim group (B: mean 49.1, SEM 0.95; T-: mean 46.4, SEM 0.95; t_{28} = 2.71, p = 0.05) and not in the bright group (B: mean 48.1, SEM 1.0; T-: mean 47.9, SEM 1.0; t_{28} = 0.20, p = 1.0).

Energetic-Tired: No significant effects of Mixture and/or Light were found.

VAS: Results of the VAS analyses are summarized in Table 2.2. The outcome of the Mixture by Light interaction for Positive Mood was consistent with that of the POMS analyses. Thus, Positive Mood scores were lower following ATD in the dim group (t_{28} = 3.46, p = 0.0089) but not in the bright group (t_{28} = 0.27, p = 0.99). Analyses of the individual Positive Mood items showed that this effect was due to decreases in Excited, Happy, and Lively (data not shown). There was also a Mixture by Light interaction for Negative Mood. Unexpectedly, post-hoc testing suggested an increase in Negative Mood following ATD in the *bright* group. Analyses of the individual Negative Mood items revealed that this effect was restricted to the "Bored" item: tryptophan-depleted participants in bright light were more bored. When this item was excluded from the Negative Mood score calculation, the Mixture by Light interaction was no longer significant. We concluded that ATD decreased VAS Positive Mood in dim but not in bright light, and had no important effect on VAS Negative Mood.

Order of mixture administration

All mixed-effects analyses presented above were repeated with Time replaced by the between-subjects factor Order (T- first, B first). This did not influence any of the observed Mixture by Light effects or outcomes of post-hoc tests (analyses not shown).

Side effects

Dizziness, Headache, and Nausea were all more severe following ATD compared to placebo (Table 2.2). However, significant Mixture by Light interactions showed that for Dizziness and Nausea this effect was restricted to the dim group (post-hoc t_{28} = -

5.64, $p < 0.0001$ for Dizziness and $t_{28} = -3.96$, $p = 0.0025$ for Nausea). The observation of ATD-induced nausea in participants in the dim group was consistent with the finding that 7 of 16 vomited during the T- condition, whereas none did so during the B condition. In the bright group, 1 person was sick following ATD, and 2 were sick following placebo. Indeed vomiting tended to occur more in the dim group after T- ($n = 10$, $p = 0.07$ by Fisher's Exact Test).

All mixed-effects analyses for the POMS Total and subscale scores were repeated after exclusion of those who vomited. Mixture by Light effects were maintained for POMS Total ($F_{1,18} = 12.06$, $p = 0.007$), Agreeable-Hostile ($F_{1,18} = 14.20$, $p = 0.0014$), Clearheaded-Confused ($F_{1,18} = 17.88$, $p = 0.0005$), Composed-Anxious ($F_{1,18} = 6.43$, $p = 0.02$), and Confident-Unsure ($F_{1,18} = 10.64$, $p = 0.0043$), and became significant for Elated-Depressed ($F_{1,18} = 5.12$, $p = 0.04$). Post-hoc effects in the Dim group were also maintained. In addition, for Energetic-Tired, the Mixture by Light interaction was now significant ($F_{1,18} = 6.05$, $p = 0.02$) and consistent with mood lowering following ATD in the dim group only ($t_{18} = 3.04$, $p = 0.03$).

Influence of seasonality

We explored the possibility that the mood response to ATD in the dim group varied depending on a person's GSS score. All mixed-effects analyses for the POMS Total and subscale scores were repeated for the dim group only with Mixture, GSS (scores standardized to a mean of 0 and a standard deviation of 1) and the Mixture by GSS interaction entered in the model. Morning baseline scores were entered as covariates as described above. A significant mixture by GSS interaction was seen on the Clearheaded-Confused subscale ($F_{1,77} = 4.38$, $p = 0.04$) and on the Elated-Depressed subscale ($F_{1,77} = 6.47$, $p = 0.01$). Post-hoc tests showed that ATD lowered Clearheaded-Confused and Elated-Depressed scores in participants with GSS scores above the mean (Clearheaded-Confused: $t_{15} = 4.24$, $p = 0.0007$; Elated-Depressed: $t_{15} = 3.67$, $p = 0.0023$) whereas scores did not change in participants with GSS scores below the mean (Clearheaded-Confused: $t_{15} = 1.29$, $p = 0.22$; Elated-Depressed: $t_{15} = 0.09$, $p = 0.93$). Visual inspection of the data showed similar trends for the other subscales. While this finding must be considered preliminary, it

may explain why, in the main POMS analyses described above, the Mixture by Light interaction for Elated-Depressed scores only approached the set significance level.

8.5 Discussion

A significant lowering of mood in response to ATD in healthy mildly seasonal women was prevented by concomitant bright light exposure (Figure 2.2, Table 2.2). In dim light, ATD resulted in a lowering of mood similar to what we and others have seen in healthy women.[453] This suggests that the dim light was not exaggerating the response to ATD. Moreover, the interaction between ATD and bright light exposure could not be attributed to demographic or psychosocial factors (Table 2.1), to seasonal or meteorological influences, to baseline mood differences between the two light groups, or to differential changes in plasma amino acid levels across the groups. Previous studies have demonstrated that ATD can reverse the effect of bright light.[235,309] Our results go further in showing that (1) bright light can prevent the effect of ATD, (2) an interaction can occur between the serotonin system and short term exposure to bright light, and (3) this interaction is not confined to patients with SAD, but is seen in a much larger percentage of the population – women who exhibit mild seasonality.

Whereas bright light exposure alone did not improve mood, it moderated the influence of ATD. Apart from person-level variables such as gender, diagnosis and family history,[30,97,123] very few things are known to affect the degree of the ATD-induced mood change. The only environmental factor that has been studied in humans for its direct effect on brain serotonin is the atmospheric level of oxygen, with greater oxygen levels being associated with increased serotonin synthesis.[315] Bright light may exert a similar, albeit indirect, effect on brain serotonin synthesis. Booij *et al.* (2005) suggested that brain serotonin function must fall below a critical threshold level before effects of ATD on mood are observed.[39] Bright light may have prevented mood changes following ATD by counteracting the decrease in brain serotonin below this threshold. This hypothesis could be tested by measuring in vivo brain serotonin synthesis.[316]

The idea that bright light is an environmental factor with a direct effect on brain serotonin function is especially salient given the low levels of bright light that most people are exposed to in everyday life. Studies of natural bright light exposure (≥ 1000 lux) at several northern latitudes (30-45 N) have reported values from 23-80 minutes in winter to 119-157 minutes in summer.[80,167,182] In a recent study of mood and social interaction in mildly seasonal individuals we found similar daily exposure levels (Study 3).[3] More importantly, exposure levels calculated for mornings, afternoons, and evenings separately were associated with good mood and positive social interaction regardless of season (Study 3).[3] Seasonal people report higher levels of neuroticism, affective lability, anxiousness, and cognitive dysregulation and may therefore be vulnerable to depressed mood.[206,304] If, by acutely increasing brain serotonin function, short-duration bright light exposure has a beneficial effect in everyday life, then this may have implications for prevention of for example major depression.

How retinal light exposure affects human brain serotonin synthesis is unknown. Studies of the circadian system of experimental animals have focused mostly on retinal afferents to the SCN,[288] and on how they are modulated by innervations from the raphe nuclei.[159,299] These serotonergic pathways to the SCN have been confirmed in monkeys and humans.[286] Less attention has been given, however, to reports of a direct projection from the retina to the dorsal raphe in some species.[138,144,345] The existence of a retinoraphe tract may help explain why neuronal firing rates, c-Fos expression, and the serotonin content in the raphe nuclei are responsive to retinal light exposure,[4,60,139,289] and would have implications for light's effects in serotonin-containing brain areas other than the SCN.[288,299] The impact of retinal input on serotonin synthesis in the raphe nuclei deserves more study. The possible existence of a retinoraphe tract in humans also needs to be investigated further.

The finding that ATD-induced dizziness, nausea, and vomiting were seen only in participants who spent their test days in dim light is relevant for ATD protocols in general. Because serotonin synthesis occurs in the brain as well as in the intestines, and emesis-inducing serotonin receptors are present in both areas, the

increase in symptoms following ATD could theoretically be due to central as well as peripheral mechanisms.[179] However, given that light acts centrally, the observation that bright light was able to prevent ATD-induced side effects suggests that they are central in origin. This is consistent with previous work showing that ATD influences mood directly rather than via cognitive interpretation of somatic side effects.[379]

As with most if not all studies comparing bright and dim light, the participants were not blind to the light condition. This raises the possibility that participants in different light group had different expectations regarding their mood. On the other hand, providing participants with explicit information concerning the changes they might expect has no known influence on the effect of ATD on mood.[379] Besides, given that the tryptophan-deficient and balanced amino acid mixtures were administered under double-blind conditions, individual expectations of the light effect would be the same on both test days, yet no effects of Light alone were found. In fact, the observed interaction effect of light exposure and serotonin on mood provides further evidence for the at times disputed argument that bright light's mood effects are not solely based on people's expectations.[399]

In conclusion, this study proposes a direct interaction between the environmental factor, bright light, a neurotransmitter, serotonin, and mood. This has implications for the role of bright light exposure in the short-term regulation of mood and behaviour in everyday life as well as for the mechanism of action of phototherapy. Future studies will be necessary to extend the present findings to psychiatric populations. In patients with SAD in remission after phototherapy we might expect the ATD-induced relapse [235,309] to be attenuated by administering bright light during test days. In symptomatic SAD patients, we might even see an acute bright light-induced mood improvement that is attenuated by ATD. The findings of the present study also imply that all sources of bright light should be carefully accounted for in any studies of mood in individuals who report seasonal changes in mood and behaviour.

Chapter 9
INTERMEZZO 2

The purpose of Study 2 was to provide experimental evidence of a direct short-term interaction between bright light exposure and brain serotonin in the regulation of mood by bright light in humans. Hypotheses 2.1 and 2.2 were both supported. Bright light moderated the mood-lowering effect of ATD (Table 2.2, Figure 2.2). It also reduced the magnitude of side-effects commonly seen in ATD studies (Table 2.2). Bright light was able to do so even though the exposure lasted only a few hours, which suggests that the interaction between bright light and brain serotonin was fairly immediate. Bright light may have prevented the effect of ATD on mood by inhibiting or counteracting the decrease in brain serotonin that is usually seen following ATD.[316] Studies in experimental animals suggest that this effect may involve an active increase in the serotonin content and firing activity of serotonergic neurons.[4,60,289]

As mentioned in Chapter 7, modern life exposes people to bright light for periods that are much shorter than the time available between sunrise and sunset.[80,167,182] Study 2 suggests that this may have an impact on the regulation of normal mood by serotonin. Consistent with this idea, studies in patients with SAD have shown that the mood improvement associated with successful bright light treatment is paralleled by an increase in markers of brain serotonin function.[194,449] It is reasonable to assume that bright light might have a similar effect in healthy individuals with milder forms of seasonality, who also show mood improvement with bright light treatment.[208,209,329] However little is known about the effect of bright light on other aspects of daily life.

Links between seasonal mood variations and seasonal changes in light exposure were first reported long before the description of SAD as a subtype of mood disorder possibly linked to the decrease in day length in winter.[118] Most studies reporting these links have focused on longer time periods of exposure (seasons, months, or weeks) or have used meteorological data to approximate daily light exposure at the level of the individual.[168,212,267,284,394] Only a few studies have

employed ambulant light monitoring to more accurately measure natural light exposure.[125,167,207,419] Guillemette *et al.* (1998) studied individuals with and without subsyndromal SAD and reported that bright light exposure was higher and depression scores were lower in summer compared to winter, but unfortunately correlations between the two variables were not reported.[167] Kripke and colleagues have found links between depression or well-being and light exposure in middle-aged adults sampled from the general population and in older healthy adults, but not in younger postpartum women.[125,207,419] In one recent report, light exposure was associated with global self-report measures of social functioning, emotional well-being and quality of life in a diverse group of postmenopausal women.[163] While the methodology used in these studies is certainly preferred over meteorological data to approximate daily light exposure at the level of the individual, the studies have limitations in that (1) only daily light exposure levels averaged across time were used to assess a possible association with good mood, and (2) none of the mood variables were measured throughout the light measurement period.

Study 3 was a naturalistic study designed to advance current knowledge about the effects of light on mood and social interaction in daily life. The event-contingent recording method developed by Moskowitz (1994) was used in combination with a light meter worn at the wrist for the entire recording period.[291] Thus, detailed information about individual light exposure levels and individual social events could both be recorded accurately, and aggregated over time periods of varying length. Previous research has shown that light exposure estimates at the wrist and at the forehead are highly correlated.[319] Mildly seasonal people were selected because they are thought to be sensitive to changes in light levels. Based on the findings of Study 2, that bright light might acutely regulate brain serotonin activity, it was expected that the possible effects of bright light on social interaction would be similar to those of tryptophan observed in Study 1.

The design of Study 3 was observational rather than experimental for several reasons. First, the effects of passive light exposure may be different from those of active light administration. It was deemed necessary to start by measuring natural light levels and study its potential impact on mood and social interaction across the

wide range of light levels that people experience in their everyday lives. If no associations were found in natural settings, then future studies of light administration must really be considered a pharmacological intervention aimed at altering the brain's normal functioning, as opposed to an attempt to cure the deficiency that modern life may have brought about. Second, one advantage of using this approach is that it allowed for a careful assessment of light – social interaction associations over short time periods within days and seasons. The additional effect of light administered at a certain point during the day might have obscured these relations. Finally, this study assessed the feasibility of asking participants to wear a light meter for 20 days per season, which was necessary given that the event-contingent recording method that was used normally requires a minimum of 70-75 recorded social interactions, which are generally sampled at a rate of 5-6 records a day. Other studies of natural light exposure have been limited to a maximum of 7 days.[80,125,163,167,182,207,419]

Chapter 10

EXPOSURE TO BRIGHT LIGHT IS ASSOCIATED WITH POSITIVE SOCIAL INTERACTION AND GOOD MOOD OVER SHORT TIME PERIODS: A NATURALISTIC STUDY IN MILDLY SEASONAL PEOPLE (Study 3)

aan het Rot M, Moskowitz DS, Young SN (in press) *J Psychiatr Res.*

10.1 Abstract

Bright light is used to treat winter depression and might also have positive effects on mood in some healthy individuals. We examined possible links between bright light exposure and social interaction using naturalistic data. For 20 days in winter and/or summer, 48 mildly seasonal healthy individuals wore a light meter at the wrist and recorded in real-time their behaviours, mood, and perceptions of others during social interactions. Possible short-term effects of bright light were examined using the number of minutes, within any given morning, afternoon or evening, that people were exposed to light exceeding 1000 lux (average: 19.6 minutes). Social interactions were labelled as having occurred under conditions of no, low or high bright light exposure. Independent of season, day, time, and location, participants reported less quarrelsome behaviours, more agreeable behaviours and better mood when exposed to high but not low levels of bright light. Given that the effects were seen only when exposure levels were above average, a minimum level of bright light may be necessary for its positive effects to occur. Daily exposure levels were generally low in both winter and summer. Spending more time outdoors and improving indoor lighting may help optimize everyday social behaviour and mood across seasons in people with mild seasonality.

10.2 Introduction

Seasonal variation in prevalence and symptom severity is a feature of several psychiatric illnesses,[145] including major depression, which is more common and often recurs in winter.[17,327,393] Winter depression is the more common variant of seasonal affective disorder (SAD).[353] The Seasonal Pattern Assessment Questionnaire (SPAQ)[349] was developed to assess the magnitude of the seasonal symptom changes in SAD but has also been used to measure the wide range of seasonality in the general population.[168,178,366] An awareness of seasonal changes in mood and behaviour is present in most people.[210,261,303]

Feeling worse in winter is most often associated with light-related variables, such as short day length and grey cloudy weather.[209,210,366] Consistent with the idea that a relative lack of exposure to bright light may be responsible for at least some of the clinical characteristics of SAD, treatment with artificial bright light is often successful in alleviating winter depression.[353,396] The effects of bright light in patients with SAD have mostly been studied over a period of weeks. However, reports of improvement after 2-3 days, in the afternoon following morning light therapy, and after as little as 1 hour, do exist.[227,352,353,376] Observations of the benefit of morning bright light fading later in the day or lasting only a single day also suggest that short-term exposure is sufficient for mood change to occur.[208,227] If bright light can improve mood in patients with SAD after even a few hours, then bright light's effects on normal mood in everyday life may also be fairly immediate.

Several studies conducted in winter at latitudes 39-60N examined the effect of light therapy on mood in healthy people. Treatment usually consisted of 2500 lux daily for various lengths of time over the course of at least a week. While some studies found that bright light could improve mood,[18,209,329] others did not.[21,152,351] Overall, findings indicated that artificial bright light, when administered over longer time periods, may mostly benefit individuals with marked seasonality, although individuals with only mild seasonality may also show positive effects when provided with appropriate light doses. None of these studies investigated the possible short-term effects of bright light.

Despite its assumed relevance to seasonal psychopathology, data on the relation between natural light exposure and mood are scarce. In one study of young women, mood and ambient light levels were measured twice daily for 32 days and found to be positively associated.[121] In another study, which included middle-aged men and women, mood was associated with the degree of exposure to bright light (≥ 1000 lux) in the week before the two-day measuring period.[125] Finally, in a group of elderly people, mood assessed during study intake was associated with light exposure the week after,[207] possibly because exposure to bright light during this week reflected habitual exposure. Overall these findings indicate that, at least in some circumstances, an increase in natural bright light exposure might benefit mood and well-being in everyday life. However, the studies were limited because either mood was measured at a single time point only, which limits the sensitivity to detect changes in response to light,[125,207] or light levels were not measured continuously across time, which prevents the determination of its speed of action.[121] Studies on the relation between everyday light exposure and mood should include multiple and frequent measurements of both.

A possible effect of light on mood suggests it might also influence behaviour. We have shown that tryptophan, the precursor of serotonin, improves social behaviour along the agreeable-quarrelsome dimension in healthy people (Study 1).[2,294] An event-contingent recording method was used which provides reliable estimates of behaviour when data are aggregated over a suitable number of days.[291] Based on recent observations in healthy volunteers that bright light exposure may affect the serotonin system within a few hours (Study 2),[1,236] the present study was designed on the premise that the effects of light on everyday social behaviour and mood would resemble those of tryptophan. In mildly seasonal healthy individuals, who are sensitive to seasonal changes in natural light levels without suffering from winter depressions, ambient light levels and social interactions were measured across 20-day periods in winter and summer. Bright light exposure was hypothesized to be associated with lower levels of quarrelsome behaviours, higher levels of agreeable behaviours, and better mood. We focused on season-independent associations that might occur over short time intervals.

10.3 Methods

Participants

The study was approved by the Research Ethics Board of the McGill University Health Centre. All participants provided written informed consent after the study had been explained and were remunerated for time spent in the study.

The study was conducted in Montreal, Canada (near latitude 45N). Participants were recruited in winter (November-March) or summer (May-September). Advertisements including the question "Do you feel less energetic in winter than in summer?" were posted in local newspapers. People who telephoned and were mildly seasonal according to the Global Seasonality Scale (see below) were invited for a screening in the lab and were given detailed study information. After providing informed consent, candidates completed the Beck Depression Inventory (BDI)[26] and the Seasonal Pattern Assessment Questionnaire (SPAQ).[349] The Global Seasonality Scale (GSS; score range 0-24) is part of the SPAQ and was used to measure the extent of seasonal change in mood, social activity, energy, sleep length, appetite, and weight. Candidates were interviewed as well, using the Structured Clinical Interview for DSM-IV, Non-Patient Edition.[385]

Mild seasonality was defined as a GSS score from 6 to 11. This includes about one third of the population at latitude 40N.[210] Only individuals meeting this criterion both at the telephone interview and during the initial screening in the lab could participate. Participants were also required to be working ≥ 30 hours per week. Night shift workers, those working alone, and those intending to change jobs within 6 months were excluded. Additional exclusion criteria were a BDI score higher than 15, any lifetime Axis I disorders, use of psychotropic medication, evidence of a serious medical condition, pregnancy and lactation. Hormonal contraceptive use was allowed but recorded in both seasons.

Between January 2004 and March 2005, 53 candidates successfully passed the screening and started the study. Participants started in winter (n = 30) and returned in summer (n = 23; 1 dropped out, 4 changed jobs, 2 were lost to follow-up) or started in summer (n = 23) and returned in winter (n = 12; 4 dropped out, 3 changed jobs, 2 were lost to follow-up, 2 became pregnant). Dropouts did not

complete the season in which they started and were not included in the data analyses. The remaining participants (n = 48) completed data collection in at least one season. The average inter-season interval for participants who completed both seasons was 25 weeks (SD 4, n = 35).

Light exposure measurements

In each 20-day study phase ambient light levels were recorded using a wrist-worn device equipped with an accelerometer and a light sensor (Actiwatch-Light®, Mini Mitter, Inc., Bend, OR, USA). It measured both motor activity and light levels every 2 minutes from 00:00 hours on day 1 till 23:59 hours on day 20. Bright light exposure, defined as ≥ 1000 lux, was calculated for different time periods (BLE, in minutes). Individual days were defined as lasting from wake time to sleep time (based on self-report, see below). In addition, given our main interest in short-term effects of light on social interaction, individual mornings, afternoons, and evenings were defined as follows: from wake time to 11:59 hours, from 12:00 hours to 16:59 hours, and from 17:00 hours to sleep time or 23:59 hours, whichever was earlier. Thus, BLE levels were calculated for individual days (20 values per person per season) and for individual mornings, afternoons, and evenings separately (60 values per person per season).

The data were visually inspected for compliance using the Actiware™-Rhythm software (version 3.2, revision 2, Mini Mitter, Inc.). Small irregular movements for extended intervals indicate sleep and were used to check self-reported wake and sleep times. If self-report data were missing, wake and sleep times were based on visual estimates. A complete absence of motor activity for extended time intervals is an indication that the device is not being worn. If more than 3 hours of data were missing on any given day, its BLE value was tagged and not used for the calculation of seasonal differences in daily exposure to bright light. If gaps lasted for more than 1 hour in the morning, afternoon, or evening, corresponding BLE values were tagged, and not used when investigating the relation between bright light exposure and social interaction. The following data analyses focus on short-term BLE and values obtained from mornings, afternoons, and evenings separately.

Event-contingent recording of social interactions

A social interaction was defined as a spoken conversation, in person or on the phone, lasting at least 5 minutes. Participants completed a standardized form about their behaviours, affect, and perceptions of others, as soon as an interaction had occurred. They also indicated the time and location and were asked to record the number of drinks if they had consumed alcohol and to not complete a form if they had consumed illicit drugs during the 3 hours before an interaction.

Each form included 3 quarrelsome, agreeable, dominant and submissive behaviours. They were taken from a list of 46 shown to provide valid and reliable scores of each dimension of social behaviour.[51,291,293,295] The list of behaviours on a form varied in a daily rotation of 4 forms to prevent participants from checking the same behaviours for every interaction. Scores for each of the 4 behaviours were calculated for each record form by computing their individual mean frequency and then subtracting the mean frequency for all behaviours. These ipsatized scores reflect the frequency with which quarrelsome, agreeable, dominant and submissive behaviours were checked, adjusted for the general rate of behaviour checking.

Two methods were used to measure mood during social interaction. First, participants indicated the extent to which they were feeling unpleasant *vs.* pleasant (affect valence) and the extent of alertness *vs.* sleepiness (affect arousal) on using a single mark on an 11 by 11 grid.[361] Form scores for affect valence and arousal were coded from the affect grid using a number between 1 and 11. Higher scores on the horizontal and vertical dimensions indicated more pleasant affect and greater arousal, respectively. Second, participants checked a list of 9 positive and negative affect adjectives on a scale from 0 to 6.[108] Positive and negative affect were calculated by adding up the individual adjective scores corresponding to positive or negative affect, and dividing each sum score by the total number of adjectives to provide a mean.

Perceptions of others were assessed on another 11 by 11 grid. Participants could indicate to what extent they perceived their social interaction partner as quarrelsome *vs.* agreeable and dominant *vs.* submissive. Participants were instructed to complete this interpersonal grid with a single mark when interacting

with one other person or with a primary other in a group, but to leave the grid blank when no primary other could be identified.[297] Higher scores on the horizontal axis indicated that others were perceived as more agreeable. Higher scores on the vertical axis indicated that others were perceived as more dominant. Scores on each dimension could range from 1 to 11.

Study overview

Before each study phase (winter, summer), participants completed the SPAQ and the BDI. Use of the light meter and the record forms was explained. Measurements started on a Tuesday. Participants were instructed to wear the light meter on their non-dominant hand at all times, to keep the device uncovered by clothing, to maintain regular wake and sleep times, to avoid naps, and to not wear sunglasses. At the end of each study phase, participants completed another BDI and a questionnaire about their experience with the light meter and record forms (see Table 3.1).

Participants were instructed to complete up to 10 record forms per day and to disperse completion throughout the day. At the start of each study phase, they were provided with 20 pre-addressed and stamped envelopes, with 10 record forms each and an additional sheet with questions pertaining to wake and sleep times, nap length, and, for women, menstruation. Forms were to be returned the day after completion. Participants completed on average 125 forms per season (SD 42).

Data analyses

Individual social interactions (recorded in the morning, afternoon, or evening of a particular day in winter or summer) were linked to corresponding light meter data. Removal of tagged light meter data resulted in the exclusion of 13.0% of record forms. Removal of forms completed within three hours of alcohol ingestion resulted in the exclusion of an additional 3.3% of the forms. A total of 8,768 record forms remained for the data analyses. The average BLE across participants, seasons, days, and time periods was 19.6 min per period (range 0-294 min).

Data were analyzed using multilevel models with maximum likelihood estimation (PROC MIXED in SAS version 8.02). Our main hypothesis was that there would be associations between short-term BLE and social interaction variables,

independent of Season. We investigated these associations with Day of the week, Time period, and Location entered as covariates in addition to Season. Record forms were coded as occurring in one of three groups according to the average level of BLE during the period of the social interaction (morning, afternoon or evening). Thus, for 42% of reported interactions, there was no BLE (0 min). For 29%, BLE was low ($0 < BLE \leq 19.6$ min). For 29% of interactions, BLE was high (> 19.6 min). In the multilevel models, the 4 covariates Season, Day, Time, and Location were entered first, followed by BLE (no, low, high) as a main effect. Preliminary analyses showed that Gender did not influence BLE levels and thus was not retained in further analyses. Differences due to varying BLE levels were calculated for all outcome measures and tested for significance at $\alpha = 0.05$. Post-hoc tests were Tukey-corrected. When the main effect for BLE was significant, estimated least-squares means and standard errors are reported separately for no, low and high BLE.

10.4 Results

Preliminary data investigation

Evening BLE levels were more likely to be tagged for being unreliable than morning ($t_{47} = -3.14$, $p < 0.003$) and afternoon data ($t_{47} = -3.24$, $p < 0.003$), which were equally likely to be tagged ($t_{47} = -1.46$, $p > 0.1$). There were no seasonal differences in tagging ($t_{81} = 0.10$, $p > 0.9$).

As anticipated, BLE was higher in summer than in winter ($F_{1,34} = 721.79$, $p < 0.0001$). In addition, we expected and found that the three other within-subjects factors Day of the week ($F_{6,278} = 22.92$, $p < 0.0001$), Time period ($F_{2,93} = 358.22$, $p < 0.0001$), and Location ($F_{3,139} = 62.22$, $p < 0.0001$) also influenced BLE. Levels were generally higher on weekends, highest in the afternoon and lowest in the evening, and lower at home and at work in comparison to recreation and elsewhere.

In winter, the average *daily* bright light exposure level (that is, from wake time to sleep time) was 26.0 minutes (range 0.5-116 minutes). In summer, the average daily bright light exposure level was 91.2 minutes (range 20-296 minutes). The difference was significant ($t_{57.4} = -6.43$, $p < 0.0001$).

Effects of season, day of the week, time of the day, and location alone

We investigated seasonal differences in social behaviour, mood, and perceptions of others using separate multilevel models. Season, a within-subjects factor with two levels (winter, summer), was the independent variable. Gender, a between-subjects factor with two levels (male, female), was initially also entered but removed because it did not change the effects of Season.

Winter was associated with lower levels of dominant behaviours ($F_{1,34}$ = 10.75, $p < 0.003$), higher levels of submissive behaviours ($F_{1,34} = 4.53$, $p < 0.05$), lower levels of affect arousal ($F_{1,34} = 20.64$, $p < 0.0001$), and less negative affect ($F_{1,34} = 46.18$, $p < 0.0001$). Seasonal differences in quarrelsomeness, agreeableness, affect valence, positive affect, and perceptions of others were not found (all p's > 0.07). Event-level means and standard errors are shown in Table 3.2. Excluding participants who only completed one season did not change the findings.

These analyses were repeated with Day of the week, Time period, or Location as the independent variable. Consistent with previous work,[51,295] they each independently influenced social interaction, across all dependent variables (data not shown).

Associations between bright light and social interaction

Multilevel models with the various social interaction variables as dependent factors and BLE (no, low, high) as an independent factor were analyzed with Season (winter, summer), Day of the week (Monday-Sunday), Time period (morning, afternoon, evening), and Location (home, work, recreation, elsewhere) entered first as covariates. For each dependent variable, the F- and p-values of the significant covariates are provided in Table 3.3. The four covariates remained significant across most of the social interaction variables even when entered into the models simultaneously. In addition, several associations between social interaction and bright light were found.

Quarrelsome behaviour: The association between BLE and quarrelsomeness was significant ($F_{2,89} = 4.46$, $p < 0.02$, see Figure 3.1a). Levels of quarrelsomeness were lower when BLE levels were high (mean ± SEM, -14.8 ± 0.9) compared to

when BLE levels were low (-13.1 ± 0.8) or zero (-13.6 ± 0.8). The difference between high and low BLE was significant (t_{89} = 2.97, p < 0.02). However, the difference between high and no BLE was not (t_{89} = 1.94, p > 0.05 before Tukey correction, p > 0.1 after Tukey correction). In addition, there was no difference between low and no BLE (t_{89} = -0.91, p > 0.6).

Agreeable behaviour: There was also a significant association between BLE and agreeableness ($F_{2,89}$ = 3.87, p < 0.03, see Figure 3.1b). Level of agreeableness was higher when BLE was high (14.4 ± 1.0) compared to when BLE was low (12.5 ± 1.0) or zero (13.0 ± 1.0). The difference between high and low BLE was significant (t_{89} = -2.75, p < 0.02). The difference between high and no BLE was not (t_{89} = -1.90, p > 0.06 before Tukey correction, p > 0.1 after Tukey correction). There was also no difference between low and no BLE (t_{89} = 0.72, p > 0.7).

Affect arousal: There was also a significant association between BLE and affect arousal ($F_{2,89}$ = 10.21, p < 0.0001, Figure 3.2a). Compared to periods without BLE (7.2 ± 0.1), participants reported higher arousal during periods with both low and high BLE (low: 7.4 ± 0.1, t_{89} = -4.36, p < 0.0002; high: 7.4 ± 0.1, t_{89} = -3.30, p < 0.005). The difference between low and high BLE was not significant (t_{89} = 0.70, p > 0.7).

Affect valence: There was a significant association between BLE and affect valence ($F_{2,89}$ = 3.89, p < 0.03, Figure 3.2b). Participants reported more pleasant affect when BLE levels were high (7.9 ± 0.1) compared to when BLE levels were low (7.7 ± 0.1) or zero (7.7 ± 0.1). The difference between high and low BLE was significant (t_{89} = -2.68, p < 0.03). After Tukey correction, the difference between high and no BLE was not significant (t_{89} = -2.13, p < 0.09). There was also no difference between low and no BLE (t_{89} = 0.40, p > 0.9).

Positive affect: There was a significant association between BLE and levels of positive affect ($F_{2,89}$ = 11.66, p < 0.0001). Participants reported progressively more positive affect as BLE increased (no: 1.9 ± 0.1, low: 2.0 ± 0.1, high: 2.1 ± 0.1). The differences between low and zero BLE (t_{89} = -2.91, p < 0.02) and between high and zero BLE (t_{89} = -4.81, p < 0.0001) were significant. After Tukey correction, the

difference between high and low BLE was no longer significant (t_{89} = -2.35, p < 0.06).

There were no significant associations between BLE and dominant behaviour (p > 0.1), between BLE and submissive behaviour (p > 0.05) and between BLE and levels of negative affect (p > 0.1). BLE was also not significantly associated with perceptions of others (p's > 0.1).

These findings did not change when Gender was included, when GSS scores were added as a moderator, when participants who completed only one season were excluded, or when phase of the menstrual cycle in women was corrected for. Finally, controlling for the prevailing arousal level during each social interaction did not affect the relation between BLE and behaviours, mood, and perceptions.

Bright light on the previous day

The multilevel models described above were repeated with BLE values taken from the same time period the day before each social interaction. This was done to rule out the possibility of a general effect (since adjacent days may be likely to be consistently low or high in BLE). There was no significant association between BLE and social interaction for any of the variables investigated (all p's > 0.1). Post-hoc differences between no, low, and high BLE were also not significant (all p's > 0.1).

10.5 Discussion

The present study included mildly seasonal individuals in whom both ambient light levels and social interactions were recorded during 20 consecutive days in both winter and summer. This study is the first to examine possible short-term effects of bright light (≥ 1000 lux) in healthy people with mild seasonality, to concurrently measure everyday light exposure and mood over multiple days, and to measure social behaviour in addition to mood as possible variables influenced by prevailing light levels. Bright light exposure in any given time period (morning, afternoon, evening) averaged 19.6 minutes. Independent of season, above-average exposure levels were associated with less quarrelsome and more agreeable behaviours, as well as better mood.

Our results raise three main issues. First, can cause and effect be inferred? Did bright light improve mood and social interaction, did good mood and positive social interaction increase bright light exposure, or were both influenced by some other unknown variable? Second, what are the potential confounding factors? Third, is there a plausible mechanism that explains our results?

The impact of bright light exposure on mood has been studied experimentally in individuals with mild to moderate seasonality before, and the findings are broadly consistent with our present observations concerning the effect of light on social interaction.[18,209,329] One novel aspect of our study was to look at short-term effects of bright light. The level of bright light exposure during a period of approximately 5 hours was positively associated with good mood (Figure 3.2b) suggesting that any effect of bright light on mood and social behaviour occurs after short-term exposure. Overall, bright light exposure averaged 26.0 minutes per day in winter and 91.2 minutes in summer, values comparable to reports from similar studies.[80,167,182] It is likely that, on most days in winter and on some days in summer, participants in the present study had insufficient bright light exposure for optimal mood. In agreement with at least one earlier study,[245] we propose that bright light can have a positive effect on well-being in both winter and summer.

The concern for possible confounding factors that might explain our findings is important. For example, in recreational settings and during the weekends, participants are (1) most likely to be exposed to higher levels of bright light, and (2) generally more agreeable and less quarrelsome, and in a better mood. To examine this possibility, we controlled not only for the season and the time of day during which the interaction took place, but also for the day of the week and the location. Even after controlling for these four variables, the associations of bright light exposure levels with mood and social behaviour were still apparent. However, while we controlled for obvious potential confounds there may be other less obvious ones that remained uncontrolled in the analyses.

The third issue is the existence of a plausible brain mechanism relating bright light to improved mood and social interaction. Bright light exposure, like tryptophan, may increase brain serotonin synthesis, and there are similarities between the

known effects of tryptophan on social interaction (Study 1)[2,294] and the identified effects of bright light on social interaction. Our hypothesis that bright light exposure might affect communal behaviours and mood in a way similar to tryptophan was confirmed. Thus, an increase in brain serotonin function is a plausible explanation for the effect of bright light on social interaction and mood. This explanation is further supported by the results of a study in which serotonin turnover rates were related to sunlight on test days but not with sunlight on preceding days.[236] Furthermore, in a group of mildly seasonal healthy women, we found that the mood lowering in response to acute tryptophan depletion was prevented by bright light exposure during test days (Study 2).[1] This study provides evidence for a relation among short-term bright light exposure, brain serotonin, and mood, thus providing a plausible mechanism of action for the non-experimental observations presented here. It remains possible, however, that other neurochemical pathways may also be involved. This would explain why bright light exposure was positively associated with participants' arousal level (Figure 3.2a), while tryptophan administration is more likely to decrease arousal.[294]

Some additional differences between the present findings and those reported previously were found. Whereas tryptophan was found to alter behaviour along the dominant-submissive axis (Study 1),[2,294] in the present study levels of dominant and submissive behaviours were little affected by short-term bright light exposure. On the other hand, there was a seasonal difference: winter was associated with less dominance and more submissiveness. This could not be explained by a shift in social interaction location. However, work settings, in which dominant and submissive behaviours are more salient,[295] were generally associated with lower light levels, and so the capacity for change may have been limited by the preponderance of low light in contexts relevant to dominant and submissive behaviours. Alternatively, behaviours along the dominant-submissive dimension might be less sensitive to short-term changes in the light environment than behaviours along the quarrelsome-agreeable dimension.

As in the recent tryptophan study (Study 1),[2] participants in the present study reported their perceptions of others. Tryptophan caused participants to perceive

others as more agreeable (and more dominant) but no such effect was associated with bright light. A person's perception of others may change only if the other's social behaviour is altered consistently across social interactions, for example by multiple-day tryptophan treatment. Therefore, given that we were studying aspects of mood and behaviour associated with short term exposure to bright light, no association with altered perception of others would be expected.

If bright light can influence mood and social behaviour, then this has potential implications for health. Hostility, the mood associated with quarrelsomeness, is a risk factor for heart disease and for all-cause mortality.[282] Agreeableness may be a significant protective factor against mortality, at least in some older people.[424]

10.6 Conclusion

The healthy, working mildly seasonal individuals who participated in the present study may often have been insufficiently exposed to bright light to ensure optimal social interaction. Above-average bright light levels were associated with lower levels of quarrelsomeness, higher agreeableness, and better mood. Especially in winter, but also on some days in summer, these participants might have benefited from additional bright light exposure, which could be derived from more outside activities or better indoor lighting. If a relative lack of light contributes to worse mood and poor social interaction, then modifications in individual exposure levels may help prevent some mental as well as physical problems.

Chapter 11
GENERAL DISCUSSION

11.1 Summary of findings

In Study 1, participants were men and women who scored high on trait irritability and angry hostility. When they were taking tablets containing the serotonin precursor, tryptophan, they reported lower levels of quarrelsome behaviours as well as higher levels of agreeable behaviours. Men but not women perceived others as more agreeable and displayed less dominant behaviours. Both men and women perceived others as more dominant. Moreover, their mood improved. In Study 2, participants were women who experienced mildly seasonal changes in their mood and behaviour. Mood worsening following acute tryptophan depletion was reported by those who spent test days in dim light, but not by those who spent test days in bright light.

Study 3 was based on the idea that bright light interacts with the serotonin system when regulating mood (see Study 2), and may therefore possibly affect other aspects of daily functioning as well (see Study 1). Associations between natural bright light exposure and affective, behavioural, and perceptual aspects of individual social interactions were studied over short time periods. Participants were mildly seasonal men and women. Hypotheses 3.1-3.2 were supported. Above-average levels of bright light exposure were associated with lower levels of quarrelsome behaviours (Figure 3.1a), higher levels of agreeable behaviours (Figure 3.1b), and better mood (Figure 3.2a). Hypothesis 3.3 was not supported. Perceptions of others were not significantly related to the prevailing bright light level. This will be discussed further in paragraph 11.5.

11.2 Serotonin and the regulation of social interaction and mood

Chapter 3 described Leary's (1957) circumplex model of interpersonal relations.[241] Within this model, the participants of Study 1 were less communal compared to those in the unselected sample studied by Moskowitz *et al.* (2001).[294] This is not surprising, as the former group had been selected on the basis of scoring high on

two questionnaires that measure trait irritability and angry hostility. The effects of tryptophan on communal behaviours were more pronounced in Study 1 than in the study by Moskowitz *et al.* (2001).[294] This is consistent with earlier studies of the effects of tryptophan manipulations on laboratory measures of aggression, in which people high on aggressive traits show an increased sensitivity to the manipulations compared to people low on these traits.[33,70,110,136] Serotonin appears to have the capacity to improve the quality of everyday social behaviour both inside and outside laboratory settings. For men and women at risk for displaying impulsive aggression, an increase in serotonin may have a constructive effect on their everyday lives.

The behavioural and perceptual changes that were seen during (and after) tryptophan administration were intricately linked with the change in affect that was observed. The covariate analyses performed in Study 1 indicated that the level of pleasant affect at the time of a social interaction was inversely related to the level of quarrelsome behaviour during that social interaction. On the other hand, the tryptophan-induced increases in pleasant affect and in agreeable behaviours (and perceptions) did not occur concurrently, even though overall mean levels of pleasant affect and agreeableness were highly correlated, as they usually are.[293] To explain the processes underlying this phenomenon, it may be useful to consider the principle of complementarity described in Chapter 3.[64,216] If tryptophan increased agreeable behaviours in one particular social interaction, then the outcome of that interaction may have benefited the overall quality of the social relation, and this in turn may have lowered levels of quarrelsome behaviours and improved mood in the next social interaction with the same partner. Alternatively, an initial reduction in quarrelsomeness (also seen in the tryptophan study by Moskowitz *et al.*) may have been followed by an increase in agreeableness once mood improved. If mood improvement was slower in the women, this may explain why the increase in agreeableness seen in the women was significant only when mood was taken into account. Finally, it is plausible that the reciprocal changes in complementary behaviours, and between behaviours and complementary perceptions, occurred concurrently rather than consecutively. Further studies will be necessary to elucidate the processes underlying the changes that were seen.

So far this Discussion has mainly focused on serotonin in relation to communal behaviours and mood. Yet changes in agentic behaviours were also seen in Study 1. Men, but not women, reported fewer dominant behaviours while taking tryptophan. This gender difference was not expected, nor were levels of dominant behaviours expected to decrease, since Moskowitz *et al.* (2001) had previously found that tryptophan increased levels of dominant behaviours in both genders.[294] This apparent discrepancy between the two studies was discussed in light of the characteristics of the present sample, where participants described themselves as hostile and irritable. In line with social rank theories of depression, described in Chapter 4, levels of dominant behaviours in the men were unusually low even during placebo treatment. This may be an indication of their low social status. Prior to the start of the study, the male participants of Study 1 may have been quarrelsome in an attempt to enhance their social dominance, which may ultimately increase social status. Failed attempts possibly contributed to their irritability. Successful attempts, however, may have improved mood, at least momentarily, thereby reinforcing the quarrelsome behaviours. When tryptophan inhibited these quarrelsome behaviours, this may have lead to an increase in participants' social acceptance. Others' experience of interacting with the participants may have been more positive than before the study, which have made them more likely to continue interacting with the participants over time.[101] Feeling included or accepted in one's social group is an important determinant of subjective state.[122] If the increase in social acceptance decreased the need for the behavioural reinforcement of social status, then this might explain why levels of displayed dominant behaviours decreased in the men.

11.3 The pros and cons of being quarrelsome

The display of quarrelsome behaviours is undesirable in many social contexts. Serotonin can suppress these potentially harmful behaviours. This raises the question of why trait quarrelsomeness is maintained in the population. For it to persist across multiple generations, one must consider the possibility that being quarrelsome might be beneficial in some situations. As suggested in the previous

paragraph, being quarrelsome may sometimes increase social inclusion, although the frequency with which this might occur is probably lower than that of social rejection in response to quarrelsomeness. Nonetheless, the reward associated with the social inclusion, even though it will probably be short-lived, increases the likelihood that the quarrelsome behaviour will recur in the future.

Gerald and Higley (2002) have formulated a hypothesis of why similar behaviours, and the low serotonin phenotype associated with it, are maintained in nonhuman primates.[153] Monkeys with low CSF levels of the serotonin metabolite, 5-HIAA, display higher levels of impulsive-aggressive and risky behaviours than those with low CSF 5-HIAA levels.[191,275,430] Male monkeys with low CSF 5-HIAA levels are also less likely to engage in reproductive behaviours and to produce offspring.[154,277] Female monkeys with low CSF 5-HIAA levels are also less likely to reproduce and their offspring is less likely to survive beyond infancy.[73,429] Gerald and Higley (2002) suggest that, despite these obvious threats to the survival of the low serotonin trait, the impulsive-aggressive and risky behaviours in these monkeys are maintained precisely because they engage in these behaviours. Among males with low levels of CSF 5-HIAA, those that do reproduce are more likely to be younger than the dominant alpha male, who usually has the most offspring.[154] The risk of displaying impulsive-aggressive behaviours may result in the short-term reward of defeating the dominant male in reproductive success. In one study, high impulsivity during adolescence predicted alpha status one year later.[130] However, the behaviours of these impulsive monkeys with low CSF 5-HIAA levels are thought to be costly in the long run. Retaliation by the other males could be an significant factor in their early death.[190] Similar processes may underlie both reproductive success and increased mortality in female monkeys with low CSF 5-HIAA levels, although in these monkeys impulsive approach may be more common than impulsive aggression.[266,429] Regardless of gender, if these impulsive behaviours were inhibited by serotonin, then it may lessen the chance to reproduce. Success of the species is therefore based on the inclusion of individuals with a wide range of impulsive-aggressive tendencies and associated brain serotonin activities.

A recent study of multiple species of macaques is consistent with this idea,

and expands it to other areas of functioning in which being impulsive may be advantageous.[428] Species characterized by a high inter-individual variability of impulsive-aggressive behaviours have been more successful in spreading across multiple geographical locations than species with a low inter-individual variability of these behaviours. Presumably, the presence of impulsive individuals in a population may increase opportunities for the group because their risk-seeking and exploratory behaviour, although often dangerous, may prove beneficial in some situations. Interestingly, only the species with the highest geographical distribution possesses the 5-HTTLPR polymorphism, which is thought to regulate individual variations in serotonin neurotransmission in humans.

In humans, too, serotonin is seen as a neuromodulator involved in keeping a balance between impulsiveness and constraint.[383,386] Carver and Miller (2006) recently reviewed some important issues about the relevance of impulsiveness and constraint to hostility.[66] They and others have argued that, to ensure an optimal outcome of behaviour, it is necessary to carefully weigh both the positive and the negative aspects of all available options, regardless of when in time they may occur. Thus, both the immediate and the delayed effects of each action must be taken into account. Constraint, or the lack thereof, is the result of this effortful cognitive processing. Impulsiveness, on the other hand, can be defined as the selection of immediate benefits without considering cues of delayed ones.

Participants in Study 1 may have derived some advantages from being quarrelsome at times, but the fact that participants were unhappy with the quality of their social interactions suggests that the long-term outcome was undesirable. By reducing mean levels of quarrelsome behaviour, tryptophan may have inhibited the impulsive gain of immediate, often small rewards (*i.e.* situational dominance) such that delayed but larger rewards became available (*i.e.* a more general social acceptance).[9] Serotonin seems to exercise control over the appropriateness of quarrelsome behaviours.

11.4 Being agreeable has long-term rewards

In Study 1, tryptophan not only reduced behaviours that are generally considered

antisocial, but also enhanced behaviours that are generally considered prosocial. This is considered a positive change in social functioning, and one that involved more than a simple decline in negative tendencies. But what is the gain of an increase in agreeableness over and above a decrease in quarrelsomeness? From an evolutionary standpoint, the acute reduction of maladaptive behaviours such as quarrelsomeness and aggression has obvious survival value. On the other hand, the additional promotion of agreeable behaviours does not.

In this respect, it might be useful to consider agreeableness as an altruistic act. Evolutionary theories of altruism are often summarized into two main models, that of kin selection (behaving altruistically is an investment in the survival of genetically related individuals) and that of reciprocal altruism (altruistic behaviour toward another is reciprocated by altruistic behaviour by the other). However, neither model explains why humans (unlike most other mammals) behave altruistically toward unrelated and unacquainted individuals.[318] In 1998 Nowak and Sigmund introduced the idea that indirect reciprocity plays a role.[317] Even though altruistic behaviour yields no reward at the time when it occurs, the reward to the donor will come at a future point in time when he or she becomes the receiver of another person's altruistic behaviour. In the short term, altruism can be costly, which is why it might prevent some from engaging in cooperative behaviour. In the long term, however, altruism increases the chance of obtaining benefit in return.[317] Similarly, the increase in agreeableness that was seen in Study 1 during tryptophan administration may therefore be interpreted as a shift toward an increased interest in longer-term benefits (as was the decrease in quarrelsomeness that was seen, as discussed in the previous paragraph). The tryptophan-induced increase in levels of agreeable behaviours that was seen might thus have implications for the role of serotonin in human altruism.

A limitation of Nowak and Sigmund's indirect reciprocity model is that it does not clearly explain what may constitute a benefit worthy of behaving altruistically. In response to this concern, Hardy and van Vugt (2006) recently proposed that behaving altruistically may increase a person's status, because the behaviour is indicative of a person's desirable qualities.[169] Status, in turn, increases access to

resources, which will ultimately benefit survival and reproduction (see Chapter 2). In keeping with Hardy and van Vugt (2006), an increase in agreeableness such as that induced by tryptophan in Study 1 may thus result in an increase in social status without the need for a display of overt dominant behaviours.

When testing their hypothesis, Hardy and van Vugt (2006) found that individuals who displayed altruistic behaviours were more likely to be perceived as leaders by others. In contrast, they were not more likely to be better liked than individuals who did not display altruistic behaviours.[169] This could be taken to mean that perceiving another person as dominant is more closely related to that person's level of altruism than perceiving the other person as agreeable. In Study 1, tryptophan increased perceptions of dominance more than it increased perceptions of agreeableness. One could speculate, based on Hardy and van Vugt's findings, that these changes in perceptions of others were an indication that participants saw others as more altruistic when they were taking tryptophan. This, in turn, may have resulted in the changes in communal behaviours that were seen. Although this explanation is highly speculative, it is consistent with research suggesting that the ability to perceive dominance-related cues is also very important in nonhuman primates.[96] Seeing others as more dominant may be an indication that others' desirable characteristics are perceived more accurately.

In summary, the tryptophan-induced increase in agreeableness that was seen in Study 1 can be explained by considering its potential long-term benefit.[169,317] Being more agreeable may contribute to constructive relations with other people, and may increase social acceptance and even benefit social status (without a need for overt dominant behaviour). These effects of tryptophan are reminiscent of the effects of serotonergic drugs on affiliative behaviours, status, and the display of constrained aggression in monkeys (see also Chapter 2).[338,342]

11.5 Bright light and the regulation of social interaction and mood

Effects of bright light on mood have been shown in a number of studies in patients with SAD, as well as in healthy volunteers who experience seasonal changes in mood without becoming clinically depressed in winter.[208,209,329,353,396] Bright light

may help prevent the dysregulation of mood: it can delay symptoms in patients with SAD if administered just prior to the normal time of onset and may even prevent depressive episodes if administered well in advance of the normal time of onset.[328,398] Consistent with the idea that bright light is involved in the regulation of normal mood, Study 2 showed that bright light administration during ATD was able to prevent the worsening of mood that is often seen following this procedure. The mildly seasonal women who participated in this study only showed ATD-induced mood worsening if they spent their test days in dim light. This study not only provides evidence for a relationship among mood regulation, bright light, and the brain serotonin system, but also shows that bright light can regulate mood over short time intervals (a couple of hours during ATD test days).

It should be noted that bright light had a greater ability to reverse an ATD-induced decline in mood than to raise mood above baseline. The comparison of mood under bright light and mood under dim light was a between-group comparison so small light-induced mood changes may not have been detected. However, it can be argued that bright light may have had a beneficial overall effect on mood. A recent study suggests that serotonin synthesis in the human brain can be influenced by altered mental state.[332] Thinking about a negative past event lowered serotonin synthesis in some brain areas, raising the possibility of a feed-forward effect in which changes in brain chemistry would reinforce negative mental states. Bright light may play a role in preventing such an effect by counteracting the lowering of serotonin in response to external stimuli. Thus, bright light may regulate mood in everyday life by helping to maintain positive mood in spite of the daily hassles that may tend to lower mood.

Study 2 also addresses some other issues that are relevant to the regulation of normal mood. Several personal variables, such as gender, diagnosis and family history,[30,97,123] and a smaller number of situational variables, such as the research setting,[31,379] have been considered as factors that could potentially affect the degree of the ATD-induced mood change. However, virtually nothing is known about environmental factors that might influence this. The only such factor that has been studied in humans for its direct effect on brain serotonin synthesis is the atmospheric

level of oxygen. Greater oxygen levels have been associated with increased serotonin synthesis (measured using brain imaging).[315] This suggests that the mood effects of ATD might be attenuated if participants were to breathe oxygen at concentrations higher than the 21% available in the Earth's atmosphere. This has not been investigated. Conversely, however, the mood effects of ATD were attenuated when participants were exposed to bright light during test days. One might hypothesize that bright light may have this effect by acutely increasing serotonin synthesis, in a manner similar to (although different from) high-concentration oxygen. There are presently no studies in humans that have directly looked at the effect of bright light on brain serotonin synthesis, although there are data to suggest that bright light's effects on the metabolism of serotonin may be fairly immediate.[236] In addition, animal research has previously shown effects of bright light on serotonin levels in the raphe nuclei.[60]

Study 2 thus offers a plausible mechanism of action for the results of Study 3. As discussed in Study 3, bright light exposure (> 19.6 minutes per morning, afternoon, or evening) was associated with communal behaviours and mood in a way similar to tryptophan administration. Therefore, an increase in brain serotonin function was considered a plausible factor involved in explaining how bright light might have had its assumed causal effects. If the idea that bright light might affect mood and social interaction even over short time periods were confirmed in an experimental design, then this would have important implications for the role of bright light as a regulator of normal functioning in everyday life.

In Study 1, tryptophan decreased levels of negative affect and increased levels of positive affect. In Study 2, ATD decreased VAS positive mood, an effect that was prevented by bright light. ATD had no consistent effects on VAS negative mood. In Study 3, bright light exposure was associated with levels of positive affect, but not with levels of negative affect. Overall, these results suggest that the effects of serotonin or bright light on mood may be more closely related to changes in positive affect. Three previous EMA studies also found a positive association between markers of serotonin function and positive but not negative mood.[113,141,436] This is consistent with the idea that serotonin and bright light may provide a buffer

against the daily hassles that occur in everyday life. The decrease in negative affect that was seen in the quarrelsome participants of Study 1 was possibly primarily a reflection of a reduction in their hostility.

An unexpected finding in Study 3 was the absence of a significant association between bright light exposure and participants' perceptions of others. Based on changes seen with tryptophan (Study 1), participants had been expected to perceive others as more agreeable and more dominant when exposed to bright light. The absence of such a finding in Study 3 might be explained by its design. In Study 1, tryptophan pills were taken three times daily for 15 days. Serotonin was elevated for the entire duration of the treatment period. In Study 3, bright light exposure, measured naturally, was intermittent and varied from day to day. The bright light-induced increases in brain serotonin, if and when they occurred, were probably short-lived. Moreover, these episodes must have been quite rare, given that bright light exposure averaged only 57 minutes per day across seasons. Therefore, the effects of changed serotonin induced by tryptophan treatment (Study 1) are likely to have had more impact than the effects of changed serotonin in response to episodic natural bright light exposure (Study 3). Whereas bright light may influence mood and social behaviour directly and over a short period of time, it may take longer and consistent change, as with giving tryptophan, for a person's perception of others to change.

11.6 Relevance to mood disorders and other aspects of health

A central aspect in the diagnosis of mood disorders is the interference of the mood state with functioning in everyday life. As described in Chapter 4, anhedonia and irritability may cause inappropriate social behaviours and perceptual biases as well as result from them. Over time, these affective, behavioural, and perceptual disturbances may increasingly contribute to a variety of health problems.[381]

People who are irritable in the absence of aversive stimuli overreact in a hostile way to minor provocation and perceived frustration.[371] Irritable or hostile individuals report high levels of negative affect.[293] They are prone to impulsive-aggressive behaviours varying from road rage to homicide.[15,305] In a large sample of

men and women, those who were hostile at age 15-30 were more likely to have depressive tendencies 5 years later.[188] Among depressed patients, hostility and related impulsive-aggressive traits have been associated with suicidal tendencies and with suicide completion.[48,114] Turecki (2005) recently reviewed evidence suggesting that death by suicide among younger males is more likely to be associated with impulsive-aggressive traits than among older ones.[114,409] Younger suicide completers are also more likely to have a substance abuse disorder.[114,459] Trait irritability may be considered a risk factor for mental health problems in general, and for mood and substance abuse disorders in particular.

In addition, irritable or hostile personality traits can predispose individuals to a variety of physical health problems, such as lung disease, gastrointestinal disorders, diabetes, and cardiovascular disease.[229,381,395,414] Indeed, hostility has been associated with early death in general.[282] Data on the underlying mechanisms, prodromal symptoms, and mortality are most readily available for cardiovascular disease. For example, in a large sample of men and women, those who were hostile at age 18-30 were more likely to be hypertensive 15 years later.[448] Among patients with cardiovascular disease, hostility has been associated with worse outcome.[45] Further, the potential effects of hostile or quarrelsome behaviour on variables related to cardiovascular functioning have also been studied in healthy individuals. In one study, healthy young men showed low heart rate variability, which is a risk factor for cardiovascular disease, when behaving in a quarrelsome manner during a laboratory task.[91] In another study by the same group, performed in women, blood pressure measured in the laboratory was higher in those with high levels of quarrelsome behaviours measured using event-contingent recording, especially in those at risk for developing hypertension due to their family history.[90] Men and women may be responsive to different kinds of interpersonal stress. In a laboratory study of social interaction between husbands and wives, blood pressure increased in response to threats to agency in men but not women, whereas it increased in response to discrepant communal goals in women but not men.[380] Additional factors contributing to decrements in cardiovascular functioning over time include elevated cortisol levels and chronic inflammation. In a recent EMA study,

the negative affect resulting from daily hassles was associated with increases in saliva cortisol levels.[204] In one couples study, levels of pro-inflammatory cytokines increased and wound healing was slower following a quarrelsome interaction in the laboratory, especially in high-hostile couples.[215]

Anhedonia is characterized by low levels of positive affect and social withdrawal.[420] Links between positive affect and mental and physical health are often reported with regards to the proposed role of positive affect in prevention, protection, recovery, and restoration. For example, British civil servants who are happier have a lower heart rate, lower cortisol levels on work days, and less inflammation in response to a laboratory stress task.[387] Among elderly suffering from a variety of acute health problems, higher levels of positive affect predict better recovery.[323] A study of emotion expression in the diaries of a group of nuns found that the use of positive words at age 22 was a predictor of longevity 6 decades later.[92] In one experimental study, healthy volunteers exposed to a cold virus were less likely to develop symptoms if they reported a positive emotional style at baseline.[78]

An impact of bright light on health outcomes has been demonstrated by a small number of studies that looked at the effect of sunlight exposure in hospital rooms on disease recovery. Two studies have found that depressed patients are hospitalized for shorter time periods if their rooms receive more bright daylight.[24,27] Bright light may have accelerated the mood improvement as well as normalized social functioning. Staying in a sunny hospital room may also reduce length of hospitalization as well as mortality following a heart infarct.[25] The presence of depressive symptoms at the time of hospitalization is known to increase mortality.[53] Bright light may reverse this by improving mood. Bright light may even prevent future cardiovascular disease in everyday life by reducing levels of an important risk behaviour, quarrelsomeness, and its associated emotional state, hostility. Finally, Walch *et al.* (2005) found that a group of patients undergoing surgery reported less stress and less pain and used fewer analgesics post-surgery if their hospital room received higher levels of sunlight. For patients in bright versus dim rooms, this resulted in a 21% cost reduction for medication.[418] Together these studies highlight

the idea that an increase in bright light exposure may offer potential benefit during the treatment and in the prevention of a variety of disease symptoms. The possible implications for public health policy are noteworthy.

11.7 Beyond serotonin

Insel and Winslow (1998) have argued that the effects of serotonin on social interactions in birds and mammals, the only organisms that display fully developed affiliative behaviours, are mediated by various neuropeptides including vasopressin and oxytocin.[202] In humans, CSF vasopressin levels have been positively associated with impulsive-aggressive behaviours.[76] Moreover, a small number of experimental studies have used intranasal vasopressin to study its effects on human social interaction. In men, vasopressin, when given intranasally, can introduce an angry response bias to neutral facial expressions and decrease the subjective approachability of happy faces.[400,401] In women, however, vasopressin was found to decrease anger-related behaviours in response to happy and angry faces, and increases affiliative behaviours and perceptions in response to neutral faces.[401] These gender-dependent behavioural and perceptual changes in response to vasopressin are accompanied by a gender-independent increase in physiological and subjective measures of anxiety in response to angry faces.[401] Overall, high vasopressin activity in humans appears to be associated with an increase in the impact of negative social experiences, but men may then respond differently to these experiences than women.[401] This is again consistent with the social evolutionary theories of depression described in Chapter 4.

Oxytocin, on the other hand, may be directly involved in the development of positive social bonds. Affiliative touch enhances plasma levels of oxytocin in women, although less so in those with a history of interpersonal stress.[269,411] Oxytocin has also been administered intranasally in experimental studies. It can increase trust, at least in men,[185] and may do so by acutely reducing the neural and neuroendocrine responses to stressful stimuli.[218,278] In addition, oxytocin may influence future social behaviour by altering certain aspects of memory.[186] There is some evidence that these effects of oxytocin are reduced in individuals with a history

of interpersonal stress whereas they may be enhanced by social support.[185,278] Overall, it seems that social stimuli and oxytocin may interact over time, with repeated reciprocal effects ultimately influencing the strength of affiliative relationships between individuals. It is perhaps not surprising that women with enduring aggressive traits have relatively low levels of plasma oxytocin.[413]

These findings are particularly interesting given that a pharmacologically induced increase in serotonin function is known to result in lower vasopressin and higher oxytocin levels.[93,243] In Study 1, some of the tryptophan-induced changes in social interactions might thus be the result of changes in central neuropeptide release, rather than a direct effect of increased serotonin. Prolonged increases in oxytocin activity in particular may explain why tryptophan's benefits could last beyond the actual treatment period.

Like in Study 1, while most of the observations in Study 3 are consistent with bright light increasing serotonin function, other systems may also have been involved. The potential effects of light exposure on vasopressin and oxytocin in humans have not been systematically studied. In one report, bright light prior to sleep did not have any major effects on vasopressin and oxytocin levels during sleep.[225] However, a small number of studies in experimental animals suggest that retinal light exposure can suppress vasopressin and stimulate oxytocin.[105,115] The direction of these effects is consistent with that of serotonin on vasopressin and oxytocin.

There is some evidence that bright light increases blood flow, and thus presumably activity, in the striatum.[107] This would explain why bright light exposure was positively associated with participants' arousal level (Figure 3.2a), while increasing brain serotonin with tryptophan is more likely to decrease arousal.[457] This may point towards involvement of the dopamine system. A putative role for dopamine and/or norepinephrine in the mechanism of action of bright light would also be consistent with the finding that the effects of phototherapy in remitted patients with SAD can be reversed by catecholamine depletion.[312] Noradrenergic antidepressants have previously been shown to enhance pro-social behaviours in patients with mood disorders as well as in healthy volunteers.[111,408]

Finally, a non-retinal factor of potential significance in Study 3 may be the UV part of natural light exposure. Regular tanning bed users prefer UV-including tanning beds over UV-excluding tanning beds, and associate the former with better mood.[133] However, the underlying brain connection remains unclear.[148,149,211]

In conclusion, the effects of serotonin on mood and social interaction may have involved cross-talk with other neurotransmitter systems. Bright light may exert its effects on mood and social interaction through multiple neurochemical pathways.

11.8 Some limitations

It can be argued that each of the three studies had some weaknesses in its design. One point of discussion pertains to features of the event-contingent recording method use in Studies 1 and 3. Several advantages as well as some disadvantages of EMA in general compared to clinical observation, self-report questionnaires, and laboratory tests of social interaction have been reviewed recently by Moskowitz and Young (2006).[296] Briefly, possible limitations include the reliance on self-report (unlike clinical observation and some laboratory tests) and the time commitment that completing record forms for multiple days entails. In addition, compliance might have been higher if electronic forms had been used rather than paper-based forms.[392]

One other possibly significant limitation of the event-contingent recording method used in Studies 1 and 3 that was not discussed by Moskowitz and Young (2006) is that the self-report of daily social interactions itself might alter participants' interpretations of those interactions. Event-contingent recording requires a level of monitoring and introspection of daily live to which participants may be unaccustomed. After multiple days of completing questionnaires, participants may start analyzing their own behaviours, as well those of others, in new ways. It is possible that initially subliminal events are given closer attention and different meaning over time. If this occurred, it may even have facilitated some of the changes that were seen in Study 1. For example, it might have helped increase participants' awareness about power differences among their social interaction partners as they were rated using the interpersonal grid, thereby increasing the size

of the tryptophan effect on perceptions of dominance. In addition, if a learning effect occurred, it might have made participants more aware of the impact of their actions on others, which might have increased their general level of constraint. The exclusion of the first three days of recording in Study 1, which was done to reduce the impact of socially desirable responding,[294] might have eliminated participants' early reaction to having to complete questionnaires about their social interactions (although there is no reason to suppose that this effect lessens over time).

Some other possible drawbacks of the methods described in this Doctoral Thesis deserve mention. The oral administration of tryptophan (3 grams/day in Study 1) has never been shown to increase actual serotonin release in humans. Previous studies have found that the oral administration of tryptophan increases levels of serotonin in monkey brain and of 5-HIAA, its major metabolite, in human CSF.[242,452] The effect of increased plasma tryptophan levels on brain serotonin synthesis has been studied in dogs [109] but not in humans. Nonetheless, the findings of Study 1, which was conducted using a placebo control with tablets administered under double-blind conditions, are consistent with what is known about the effects of tryptophan and serotonin on aggression.

In Study 2, ATD was also conducted under double-blind conditions. However, the light conditions were not blinded. In clinical trials of phototherapy, during the search for a suitable placebo for bright light, researchers have looked into the use of grey filters to cover light boxes, the use of red light instead of full-spectrum light, active light avoidance, and even imaginary light administration.[227,233,346,367] The source of their concern is the idea that bright light may have a positive effect on mood because people expect it to have a positive effect on mood.[117] At least one imaging study suggests that thinking about positive events might increase brain serotonin synthesis levels.[332] In Study 2 bright light itself did not improve mood. If a placebo effect caused by people's expectations occurred, it must have been very small. Nonetheless, the effects of bright light and dim light on human brain serotonin synthesis levels should be compared using imaging.

Overall, the findings of Study 3 are most limiting in their interpretation

because the design was correlational rather than experimental. A large number of clinical trials of phototherapy suggest that bright light can cause mood improvement.[160,412] This is in keeping with common knowledge, that light enhances good mood. Importantly, however, rather than a strict cause-effect relationship, the association between light and mood may be more complex. If people have few social interactions, then this may result in less light exposure from outdoor activities, which might then contribute to a lowering of mood, which in turn may prevent people further form interacting socially such that being exposed to a necessary minimum amount of bright light may become more and more difficult over time.[180,442] This may explain why patients with SAD, who might need more light to maintain good mood, do not get more bright light exposure in winter even though they do in summer.[164] Bright light may be a key regulator of the relationship between social interaction and mood in everyday life.

Chapter 12
CLOSING WORDS

12.1 Implications

In a recent study, young women were interviewed about their overall experience with SSRIs.[222] Prior to starting their medication, the women perceived difficulty participating in social interactions and a general inability to deal with ordinary activities in daily life. Most of the women found that the SSRIs provided them with resources to be sociable and outgoing. Mood improvement was considered a secondary effect.

Neurotransmitters, including serotonin, have mostly been studied in relation to personal processes, rather than in relation to interpersonal or social events. This is quite surprising, given the importance of good social functioning for mental health. Moreover, the study of the effects of therapeutic interventions on social functioning is essential in relation to their role in the treatment of mental disorders. Experimental studies in psychiatry have traditionally focused on aspects of aggression. Despite the potential clinical relevance of these studies, a limitation is that most took place in laboratory settings. More recent studies have looked at other behaviours related to social functioning, but again these have been limited to laboratory settings. Yet in psychology, research on human social interactions has advanced to the stage where its multiple aspects (*e.g.*, different facets of affect, a variety of social behaviours, perceptions of others, contextual variables) can be reliably measured over several weeks outside the laboratory.[291] Despite these developments in what is now known as EMA, there have been only a few studies on the role of neurotransmitters in the social interactions that people have in their everyday lives.

In Study 1, individuals who initially regarded themselves as quarrelsome became less quarrelsome as well as more agreeable when they took tryptophan. The improvement in mood that they reported was considered the result of the enhanced quality of their social lives (due to greater acceptance or inclusion). In this population, a long-term reduction in hostility and irritability may decrease the risk of clinical mood dysregulation and might even help prevent the occurrence of future

problems in physical health.[282,409,448] This provides rationale for investigating non-pharmacological factors that may stimulate the brain serotonin system.

Study 2 highlights an environmental factor, long implicated in the occurrence of seasonal variability in psychiatric symptoms, which may be directly involved in the regulation of mood. Bright light was able to prevent the mood-lowering effect of acute tryptophan depletion, an experimental laboratory-based method that results in a decrease in brain serotonin synthesis. Bright light may have done so by acutely enhancing brain serotonin synthesis.[236] Thus, bright light constitutes a non-pharmacological factor that may decrease the risk of clinical mood dysregulation. This idea has potential implications for the mechanism of action of phototherapy. Moreover, the existence of an acute effect (in the range of a few hours during test days) implies that bright light can regulate mood even over short time periods, at least in women who consider themselves mildly seasonal.

In Study 3, this idea was extrapolated to pleasant and unpleasant affect experienced during everyday social interactions, as well as to behavioural and perceptual aspects of these social interactions. Individual daily levels of bright light exposure were generally low. Only the higher levels of exposure were associated with lower levels of quarrelsome behaviours, higher levels of agreeable behaviours, and good mood. If bright light exposure can have beneficial effects in daily life, then this provides rationale for further research into the possible health advantages of increasing bright light exposure in people's natural environments. These findings might be especially relevant to northern countries like Canada as well as to much of Europe, both of which extend its borders to near-polar latitudes.

Seasonal individuals judge their indoor light exposure to be of poorer quality compared to non-seasonal individuals.[444] They prefer to be in well-lit rooms and choose higher levels of lighting in experimental settings.[183] Hospital nurses may report lower levels of stress at work when they are exposed to sufficient levels of sunlight.[6] Sleep problems and general fatigue at work are less common with increasing levels of bright light exposure to the eyes.[13] Recent studies on workplace architecture suggest that higher light exposure levels can be achieved without interference to work-related tasks due to for example glare.[13] The successful

implementation of modifications to existing indoor light sources offers the potential to enhance social behaviour and mood in everyday life. From a public health perspective, having adequate bright light exposure might prove as important as eating a healthy diet or maintaining sufficient exercise.

12.2 Future studies

The findings presented in this Doctoral Thesis have generated several new research questions. First, what impact does tryptophan administration in one person have on the moods, behaviours, and perceptions of others? One example of how serotonergic interventions might affect both research participants and their close others is provided by a study of Tse and Bond (2002).[406] They studied the effects of 2-week SSRI treatment on student volunteers and their flatmates and found changes both in the behaviours of the treated volunteers and in the perceptions of their untreated flatmates. Citalopram increased cooperativeness and nonverbal dominant behaviours measured during a laboratory interaction between the treated volunteers and a stranger. In addition, citalopram decreased ratings of submissiveness in the volunteers by their flatmates. This suggests that flatmates may have responded to the changed behaviours of the treated volunteers. Social interactions involve mutual responding between two or more individuals. A future study of the effects of tryptophan on the flow of social interactions may include event-contingent recording in both treated volunteers and their close others.

A second question, related to serotonin's role in the regulation of human social interactions, pertains to the heritability of impulsive-aggressive traits. Relatives of patients with mood disorders have elevated irritability and hostility scores on personality questionnaires administered in laboratory settings.[77,356] It is presently unknown if these findings translate to higher levels of quarrelsome behaviours and lower levels of agreeable behaviours in the everyday lives of these relatives. This genetic risk is possibly passed on via allelic variations in the serotonin transporter gene, in particular the 5-HTTLPR polymorphism that is known to affect the functional expression of this gene.[247] Indeed there is some evidence that individuals carrying the less active s-allele of the 5-HTTLPR polymorphism

report levels of angry hostility and impulsive aggression.[165,248] Future studies may compare the social interactions of individuals with and without a family history of mood disorders. Additionally, studies might directly compare the social interactions of individuals grouped according to the presence of absence of the s-allele of the 5-HTTLPR polymorphism in their genotype.

The findings of Study 3 have provided a rationale for studying the effects of active bright light administration on everyday social interaction. One of the reasons for designing Study 3 as a non-experimental study was to see if even natural variations in bright light exposure could be associated with variations in mood and social behaviours. Given that this was so, it can be argued that most people in everyday life are exposed to insufficient levels of bright light for optimal social functioning. A future study of bright light administration could explore what the potential benefits of alleviating this bright light deficiency would be. Moreover, whereas a study of natural bright light exposure is informative in that it provides information about the effects of bright light under current living conditions, a study of multiple-day bright light administration will provide more information about the impact of frequent boosts in bright light exposure on mood and social interaction. This latter approach might reveal more insight in the effect of bright light on agentic behaviours and on perceptions of others.

Studies 1 and 2 included pharmacological manipulations of brain serotonin levels. These studies could be repeated using manipulations of other neurotransmitter systems such as the catecholamines, norepinephrine and dopamine. A small number of laboratory studies have investigated some aspects of human social interaction in relation to changes in norepinephrine activity.[173,176,405,408] There is also evidence that noradrenergic medications for depression improve social functioning.[111] Further, Depue and colleagues have argued for a role of dopamine in extravert personality and affiliative behaviour.[102,103] Thus, it would be of interest to repeat Study 1 using one of the catecholamine precursors instead of tryptophan.

It is of note that the antidepressant effect of bright light therapy in patients with SAD can also be reversed using alpha-methyl-para-tyrosine (AMPT), which induces catecholamine depletion.[234,312] This suggests that the mechanism of action

of bright light may include a role for norepinephrine and/or dopamine. A variant of the ATD technique, known as acute phenylalanine tyrosine depletion (APTD) has previously been shown to lower aspects of mood in healthy women.[255] Bright light may be able to prevent the mood worsening that can be induced either by AMPT or by APTD.

12.3 Conclusions

Constructive social interactions are important for good mood just as good mood is important for constructive social interactions. Nevertheless, psychiatric research on the aetiology and treatment of mood disorders has focused mostly on mood alone. This is surprising especially because certain interpersonal traits are known to predispose individuals to future mood problems, including depression and suicide. However, the study of the neurobiological factors underlying human social interaction has been limited by the lack of a suitable method. EMA, a research technique developed in psychology, has only recently been applied to answer questions specifically relevant to psychiatry. A major advantage of this technique is that recording of the variables of interest takes place in daily life, as opposed to in the laboratory. The event-contingent recording method used in this Doctoral Thesis was developed by social psychologists to study multiple aspects of everyday social interactions.

The domains of social functioning that are studied using this approach pertain to the four poles that define Leary's circumplex model of interpersonal relations: quarrelsomeness, agreeableness, dominance, and submissiveness (see Chapter 3). In psychiatry, only one of these poles (quarrelsomeness) has been studied in detail with respect to the role of different neurotransmitters, possibly because the interpersonal processes that characterize the pathology associated with this pole (aggression) are very salient.[359] Much less is known about the role of neurotransmitters in the behaviours, perceptions, and cognitions that center around the other poles. The research described in this Doctoral Thesis is a small step toward dividing attention more evenly among the four poles of Leary's circumplex model.

Within the realm of everyday life, serotonin seems to mediate a multitude of interpersonal processes related to the various domains of social functioning in humans. These are evolutionarily old processes that have existed across species for millions of years, and that preceded the development of conscious thought. The regulation of constructive social interaction by serotonin is relevant to earlier findings of associations between certain interpersonal traits and low serotonin function. Individuals characterized by these traits may be predisposed to future psychiatric illness. An increase in serotonin may help prevent this.

Bright light has long been considered an important environmental factor in the regulation of human well-being. The data presented in this Doctoral Thesis are suggestive of a role for serotonin in the regulation of mood as well as aspects of social functioning by bright light. Further experimental studies of the effects of bright light on the activity of neurotransmitter systems are necessary to increase knowledge about the aetiology and treatment of disorders with a seasonal component, as well as of disorders possibly caused by the low levels of bright light exposure that are so common in modern life.

Human mood and social interaction are influenced by people's motivations to be included and accepted by others in their environment. The identification of the various neurobiological and environmental factors that may help regulate good mood and constructive social interaction may benefit health not only at the level of the individual, but also at the level of society as a whole.

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LIST OF ABBREVIATIONS

5-HIAA	-	5-hydroxyindoleacetic acid
5-HTTLPR	-	serotonin transporter length promoter region
AMPT	-	alpha-methyl-para-tyrosine
APTD	-	acute phenylalanine tyrosine depletion
ATD	-	acute tryptophan depletion
CSF	-	cerebrospinal fluid
B	-	balanced amino acid mixture
BDHI	-	Buss-Durkee Hostility Inventory
BDI	-	Beck Depression Inventory
BIS-11	-	Barratt Impulsiveness Scale, version 11
BLE	-	bright light exposure
BMI	-	Body Mass Index
DSM-IV	-	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
EMA	-	ecological momentary assessment
GSS	-	Global Seasonality Scale
ICD-10	-	International Statistical Classification of Diseases and Related Health Problems, 10th ed.
IF	-	ipsatized frequency
m-CPP	-	meta-chlorophenylpiperazine
NEO-PI-R	-	Revised NEO Personality Inventory
PLB	-	placebo
POMS	-	Profile Of Mood States
PSQ	-	post-sleep questionnaire
SAD	-	seasonal affective disorder
SAS	-	Statistical Analysis System
SBI	-	Social Behaviour Inventory
SCN	-	suprachiasmatic nucleus
SD	-	standard deviation
SEM	-	standard error of the mean
SMAST	-	Short Michigan Alcoholism Screening Test
SPAQ	-	Seasonal Pattern Assessment Questionnaire
SSRI	-	selective serotonin reuptake inhibitor
T-	-	tryptophan-deficient amino acid mixture
TRP	-	tryptophan
VAS	-	Visual Analogue Scale(s)

RESEARCH COMPLIANCE CERTIFICATE STUDY 2

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January 19, 2004

Dr. Simon N. Young
Department of Psychiatry
1033 Pine Avenue West
Montreal, Quebec H3A 1A1

Dear Dr. Young,

We have received correspondence in support of the research proposal AØØ-B31-03B entitled "Effects of Bright Light Exposure on the Mood Response to Acute Tryptophan Depletion" which was reviewed by the Institutional Review Board, Faculty of Medicine at its meeting of October 27, 2003.

The responses and revisions were found to be acceptable and we are pleased to inform you that final approval for the revised protocol and study instruments (November 2003) and revised consent form (January 2004) was provided on January 20, 2004, valid until **October 2004**. The certificate of approval (executed) is enclosed.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial review and approval. The annual review should be submitted at least one month before **October 2004**. Should any modification to the study or unanticipated development occur prior to the next review, please advise the IRB promptly.

We ask you to take note that it is the responsibility of the investigator to deposit a copy of the approved research protocol and consent form with the Research Ethics Board of each hospital where patients are enrolled or study data is collected. **Failure to do so may result in the invalidity of data collected and possible freezing of research funds.**

Yours sincerely,

Serge Gauthier, M.D.
Co-Chair
Institutional Review Board

cc: Ms. L.. Bourgon – DHRC
Ms. L. Fateen – MUHC/RVH
A10-B31-03B

TABLE 1.1

Characteristics of study participants

	Group; mean (SD)	
	Men (n = 20)	**Women** (n = 19)
Age (years)	34.1 (10.1)	30.1 (9.1)
NEO-PI-R Angry Hostility score †	22.1 (3.6)	22.6 (3.5)
BDHI Irritability score †	8.6 (1.5)	9.2 (1.4)
BDI total score before study	8.0 (4.1)	8.3 (4.2)
BDI total score after study	5.9 (4.2)	5.4 (5.6)
SMAST score *	1.1 (1.8)	0.2 (0.4)
BIS-11 score	65.7 (8.5)	70.3 (12.0)

BDHI = Buss-Durkee Hostility Inventory; BDI = Beck Depression Inventory; BIS-11 = Barratt Impulsiveness Scale, version 11; SD = standard deviation; SMAST = Short Michigan Alcoholism Screening Test; NEO-PI-R = Revised NEO Personality Inventory.

† Scales used to determine high trait quarrelsomeness. * p = 0.037.

TABLE 2.1

Demographic and psychosocial characteristics for each light group.

	Group; mean (SD) where applicable	
	Dim (n = 16)	**Bright** (n = 14)
Age (years)	24 (5)	22 (4)
Education, % with post-secondary degree	44	36
Occupation, % student	69	86
Living situation, % living alone	19	21
BMI (kg/m^2)	23 (4)	22 (4)
BDI score at lab screening	5.2 (4)	5.3 (4)
Current alcohol use (drinks/week)	3.3 (3)	4.9 (5)
GSS score at lab screening	8.7 (3)	9.3 (2)
Living in Canada (% of life)	70 (42)	65 (43)
Self-reported normal sleep time (h:min)	23:51 (0:59)	23:36 (0:50)
Self-reported normal wake time (h:min)	8:10 (0:53)	7:54 (0:34)

BDI = Beck Depression Inventory; BMI = Body Mass Index; GSS = Global Seasonality Scale; SD = standard deviation.

TABLE 2.2

Outcome of mood and side effects analyses based on hierarchical linear models.

	Factors included in the models; outcomes of *F*-tests (corresponding *p*-values) are shown for those factors with $p \leq 0.10$.				
	Morning baseline $F_{1,139}$ =	**Time** $F_{2,56}$ =	**Light** $F_{1,28}$ =	**Mixture** $F_{1,28}$ =	**Mixture by Light** $F_{1,28}$ =
POMS					
Total score	38.34 (<0.0001)			7.25 (0.01)	6.62 (0.02)
Agreeable-Hostile	7.77 (0.0061)	3.74 (0.03)			4.57 (0.04)
Clearheaded-Confused	31.66 (<0.0001)				15.16 (0.0006)
Composed-Anxious	46.55 (<0.0001)			5.14 (0.03)	3.87 (0.059)
Confident-Unsure	17.74 (<0.0001)			7.36 (0.01)	9.35 (0.0049)
Elated-Depressed	56.76 (<0.0001)				2.90 (0.0998)
Energetic-Tired	5.42 (0.02)				
VAS					
Positive Mood				6.55 (0.02)	4.57 (0.04)
Negative Mood		6.73 (0.0024)			5.20 (0.03)
Negative Mood – Bored		8.37 (0.0007)			
Dizziness			4.24 (0.05)	24.74 (<0.0001)	7.44 (0.01)
Headache				16.06 (0.0004)	
Nausea		2.74 (0.07)	2.99 (0.10)	7.65 (0.01)	7.28 (0.01)

POMS = Profile Of Mood States; VAS = Visual Analogue Scale.

TABLE 3.1

Demographics and questionnaire scores in winter and summer.

	Group; mean (SD) where applicable			
	Participants who completed both seasons (*n* = 35)		**Participants who completed only one season** (*n* = 13)	
	Winter	*Summer*	*Winter*	*Summer*
Number of participants	35	35	6	7
Gender, % female	54	54	50	86
Hormonal contraceptive use in women, % yes *	47	42	33	0
Age (years)	31 (8)	31 (8)	27 (3)	31 (10)
GSS score at lab screening	8.0 (2)	7.6 (3)	7.5 (2)	8.4 (1)
Seasonality is a problem, % yes	29	14	17	29
BDI score pre-study	3.0 (3)	2.3 (3)	4.2 (5)	3.4 (6)
BDI score post-study	2.5 (4)	1.8 (3)	0.8 (1)	1.7 (1)
Number of forms completed per day	6.5 (2)	6.2 (2)	6.3 (1)	4.9 (2)
Difficulty recording interactions †	2.1 (1)	2.2 (1)	2.0 (1)	2.4 (1)
Accuracy of interactions †	4.9 (1)	4.6 (1)	4.8 (1)	4.3 (1)
Difficulty wearing light meter † **	2.3 (1)	1.9 (1)	2.5 (1)	1.7 (1)
Accuracy of light meter †	4.6 (1)	5.0 (1)	5.0 (1)	4.7 (1)

BDI = Beck Depression Inventory; GSS = Global Seasonality Scale; SD = standard deviation.

† Difficulty and accuracy of light and social interaction measurements assessments were based on a 6-point scale, where 1 was labelled "no difficulty" or "not at all accurately" and 6 was labelled "great difficulty" or "very accurately".

* Significant difference between those who started in winter and those who started in summer ($p < 0.007$).

** Significant difference between those who completed both seasons and those who completed one season only ($p < 0.03$ for both).

TABLE 3.2

Seasonal differences in social interaction variables.

	Season; least squares mean (SEM)	
	Winter	*Summer*
Quarrelsome behaviour (ipsatized frequency x 100)	-13.9 (0.8)	-14.2 (0.8)
Agreeable behaviour (ipsatized frequency x 100)	12.7 (0.9)	12.4 (0.9)
Dominant behaviour (ipsatized frequency x 100) *	6.0 (0.7)	7.7 (0.7)
Submissive behaviour (ipsatized frequency x 100) *	-4.8 (0.7)	-5.9 (0.7)
Positive affect (averaged item score)	1.9 (0.1)	1.9 (0.1)
Negative affect (averaged item score) *	0.4 (0.04)	0.5 (0.04)
Affect valence (grid score)	7.6 (0.1)	7.7 (0.1)
Affect arousal (grid score) *	7.2 (0.1)	7.4 (0.1)
Perceptions of agreeableness (grid score)	8.0 (0.2)	8.0 (0.2)
Perceptions of dominance (grid score)	7.4 (0.1)	7.4 (0.1)

SEM = standard error of the mean. * $p < 0.05$.

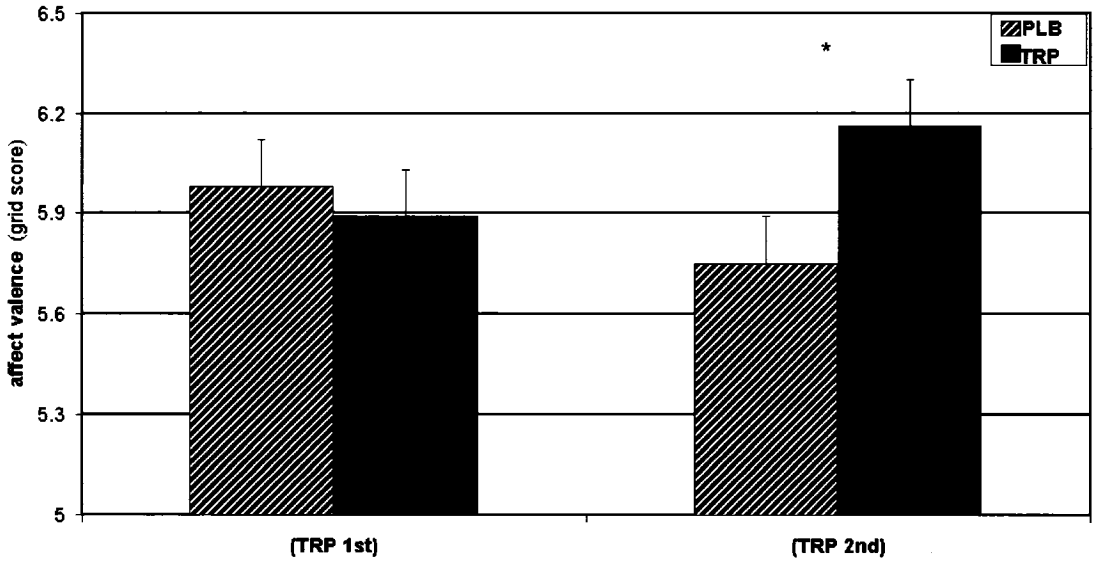
TABLE 3.3

Covariates in light analyses.

	Covariates included in the models; outcomes of *F*-tests and corresponding *p*-values are shown for those covariates with $p \leq 0.05$.			
	Season $F_{1,34}$ =	**Day of week** $F_{6,278}$ =	**Time period** $F_{2,93}$ =	**Location** $F_{3,189}$ =
Quarrelsome behaviour		3.60		5.30
Agreeable behaviour		4.54	13.19	5.72
Dominant behaviour	5.63	3.29	5.59	9.00
Submissive behaviour		3.15		3.25
Positive affect		10.05	46.04	72.37
Negative affect	46.26	5.58	5.90	9.08
Affect valence		5.97	17.46	38.83
Affect arousal	6.71	3.96	28.91	14.90
Perceptions of agreeableness		2.38	10.15	21.28
Perceptions of dominance		3.40	14.39	5.18

FIGURE 1.1

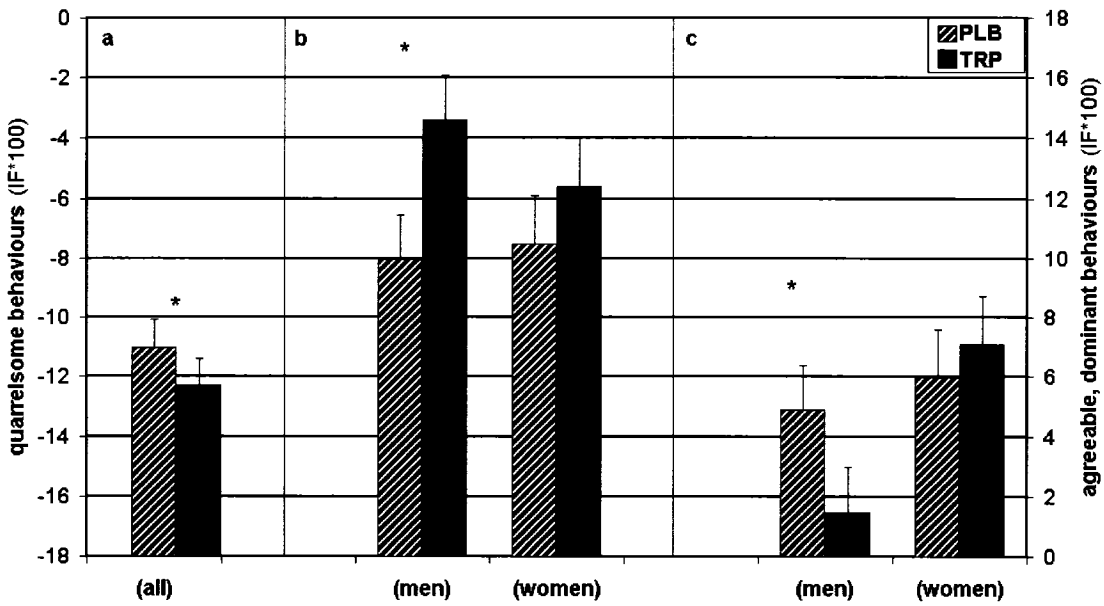
Affect valence during tryptophan and placebo phases of treatment.



Values are estimated least squares means and standard errors. The horizontal axis crosses the vertical axis at 5 to indicate the middle of the individual axes on the affect grid.

FIGURE 1.2

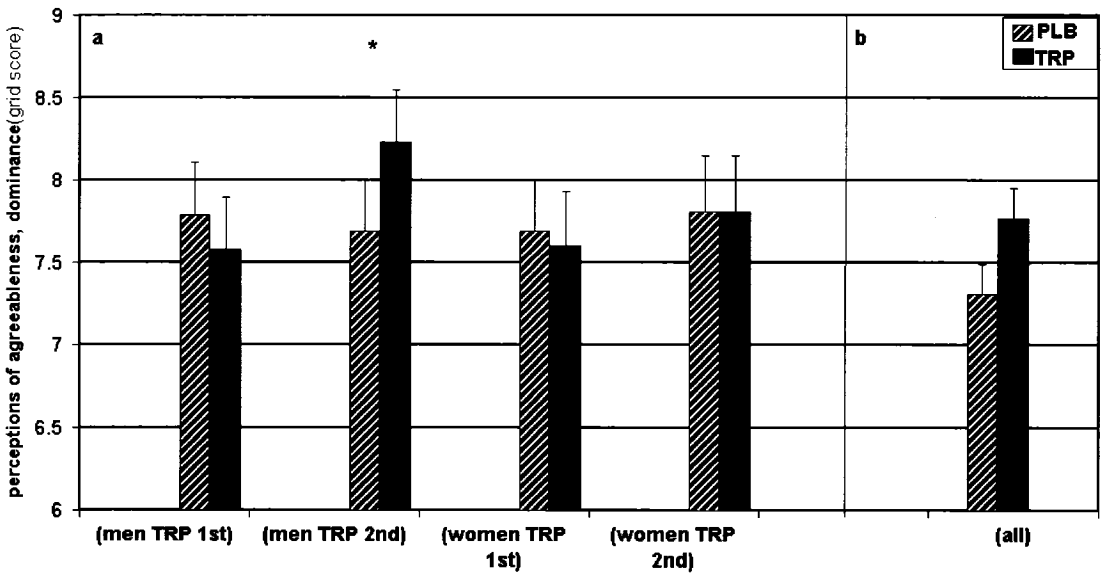
Daily ipsatized frequencies of (a) quarrelsome, (b) agreeable and (c) dominant behaviours during tryptophan and placebo phases of treatment.



Values are estimated least squares means and standard errors. IF = ipsatized frequency.

FIGURE 1.3

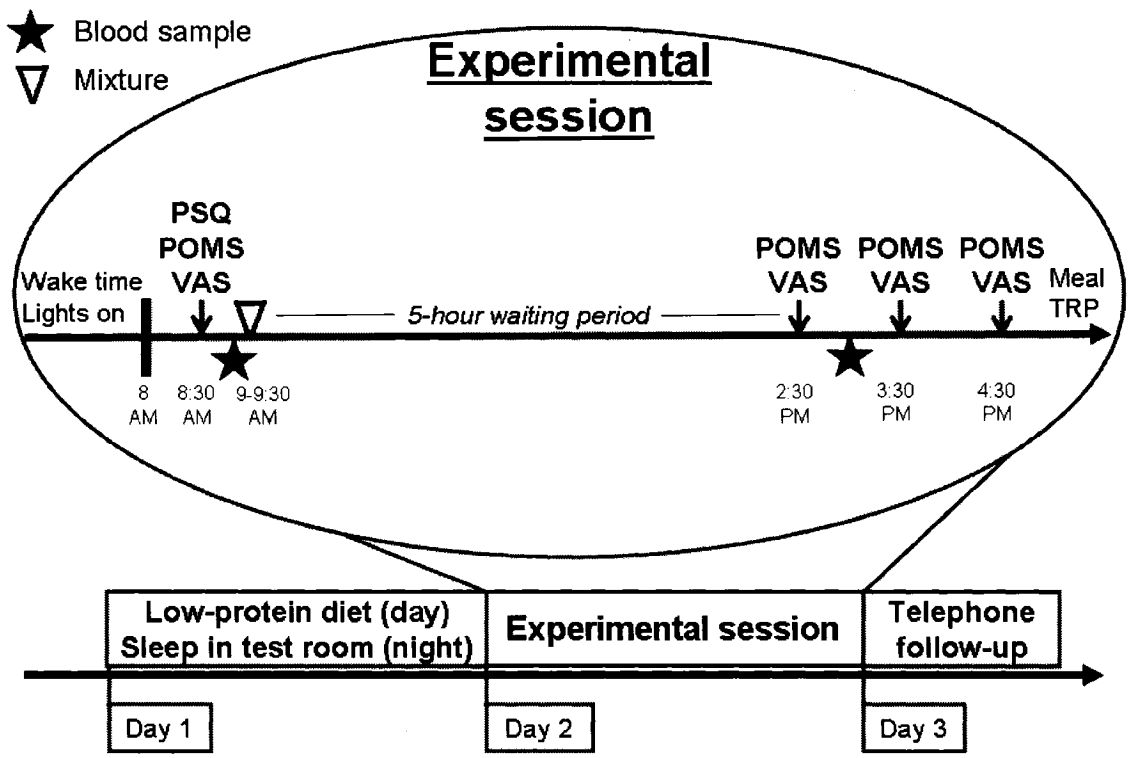
Perceptions of (a) agreeableness and (b) dominance during tryptophan and placebo phases of treatment.



Values are estimated least squares means and standard errors. The horizontal axis crosses the vertical axis at 6 to indicate the middle of the individual axes on the interpersonal grid.

FIGURE 2.1

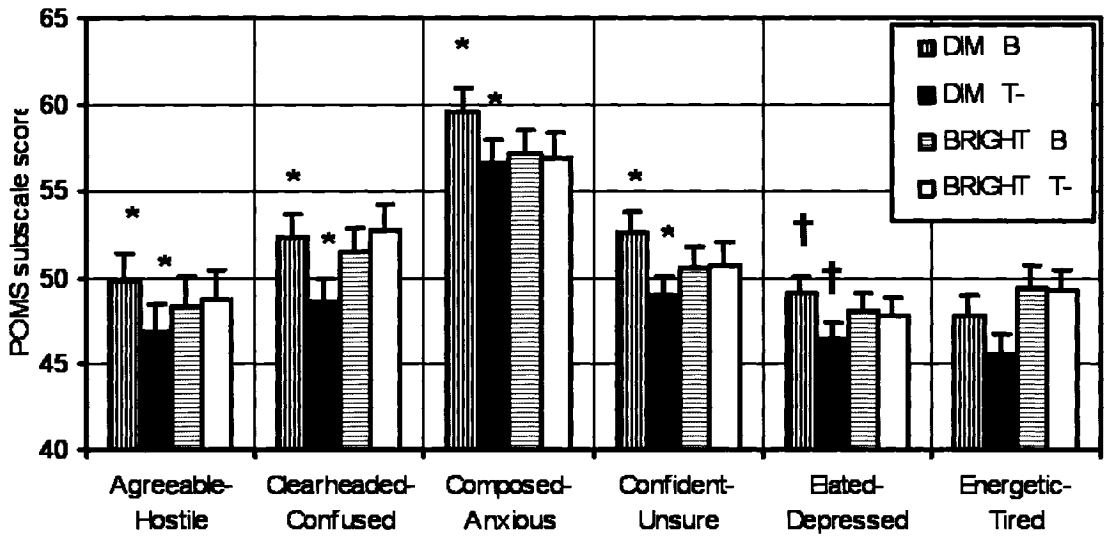
Timeline of events on the two test days for a typical participant.



Wake times varied according to self-reported normal sleep/wake schedules.

FIGURE 2.2

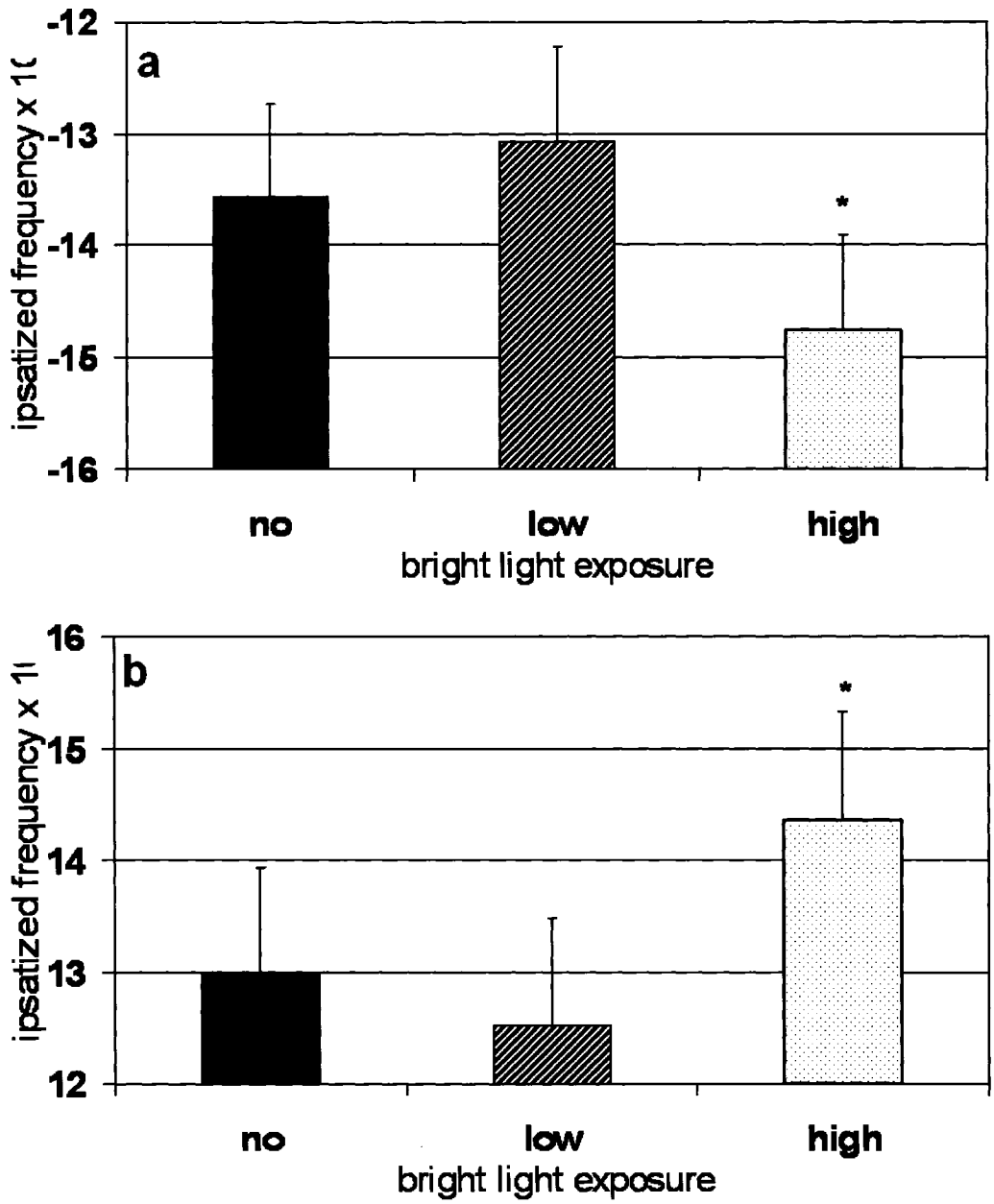
POMS subscale scores per light group and mixture.



POMS = Profile of Mood States; B = balanced amino acid mixture; T- = tryptophan-deficient amion acid mixture. Values are estimated least-squares means and standard errors of the mean. * $p < 0.05$. † $p = 0.05$.

FIGURE 3.1

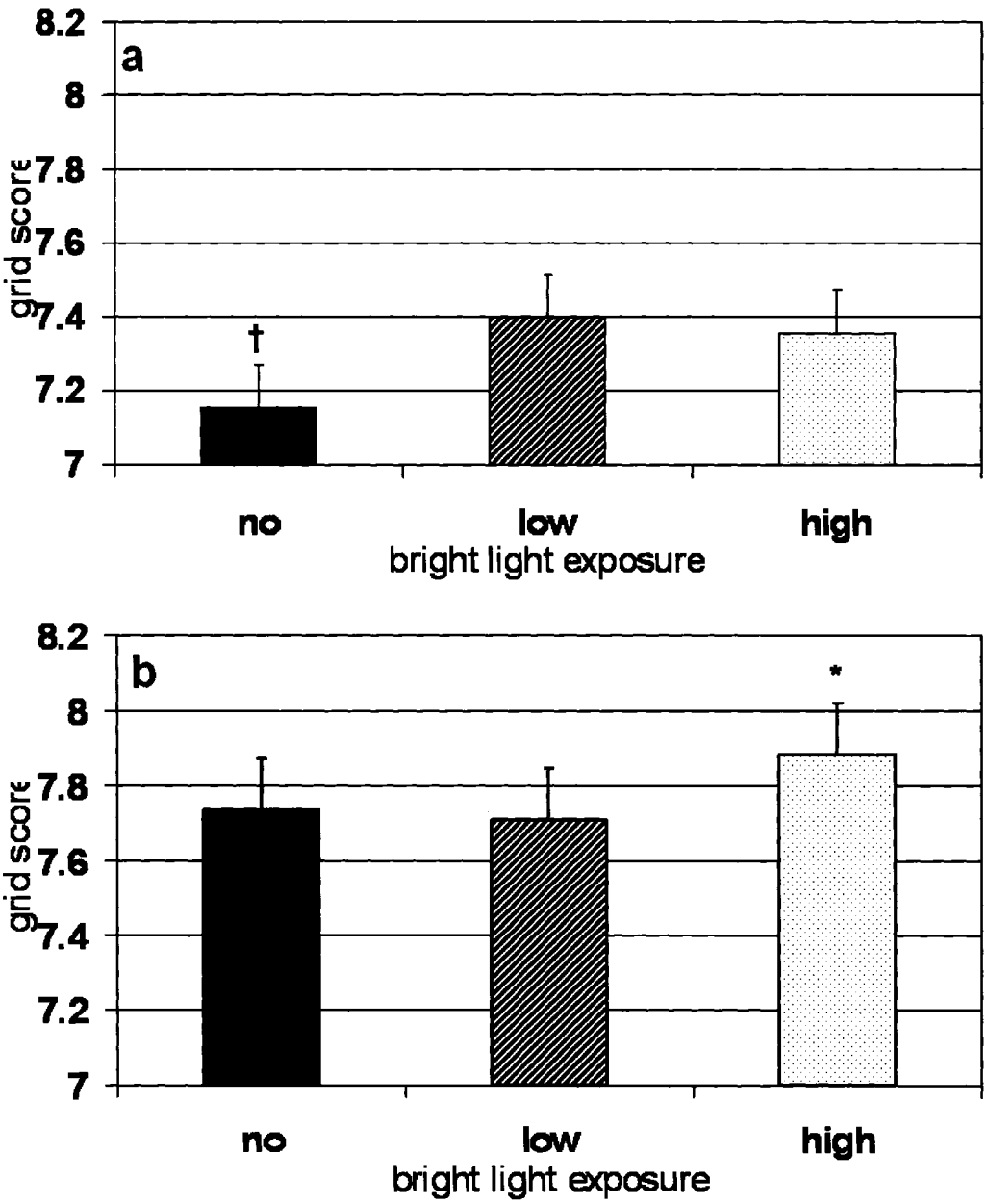
Quarrelsomeness (a) and agreeableness (b) during time periods of no, low, or high levels of bright light exposure.



Values are estimated least squares means of ipsatized frequencies (multiplied by a factor 100) and standard errors. * Significantly different from social interactions with low bright light exposure.

FIGURE 3.2

Affect arousal (a) and valence (b) during time periods of no, low, or high levels of bright light exposure.



Values are estimated least squares means of grid scores and standard errors. The horizontal axis crosses the vertical axis at 5 to indicate the middle of the individual axes on the affect grid.
* Significantly different from social interactions with low bright light exposure.
** Significantly different from social interactions with low or high bright light exposure.