Coffee, caffeine, mood and emotion – an overview

The terms 'mood' and 'emotion' are often used interchangeably in colloquial conversation. However, in scientific terms, mood and emotion have different definitions. A mood is a relatively long-lasting affective state[32]; while an emotion is of shorter duration. It has been suggested that emotions can be defined by episodes of synchronised change, with components such as bodily reactions (such as blushing), and motor expressions[33].

In Europe, mental health and mental disorders (including depression and anxiety) pose a significant public health challenge[34]. Every year, 1 out of 15 people suffer from major depression in Europe, and if anxiety and all forms of depression are included, nearly 4 out of 15 people are affected[35].

Evidence suggests that diet and exercise can affect neuronal development and physiology and protect the brain from neurological illnesses or injuries[36]. Of note, coffee, cocoa and tea are being actively investigated because they are rich in polyphenolic compounds that may have beneficial effects on mental health, including behaviour, mood, depression and cognition[37].

Caffeine and mood

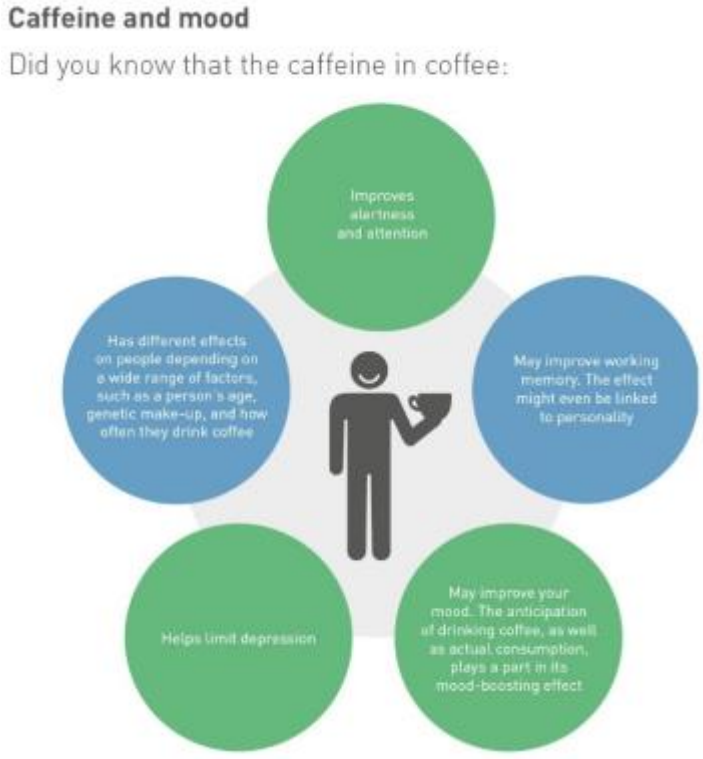
Low to moderate doses of caffeine (equivalent to that found in around 2-5 cups of coffee per day) improve hedonic tone or the degree of pleasantness and reduce anxiety[4]. In comparison, high doses can increase tense arousal, including anxiety, nervousness, and jitteriness. A dose-related improvement in subjective measures of calmness and interest are found after consuming caffeine, suggesting that mood improvement may depend on baseline arousal[26]. Research has suggested that a repeated intake of 75mg of caffeine (the equivalent of approximately 1 cup of coffee) every 4 hours confirmed a pattern of sustained improvement of mood over the day. Highly-fatigued subjects are more likely to experience larger subjective mood changes than non- or moderately-fatigued subjects. There are also indications of negative mood impact associated with over-arousal[26].

Studies have reviewed the impact of other intakes of caffeine: in one such study, a single 60mg caffeine dose elicited a clear enhancement of sustained attention and alertness, contentment and mood[38]. A further study concluded that an intake of 100mg caffeine significantly decreased lethargy/fatigue and increased vigor[39]. The European Food Safety Authority (EFSA) concluded that a cause and effect relationship between improved alertness and attention and 75mg caffeine (the amount in a regular cup of coffee) had been established[1].

Older adults seem to be more sensitive to the mood-enhancing effects of caffeine than younger individuals[40]. Mood effects are also influenced by the time of consumption, with the most prominent effects showing in the late morning[40]. In fact, it has been suggested that caffeine could potentially be used as a nutrition supplement for older adults, enhancing mood and improving cognitive performance in their daily living tasks[41]. However, further research is needed before any firm conclusions can be drawn.

Research also suggests that caffeine tends to have a more beneficial effect on habitual consumers' moods (compared to non-consumers), but there are greater improvements in performance when drunk by non-consumers[42]. It also seems that mood is not only modulated by caffeine itself but also by the expectation of having consumed caffeine, which improves mood together with attention[10].

The effect of caffeine in stimulating self-reported alertness and mood was not thought to persist for extended periods of time, with the effects peaking during the first four hours after ingestion. Research in office workers suggests that consuming caffeine with ornithine (an amino acid involved in protein metabolism, found in foods such as dairy products and meat, and which can be synthesized in the body) in the morning had a positive effect on self-reported mood (especially reducing "feelings of fatigue", and increasing "willingness to work", and "vigor") in the late afternoon, suggesting that ornithine potentiated the physiological action of caffeine[43].



Extensive research on caffeine intake has been associated with a range of reversible physiological effects at both lower and higher levels of intake, suggesting that caffeine intake has no significant or lasting effect on physiological health[44].

Caffeine, carbohydrates and mood

Consuming nutrients and biologically-active compounds together is of interest to researchers, as it gives a greater understanding of the impact of food and drink in the body. The combination of caffeine and carbohydrates has been of particular interest[45,46].

Administered in common beverages with appropriate placebo controls, one study reviewed the impact of coffee and glucose on mood and performance both separately and together, and concluded that neither glucose nor caffeine showed a significant effect on cognitive performance. This was surprising in the case of caffeine, as multiple studies suggest it improves cognitive performance (as referenced in the prior 'Caffeine and Mental Alertness' subtopic). The authors acknowledged that significant confounding factors may have interfered with the results, and that caffeine did result in increased perceived preserved mental energy under test conditions, although further work to consider whether these mood changes would also result in increased motivation during a challenging task, would be advisable[45].

Further research combining a moderate dose of caffeine (200mg) together with a low carbohydrate intake (50g white bread) positively influenced mood and cognitive performance, while carbohydrate intake alone did not[46]. In this research, the key element leading to improved mood and mental performance was the presence of caffeine.

A small pilot study reported that caffeinated coffee had a more robust positive effect on high-level mood and attention processes than decaffeinated coffee. Interestingly, the authors found that decaffeinated coffee could also improve mood and performance. This suggests that substances other than caffeine, such as chlorogenic acids, may also affect mood and performance[47]. However, this effect needs to be confirmed in a larger group of individuals.

Caffeine and effect on depression

Research suggests that caffeine may help to relieve depressive symptoms or help to protect against depression. A 2016 meta-analysis accounting for a total of 346,913 individuals and 8,146 cases of depression suggested that coffee consumption may have a protective effect. A dose-response analysis suggests a J-shaped curve, with the beneficial effect reported for up to approximately 300mg caffeine (approximately 4 cups of coffee) per day[48].

A number of specific studies have investigated caffeine consumption in relation to the

risk of depression.

- A study of 50,739 women (average age 63 years), part of the Nurses' Health Study, suggested that women who consumed 2-3 or at least 4 cups of caffeinated coffee per day were, respectively, 15% or 20% less likely to develop depression, compared to those who drank at most one cup of caffeinated coffee per week. The consumption of decaffeinated coffee had no impact on depression risk. This observational study suggests the possibility of a protective effect of caffeine on depression risk[49].
- A cohort study of Finnish men reported a 77% risk reduction for depression in heavy coffee drinkers (those who consumed over 813mg caffeine daily). This effect was limited to coffee and was not found with either tea or caffeine alone[50].
- A Japanese cross-sectional study reviewed the impact of consumption of both green tea and coffee on depressive symptoms, suggesting that both green tea (more than 4 cups per day) and coffee (more than 2 cups per day) may offer protection against depression[51].
- A cross-sectional study in 10,177 Korean individuals aged 20-97 years, who participated in the fifth Korean National Health and Nutrition Examination Survey, suggested that coffee consumption may have a small protective effect on the risk of depression[52].

Research on depressive symptoms in participants who received either caffeinated coffee (150mg caffeine), or decaffeinated coffee (9mg caffeine) showed that caffeinated coffee increased co-operative game behaviour and sadness communication, suggesting that caffeinated coffee may improve social support and relieve depressive symptoms[53].

Finally, coffee and caffeine consumption might be favoured by some specific patient groups, including patients with bipolar disorders, who were reported to consume more social drugs such as tobacco and coffee than the general population[54], and schizophrenic patients[55]. It has been hypothesized that patients smoke and drink coffee to reduce medication side effects such as anhedonia (inability to feel pleasure), or to improve cognitive symptoms linked to the treatment.

Caffeine and emotion

Caffeine reliably increases arousal, but it is currently unclear if and how it influences other dimensions of emotion such as positive versus negative feelings.

One study evaluated emotional responses to coffee beverages to develop a lexicon to describe the feelings that occur during coffee drinking. The results suggested that coffee drinkers sought different emotional experiences from their drink: some preferred coffee to elicit positive-lower energy feelings, some liked to be aroused by the positive-high energy emotions, whilst others desired feelings of a focused mental state[56].

Research has suggested that caffeine may accentuate non-habitual caffeine consumers'

emotional responses to negative situations, but not how they choose to regulate such responses[57]. Further research has considered the impact of caffeine consumption in situations where emotions were already stimulated by watching negative film clips, concluding that caffeine consumption produces increases in self-reported measures of tension, anxiety and anger. This effect was altered when consumed with theanine (found in tea) which decreased this effect of caffeine[58].

Dopamine

Dopamine is a neurotransmitter that helps to control the brain's reward and pleasure centres. It also helps to regulate emotional responses.

Research has suggested that dopamine may mediate some of the behavioural effects of caffeine. After drinking a cup of coffee, caffeine is absorbed into the blood stream and transported around the body to the brain. In the brain, adenosine acts as a central nervous system depressant and promotes feelings of tiredness. Due to its similar structure, caffeine may bind to the adenosine receptors, acting as an imposter and blocking the actions of adenosine, leading to feelings of alertness[59]. For further explanation, watch this video on coffee and its effect on the brain.

Research suggests that caffeine consumption may be associated with an increase in the availability of dopamine receptors in the brain, suggesting that caffeine may enhance arousal in part by up-regulating dopamine receptors[60].

Conclusion

A moderate intake of caffeine has been shown to have a beneficial effect on alertness and mood, whilst higher intakes of caffeine may increase feelings of anxiety and jitteriness. The effect on mood is more noticeable in regular coffee drinkers, whilst performance seems to be more improved in those who are not regular coffee drinkers. Caffeine intake is also associated with a reduced risk of developing depressive symptoms across different population groups.

The impact of caffeine consumption on emotions is harder to define and research in this area is somewhat limited, however some work suggests that caffeine may stimulate emotional responses through its interaction with dopamine.

Caffeine and sleep

Sleep in humans can be affected by caffeine. There is an association between a daily intake of caffeine, sleep quality, and daytime sleepiness[61,62].

The most-documented effects of caffeine on sleep consist principally of prolonged sleep latency, shorter total sleep time, worsening of perceived sleep quality, increases in light sleep and shortening of deep sleep time, as well as more frequent awakenings. Rapid Eye Movement (REM) sleep is less affected[61,62]. REM sleep is a stage in the normal sleep cycle during which dreams occur and the body undergoes marked changes, including rapid eye movement, loss of reflexes, and increased pulse rate and brain activity.

The effects of caffeine on sleep depend not only on the amount of caffeine ingested at bedtime, but also on the amount of caffeine ingested over the whole day.
Human sensitivity to the effects of caffeine on sleep is variable and its exact basis is still debated. A 2016 systematic review of research on coffee, caffeine and sleep concluded that individuals will respond differently to caffeine based on a variety of factors including age, sensitivity levels, regular coffee and caffeine intake, time of consumption and genetic variability[62].

Sleep cycles

Normal sleep is divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further divided into three progressively deeper stages of sleep: sleep begins in NREM and progresses through deeper NREM stages, before the first episode of REM sleep occurs approximately 80 to 100 minutes later. Thereafter, NREM sleep and REM sleep cycle over a period of approximately 90 minutes[63].

The effect of caffeine on sleep

It is clear that caffeine intake can affect sleep, but a large intra-individual variability in the effects of caffeine is observed. A number of factors can affect the response to caffeine consumption and the subsequent impact on sleep, as outlined below.

Genetic variability

Although the research in this area is limited, it is clear that there is a genetic variability in the metabolism of caffeine, and several genes have been identified that affect an individual's sensitivity to caffeine.

- The plasma concentration of caffeine after the ingestion of a given amount of caffeine may largely vary between subjects, suggesting a greater sensitivity of slow metabolizers[64].

- Several genes have been identified that affect an individual's sensitivity to caffeine. In humans, the distribution of distinct genotypes of the adenosine A2A receptor gene (ADORA2A) differs between self-rated caffeine-sensitive individuals with reduced sleep quality, and caffeine-insensitive individuals[65]. Both the DARPP-32 and PRIMA1 genes have also been implicated in caffeine sensitivity and caffeine induced insomnia respectively[66]. The same amount of caffeine can therefore affect two otherwise similar individuals differently, depending on their genetic make-up.
- Similarly, the probability of having a further genetic variation of the ADORA2A genotype decreases as habitual caffeine intake increases, suggesting that persons with this specific genotype may be less vulnerable to caffeine dependence[67].

Age

Only a few studies have evaluated the age-related effects of caffeine on sleep, and confounding factors are often present. Some research suggests that older adults may be more sensitive to the effects of caffeine. However, caffeine exposure may vary as a function of body weight. For example, older adults tend to consume the same amount of caffeine as younger adults but typically weigh less. Older adults may also self-limit the amount of caffeine they consume due to perceived sleep problems[62].

- Overall, caffeine produced similar effects in young adults (20-30 year-olds) and middle-aged subjects (45-60 year-olds). Only a few EEG spectral frequency bins were more affected by caffeine in middle-aged subjects than in young subjects[68].
- A further study, by the same group, investigated daytime recovery sleep in the morning after 25 hours of wakefulness. Caffeine decreased sleep efficiency, sleep duration, slow-wave sleep and REM sleep during daytime recovery sleep similarly in both age groups. Middle-aged subjects showed greater decrements in sleep duration and sleep efficiency than young subjects during daytime recovery under placebo, compared to nocturnal sleep. Due to lower brain synchronization related to age and caffeine, these subjects had greater difficulty in overriding the circadian waking signal during daytime sleep and, as a result, had fragmented sleep[69].
- A study of 22 young adults and 24 middle-aged adults concluded that caffeine increased sleep latency, shortened total sleep duration, and reduced sleep efficiency. The effects were more pronounced at a higher dose in middle-aged adults than in young adults. The higher dose of caffeine also increased absolute stage 1 sleep in young adults, whereas it decreased absolute stage 2 sleep in middle-aged adults. These results indicate that, compared to young adults, middle-aged adults are generally more sensitive to the effects of a high dose of caffeine on sleep quantity and quality[70].

Habitual intake of caffeine

Research suggests that the effects of caffeine are less marked in those who regularly drink coffee when compared to occasional coffee drinkers[71].

- Results from a research survey published in 2015 concluded that sleep quality was poorer in those who perceived themselves to be dependent upon caffeine, particularly amongst females. Caffeine dependence was associated with poorer sleep quality, increased daytime dysfunction, and increased levels of night-time disturbance[72].

Time of consumption

Caffeine consumed closer to sleep time has the greatest potential for sleep disruption, although there are only limited studies assessing the timing of caffeine administration.

- A 2013 study assessed the impact of caffeine consumption on sleep at different periods before sleep, suggesting that caffeine consumed up to 6 hours beforehand may reduce total nightly sleep and reduce sleep quality[73].

The effects of caffeine abstinence

A 2008 systematic review, including randomized trials, suggests that caffeine abstinence for a whole day could improve sleep quality and could be recommended by health practitioners when giving sleep hygiene advice[74]. The authors concluded that caffeine abstinence significantly lengthened sleep duration and improved sleep quality. Furthermore, subjects had less difficulty falling asleep on days when they drank decaffeinated coffee. However, people's sensitivity to caffeine varies and individuals may or may not find that caffeine affects their sleep[62].

The effect of caffeine on sleep in young people

Caffeine helps restore better levels of wakefulness and counteracts degraded cognitive task performance due to sleep deprivation. However, caffeine may produce detrimental effects on subsequent sleep, resulting in daytime sleepiness, which may be a matter of concern, especially in adolescents[75]. Many adolescents use multiple forms of technology late into the night and concurrently consume caffeinated beverages to stay alert.

- A study looking at the effects of caffeine and technology on sleep duration and daytime functioning in young people showed that sleep was significantly related to the multi-tasking index[76]. Teenagers who scored 1.5-2 fold higher on multi-tasking indices slept less than 8-10 hours on school nights. Among the 33% of teenagers who fell asleep during school, caffeine consumption tended to be 76% higher than in those not falling asleep. The study suggests that, as a consequence, these teenagers were not fully functional throughout the day due to excessive

daytime sleepiness, rather than because of the daytime effects of caffeine.

- Likewise, in a survey looking at adolescent caffeine use, it appeared that 95% used caffeinated drinks, primarily soft drinks or soda, but also coffee. In contrast with high soda users, mixed users who drank more coffee expected more energy enhancement from caffeine, and they were more likely to get up early and report more daytime sleepiness, which led to the use of caffeine to 'get through the day'[77].
- A study of a group of students during an exam period suggested that sleep quality and alcohol consumption significantly decreased, while perceived stress and caffeine consumption significantly increased. However, despite the fact that students shortened their time in bed and showed symptoms of insomnia, the authors concluded that sex, age, health status, as well as the amounts of alcohol and caffeine consumed had no significant influence on overall sleep quality[78].

Caffeine, jet lag, and shift work

Jet lag and shift work sleep disorder can result in sleepiness and increase the risk of injury. Shift work sleep disorder is a circadian rhythm sleep disorder characterized by insomnia and excessive sleepiness, affecting people whose work hours are scheduled during the typical sleep period.
According to the results of a systematic review, caffeine may be effective at improving performance in people who work shifts, or in those who are suffering from jet lag[79]. However, there is no data for subjects over the age of 40, who represent a population more likely to be affected. This research gap limits the conclusions that can be drawn and calls for more studies in this field.

Research in shift workers

- One intervention study has assessed counter measures for sleep-wake problems associated with night work, and suggested that a combination of napping and ingestion of caffeine was best for improving alertness. A decrease in subjective sleepiness was also observed in individuals working a night shift following caffeine consumption[80].
- Further work on the effect of caffeine consumption during night shifts suggests that caffeine increases alertness and clear-headedness after a period of wakefulness, but can also disturb subsequent daytime recovery sleep. Caffeine intake is associated with a higher core body temperature and this in turn is associated with a longer latency to sleep. Furthermore, sleep disturbances associated with caffeine consumed near the circadian trough of alertness are likely to still be present when daytime recovery sleep occurs around 5 hours later, potentially causing disturbed sleep[81].

Caffeine and jet lag

Jet lag is often experienced after a long haul flight across different time zones and can cause extreme sleepiness or wakefulness at inappropriate hours. To counter jet lag, it helps to adjust to the new time zone quickly, sleeping, waking and eating at times appropriate to that area. Coffee consumption is associated with increased alertness and may help to manage feelings of sleepiness in those who experience jet lag.

A review of the research suggests that caffeine may be effective at improving performance in those who are suffering from jet lag[82]. However, for those taking short stopovers of 1-2 days in a different time zone, adapting to the local clock may not the best strategy. Sensible naps, combined with a moderate intake of caffeine during times of appropriate wakefulness and short-term use of sleeping aids, appear to be the most effective ways to maintain alertness and sleep in these situations[82].

Caffeine and dependence

Brain mapping technology

The issue of possible dependence on caffeine has been debated for many years. In humans, the widely recognized behavioral stimulant, and mildly reinforcing, properties of caffeine are likely to be responsible for the maintenance of caffeine consumption[83].

People may also drink coffee from habit: the possible reinforcing effects of coffee may not be due to the caffeine per se, but linked to the pleasurable aroma and taste of coffee, as well as the social environment that usually accompanies coffee consumption[84].

Learn more about caffeine's effect on the brain by watching a video here.

Drugs of abuse such as cocaine, morphine and nicotine specifically activate the dopaminergic mesolimbic brain circuit of dependence and reward at low doses.

- Pre-clinical studies have reported that caffeine given to rats, in doses corresponding to human consumption levels (1-5mg/kg body weight, i.e. 1-5 large cups of coffee in one sitting), fails to increase energy metabolism[85] and dopamine release[86,87] in this circuit.

This research has also been extended to humans.

- Subjects in one study received 3 mg/kg body weight of caffeine, or the equivalent

of about 2 large cups of coffee. Cerebral blood flow measurements showed that, as in rats, caffeine did not activate the brain circuit of dependence in humans, but activated regions involved in attention, vigilance and anxiety (the internal parietal zone), as well as regions controlling vegetative functions (the hypothalamus and anterior insular cortex)[88].

These results represent the first 'brain mapping' approach to the study of dependence in humans, and confirm the pre-clinical data reporting no involvement of the circuit of dependence in the physiological effects of caffeine[86,87]. In other words, based on brain mapping technology, caffeine does not fulfil the criteria to be described as a drug of dependence.

Withdrawal

Among the symptoms linked to drug dependence is withdrawal. In 2013, the American Psychiatric Association released an updated edition of its *Diagnostic and Statistical Manual of Mental Disorders*, the DSM-5, which provides standardized criteria for the classification of mental disorders. For the first time since its launch in 1952 it addresses 'caffeine withdrawal'. In the manual, caffeine withdrawal is defined as a syndrome resulting from abrupt cessation or reduction in caffeine, following prolonged daily use[89].

Only a subset of the population of coffee/caffeine consumers suffer withdrawal symptoms (headache, reduced alertness, and drowsiness). These symptoms generally begin about 12-24 hours after sudden cessation of caffeine consumption and reach a peak after 20-48 hours. Importantly, these symptoms can be avoided altogether if caffeine intake is decreased progressively[83].

- A study measuring cerebral blood velocity, after the exposure of subjects to either 400mg caffeine or placebo for two weeks, reported that acute caffeine abstinence produced significant increases in blood flow velocity that, consistent with earlier studies, highlight the link between vascular changes and the caffeine withdrawal symptoms of headache, increased drowsiness and decreased alertness[90].
- Likewise, the ingestion of 250mg caffeine, by caffeine consumers (mean intake of 375mg caffeine per day), after 30 hours of abstinence, had a greater effect than placebo on mood and choice reaction time (i.e. the reaction time for a task in which an individual has to make one of two or more choices). Caffeine also improved selective attention and memory in both those who had abstained from caffeine and those who had maintained their habitual intake levels, suggesting no evidence of withdrawal on these markers of mental performance[91].
- A 2012 review on the role of caffeine as a performance enhancer also concluded that caffeine's beneficial effects on both simple and complex attention tasks could not be attributed to withdrawal reversal[6].

Another study, using quantitative perfusion magnetic resonance imaging, reported that cerebral blood flow increased during the abstinence period and reduced after caffeine ingestion, in both those who abstained or did not abstain from caffeine before the test. This study also showed that in high consumers (950mg/day), the cerebrovascular adenosine system has a limited capacity to compensate for the high amount of daily caffeine used. However, this study is limited by several factors, including the arbitrary classification of daily caffeine intake and possible under-reporting of withdrawal symptoms[92].

Conclusions

The well-established beneficial effect of caffeinated coffee on mental performance has been confirmed by EFSA, which states that a cause and effect relationship has been established between a 75mg serving of caffeine – the amount found in approximately one regular cup of coffee – and both increased attention (concentration) and alertness, mainly in situations of low arousal.

- Caffeine may also improve safety and performance during work at night and night driving.
- Positive effects on mood and reaction time have also been documented.

There is an association between the daily intake of caffeine, sleep problems and daytime sleepiness; however, these effects depend on the amount of caffeine ingested over the whole day and also vary with the genetic background of individuals. Those individuals who do experience sleep problems following consumption of caffeinated coffee may choose, or be advised, to switch to decaffeinated products in the afternoon/evening.

In addition, brain mapping technology suggests that the physiological effects of caffeine do not lead to either dependence. Whilst some individuals may experience caffeine withdrawal, these symptoms are short-lived and can be avoided altogether if caffeine intake is decreased progressively.

References

32. Frijda N.H. (1993) 'Moods, emotion episodes and emotions' in '*Handbook of Emotions'* Lewis M., Haviland J.M. eds., pp381-403. Guilford Press, New York.
33. Scherer K.R. (2005) What are emotions? And how can they be measured? *Soc Sci Info*, 44(4): 695–729.
34. WHO, R63 Fact sheet on mental health, WHO Regional office for Europe. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/215275/RC63-Fact-sheet-MNH-Eng.pdf?ua=1
35. WHO, Data and Statistics Prevalence of Mental Health Disorders. Available at: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-

statistics
36. Meeusen R. (2014) Exercise, Nutrition and the Brain. *Sports Med*, 44(1):47-56.
37. Garcia-Blanco T. et al. (2016) Tea, cocoa, coffee, and affective disorders: vicious or virtuous cycle? *J. Affect Disord,* published online ahead of print.
38. Wilhelmus M.M. et al. (2016) Effects of a single, oral 60mg caffeine dose on attention in healthy adult subjects. *J Psychopharmacol*, published online ahead of print.
39. Judelson D.A. et al. (2013) Effects of Theobromine and Caffeine on Mood and Vigilance, *J Clin Psychopharmacol*, 33(4):499-506.
40. Smit H.J. and Rogers P.J. (2006) Effects of caffeine on mood. In Caffeine and the activation theory. *Effects on health and behavior*, Smith B.D., Gupta U., Gupta B.S., eds, CRC Press, Boca Raton, FL, pp. 229-82.
41. Tallis J. et al. (2013) Assessment of the ergogenic effect of caffeine supplementation on mood, anticipation timing, and muscular strength in older adults. *Physiol Reps,* 1(3):e00072.
42. Haskell C.F. et al. (2005) Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. *Psychopharmacol*, 179:813-25.
43. Misaizu A. et al. (2014) The Combined Effect of Caffeine and Ornithine on the Mood of Healthy Office Workers. *Prev Nutr Food Sci.* 19(4):367–372.
44. Turnbull D. et al. (2016) Neurobehavioral hazard identification and characterization for caffeine. *Regul Toxicol Pharmacol,* 74:81-92.
45. Ullrich S. et al. (2016) Feeling smart: Effects of caffeine and glucose on cognition, mood and self-judgment. *Physiol Behav,* 151:629-37.
46. Maridakis V. et al. (2009) Sensitivity to change in cognitive performance and mood measures of energy and fatigue in response to morning caffeine alone or in combination with carbohydrate. *Int J Neurosci*, 119:1239-58.
47. Cropley V. et al. (2012) Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. *Psychopharmacol,* 219(3):737-49.
48. Grosso G. et al. (2016) Coffee, tea, caffeine and risk of depression: a systematic review and dose-response meta-analysis of observational studies. *Mol Nutr Food Res,* 60(1):223-3.
49. Lucas M. et al. (2011) Coffee, caffeine, and risk of depression among women. *Arch Intern Med*, 171:1571-8.
50. Ruusunen A. et al. (2010) Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public Health Nutr*, 13:1215-20.
51. Pham N.M. et al. (2013) Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. *Pub Health Nutr,* 4:1-9.
52. Park R.J. and Moon J.D. (2015) Coffee and depression in Korea: the fifth Korean National Health and Nutrition Examination Survey. *Eur J Clin Nutr,* 69(4):501-4.
53. Tse W.S. et al. (2009) Caffeinated coffee enhances co-operative behavior in the Mixed Motive Game in healthy volunteers. *Nutr Neurosci*, 12:21-7.
54. Maremmani I. et al. (2011) Are "social drugs" (tobacco, coffee and chocolate) related to the bipolar spectrum? *J Affect Disord,* 133:227-33.
55. Strassnig M. et al. (2006) Increased caffeine and nicotine consumption in community-dwelling patients with schizophrenia. Schizophr Res, 86:269-75.
56. Bhumiratana N. et al. (2014) The development of an emotion lexicon for the coffee drinking experience, *Fd Res Int,* 61:83-92.

57. Giles G.E. et al. (2016) Caffeine accentuates emotional responses, not emotion regulation choice. *FASEB Journal,* 30(1) Supplement 898.
58. Giles G.E. (2016) Caffeine and theanine exert opposite effects on attention under emotional arousal. *Can J Physiol and Pharmacol*, 95(1):93-100.
59. Biaggioni I. et al. (1991) Caffeine and theophylline as adenosine receptor antagonists in humans. *J Pharmacol & Exper Therap*, 258(2):588-593.
60. Volkow N.D. et al. (2015) Caffeine increases striatal dopamine D2/D3 receptor availablility in the human brain. *Transl Psychiatry,* 14(5):e549.
61. Roehrs T. et al. (2008) Caffeine: sleep and daytime sleepiness. *Sleep Med Rev*, 12:153-62.
62. Clark I. and Landolt H.P. (2016) Coffee, Caffeine, and Sleep. *Sleep Med Rev*, 31:70-78.
63. Iber C. et al. (2007) *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. 1st ed. Westchester, IL: The American Academy of Sleep Medicine.
64. Birkett D.J. et al. (1991) Caffeine renal clearance and urine caffeine concentrations during steady state dosing. Implications for monitoring caffeine intake during sports events. *Br J Clin Pharmacol*, 31:405-8.
65. Retey J.V. et al. (2007) A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Ther*, 81:692–8.
66. Byrne E.M. et al. (2012) A genome-wide association study of caffeine related sleep disturbance: confirmation of a role for a common variant in the adenosine receptor. *Sleep,* 35(7):967-75.
67. Cornelis M.C. et al. (2007) Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am J Clin Nutr*, 86:240–4.
68. Drapeau C. et al. (2006) Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. *J Sleep Res*, 15:133-41.
69. Carrier J. et al. (2009) Effects of caffeine on daytime recovery sleep: A double challenge to the sleep-wake cycle in aging. *Sleep Med*, 10:1016-24.
70. Robillard R. et al. (2015) Sleep is more sensitive to high doses of caffeine in the middle years of life. *J Psychopharmacol*, 29(6):688-97.
71. Porkka-Heiskanen T. (2011) Methylxanthines and sleep. *Handb Exp Pharmacol*, (200):331-48.
72 Ogeil R.P. and Phillips J.G. (2015) Commonly used stimulants: Sleep problems, dependence and psychological distress. *Drug & Alc Dep*, 153:145-51.
73. Drake C. et al. (2013) Caffeine Effects on Sleep Taken 0, 3, or 6 Hours before Going to Bed. *J Clin Sleep Med,* 9(11): 1195-1200.
74. Sin C.W.M. et al. (2008) Systematic review on the effectiveness of caffeine abstinence on the quality of sleep. *J Clin Nursing*, 18:13-21.
75. Snel J. et al. (2011) Effects of caffeine on sleep and cognition. *Prog Brain Res*, 190:105-17.
76. Calamaro C.J. et al. (2009) Adolescents living the 24/7 lifestyle: effects of caffeine and technology on sleep duration and daytime functioning. *Pediatrics*, 123:e1005-10.
77. Ludden A.B. et al. (2010) Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons and sleep. *Health Educ Behav*, 37:330-342.
78. Zunhammer M. et al. (2014) Sleep quality during exam stress: the role of alcohol, caffeine and nicotine. *PLoS One,* 9(10):e109490.
79. Ker K. et al. (2010) Caffeine for the prevention of injuries and errors in shift workers. *Cochrane Database Syst Rev*, (5):CD008508.
80. Schweitzer P.K. et al. (2006) Laboratory and field studies of naps and caffeine as practical countermeasures for sleep-wake problems associated with night work. *Sleep*, 29(1):39-50.

81. Mc Hill A.W. et al. (2014) Effects of caffeine on skin and core temperatures, alertness, and recovery sleep during circadian misalignment. *J Biol Rhythms,* 29(2):131-43.
82. Arendt J. (2009) Managing jet lag: Some of the problems and possible new solutions. *Sleep Med Rev*, 13:249-56.
83. Nehlig A. (2004) Are we dependent on coffee and caffeine: an update. In Nehlig A, ed. *Coffee, Tea, Chocolate and the Brain*. Boca Raton, FL: CRC Press;133-146.
84. Satel S. (2006) Is caffeine addictive? A review of the literature. *Am J Drug Alc Abuse*, 32:493-502.
85. Nehlig A. et al. (2000) Dose-response study of caffeine effects on cerebral functional activity with a specific focus on dependence. *Brain Res*, 858:71-77.
86. Acquas E. et al. (2002) Differential effects of caffeine on dopamine and acetylcholine transmission in brain areas of drug-naive and caffeine-pretreated rats. *Neuropsychopharmacol*, 27:182-193.
87. De Luca M.A. et al. (2007) Caffeine and accumbens shell dopamine. *J Neurochem*, 103:157-163.
88. Nehlig A. et al. (2010) SPECT assessment of brain activation induced by caffeine: no effect on areas involved in dependence. *Dialogues Clin Neurosci*, 12:255-63.
89. American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM V) ISBN 978-0-89042-554-1DSMV.
90. Sigmon S.C. et al. (2009) Caffeine withdrawal, acute effects, tolerance, and absence of net beneficial effects of chronic administration: cerebral blood flow velocity, quantitative EEG, and subjective effects. *Psychopharmacol* (Berl), 204:573-85.
91. Addicott M.A. et al. (2009) A comparison of the effects of caffeine following abstinence and normal caffeine use. *Psychopharmacol* (Berl), 207:423-31
92. Addicott M.A. et al. (2009) The effect of daily caffeine use on cerebral blood flow: How much caffeine can we tolerate? *Hum Brain Mapp*, 30:3102-14.