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THE PILL AND THE WILL

Pharmacological and psychological modulation of cognitive and affective processes

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Cover illustration by Myrto Sklivanioti Greenfield. The parable of the blind men and the elephant (origin: the Buddhist text Tittha Sutta c. 500 BCE) is a metaphor that illuminates the elusive nature of reality (*the elephant*) and the research (*the blind men*) that tries to examine and understand it. Each examination, each study adding a small piece to the larger puzzle, needs to be communicated and put in context.

THE PILL AND THE WILL:

Pharmacological and psychological modulation of cognitive and affective processes

Thesis for Doctoral Degree (Ph.D.)

By

Myrto Sklivanioti Greenfield

The thesis will be defended in public at Erna Möllersalen, Blickagången 16, Huddinge, Stockholm, June 16th 2023, 9:00.

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To Eryx and Leon,

‘*…this is part of what it means to think: to be right, it must be possible to be wrong*’, Noam Chomsky (and Karl Popper)

Popular science summary of the thesis, English

Imagine that while you are trying to concentrate to read this text, someone starts talking on the phone next to you about something interesting. You try to ignore it, but the effort required to focus on the text becomes greater. You get annoyed and even a little upset about this loud conversation. You are in the library after all! Your attention is hijacked, you feel like rebuking the 'offender', but it feels inappropriate to do so and you try to calm down telling yourself that it must be an important call, and you remind yourself that you also accepted important calls in the library before. You take a deep breath and try to shift your focus back to the text (that you really want to finish).

Well done! You just exerted cognitive control; intentionally and willfully, albeit with some effort, you resisted distractions and inhibited socially inappropriate reflexive reactions to focus on the task at hand. You may also have noticed that distractions can come in different forms. Cognitive processes where emotion is involved are sometimes called 'hot' cognition, for example when you try not to get angry with your colleague checking his phone during your important presentation at work, and cognitive processes where emotion is not involved are referred to as 'cold' cognition, for example when cognitive control is needed to resist checking your phone during your colleague's presentation.

This ability is vital both for good daily functioning and good mental health. Although it can decline under certain conditions for anyone of us (for example when tired, stressed, overwhelmed), sustained poor cognitive control and emotion dysregulation is central in many psychiatric diagnoses. ADHD (Attention-Deficit/ Hyperactivity Disorder) is one such diagnosis where it is being more and more recognized that both 'hot' and 'cold' cognitive control processes may be impaired.

Most psychiatric medications affect neurotransmitters such as serotonin, dopamine and noradrenalin, chemical messengers that help regulate brain (and body) functions, but little is known about how they may alter cognition and emotion. For example, the role of the most widely used antidepressants, the serotonin reuptake blockers (SSRI), in cognitive control is not well understood. It is not known either whether psychostimulants, the most widely used medications in ADHD, that affect dopamine and noradrenalin in the brain, are as effective in treating emotion dysregulation as they are in treating inattention and hyperactivity.

In this thesis, my aim was to study important aspects of cognitive control in healthy participants and individuals with ADHD. This was done by examining how cognitive control could be modified pharmacologically by SSRI and stimulant medications, psychologically by reappraisal, a strategy that can help us change our emotional experience by adjusting our instinctive thoughts, and practically by skills training with task repetition.

For this undertaking, we examined performance at the behavioural level, brain activity at the cortical and subcortical level, and sympathetic nervous system activity (a system that without conscious control regulates bodily functions such as blood pressure and breathing) at the peripheral physiological level.

We found that a single dose of escitalopram, a commonly used SSRI, led to reduced experience of negative emotions in healthy individuals, who subjectively reported lower rates of emotion intensity when we showed them pictures with negative content, and objectively showed changes in arousal as assessed by skin conductance and in prefrontal cortex activation, a brain area strongly associated with cognitive control, as assessed by near infrared spectroscopy (fNIRS), a neuroimaging technique.

A similar reduction of subjective emotional experience was found when a single dose psychostimulant medication was given instead, although probably through different mechanism.

Furthermore, we looked at how patients with ADHD experience and regulate emotion and found differences (impairment) compared to healthy individuals. We also found differences in brain structure and function: some areas related to emotion processing were on average smaller in patients with ADHD, who also seemed to use a different strategy to regulate emotions compared to healthy individuals. For example, when they were asked to do a demanding task to regulate their emotions, unlike the healthy volunteers, the ADHD patients did not successfully deactivate the 'default mode network', known as the mind-wandering network, while instead they deactivated attention-related areas, the so-called dorsal attention network. Crucially, it was not found that stimulant medication helped normalize these behavioural and brain activation differences.

Feeling less intense emotion can be a side effect or a desired outcome depending on the circumstance. In our experiments, this phenomenon proved advantageous in the context of a task requiring cognitive control of emotional distractions, where the participants performed better after they had taken a dose of the antidepressant medication, escitalopram, compared to placebo. It is likely that escitalopram made the negative emotional content less intense and thus less distracting. Interestingly, escitalopram did not improve the performance when the distraction was not emotional. Moreover, in these studies, psychological intervention and skills training with task repetition proved to be more effective in improving both 'hot' and 'cold' cognitive control compared to pharmacological intervention with both SSRI and stimulant medication.

These findings help build a body of knowledge regarding cognitive and emotional processes that are components of practically all psychiatric disorders, regardless of categorical diagnosis. Ultimately, improved knowledge in this field will ultimately lead to a paradigm shift in psychiatric praxis, helping to formulate hypothesis-driven and science-informed working theories that will guide the patients' treatment plan.

Popular science summary of the thesis, Greek (Περίληψη της διδακτορικής διατριβής, Ελληνικά)

Φαντάσου ότι ενώ συγκεντρώνεσαι για να διαβάσεις αυτό το κείμενο, κάποιος μιλάει στο τηλέφωνο δίπλα σου για κάτι ενδιαφέρον. Η προσπάθεια εστίασης στο κείμενο γίνεται μεγαλύτερη και πιο απαιτητική. Επίσης εκνευρίζεσαι και θυμώνεις λίγο με αυτή τη φασαρία (εύλογα αφού βρίσκεστε στη βιβλιοθήκη!). Η συγκέντρωσή σου διασπάται και νιώθεις ότι θέλεις να ξεσπάσεις και να βάλεις τις φωνές στο πρόσωπο που σε ενοχλεί, αλλά νιώθεις πως αυτό θα ήταν απρεπής συμπεριφορά, οπότε ηρεμείς και σκέφτεσαι ότι μάλλον πρόκειται για μια πολύ σημαντική κλήση και θυμίζεις στον εαυτό σου ότι έχει συμβεί να δεχθείς και εσύ σημαντική κλήση στη βιβλιοθήκη στο παρελθόν. Παίρνεις μια βαθιά εισπνοή και συγκεντρώνεσαι πάλι για να διαβάσεις το κείμενο που θέλεις πραγματικά να ολοκληρώσεις.

Συγχαρητήρια! Μόλις άσκησες 'γνωστικό έλεγχο': σκόπιμα και ηθελημένα, παρόλο που χρειάστηκε κάποια προσπάθεια, αντιστάθηκες σε περισπασμούς και απρεπείς συμπεριφορές, προκειμένου να εστιάσεις σε αυτό που ήταν πιο σημαντικό για εσένα (και πιο αποδεκτό κοινωνικά). Μπορεί επίσης να έχεις παρατηρήσει ότι οι περισπασμοί μπορεί να είναι διαφορετικής φύσης: σε κάποιες περιπτώσεις συναισθήματα πρέπει να ρυθμιστούν ώστε να συγκεντρωθείς σε αυτό που κάνεις, για παράδειγμα όταν προσπαθείς να ελέγξεις το θυμό σου ενώ κάνεις μια σημαντική παρουσίαση στη δουλειά και κάποιος συνάδελφος σου κοιτά το κινητό του. Σε άλλες περιπτώσεις δεν εμπλέκονται συναισθηματικές περιστάσεις, παρά μόνο 'νοητικές', για παράδειγμα όταν χρειάζεται να αντισταθείς στο να κοιτάξεις το κινητό σου κατά τη διάρκεια της παρουσίασης ενός συναδέλφου σου.

Αυτές οι ικανότητες είναι μεγάλης σημασίας τόσο για να ανταπεξέρχεται κάποιος στις καθημερινές προκλήσεις όσο και για την ψυχική του υγεία. Πράγματι, αν και μπορεί να επηρεαστούν αρνητικά κάτω από ορισμένες συνθήκες για τον καθένα μας (όπως, για παράδειγμα, όταν είμαστε κουρασμένοι, αγχωμένοι, καταπονημένοι), ο χρονίως πάσχων γνωστικός έλεγχος και η απορρύθμιση των συναισθημάτων είναι εξέχουσας σημασίας σε πολλές ψυχιατρικές διαγνώσεις. Το ADHD (Διαταραχή Ελλειμματικής Προσοχής / Υπερκινητικότητας) είναι μία από αυτές, όπου αναγνωρίζεται όλο και περισσότερο ότι και οι δύο μορφές γνωστικού ελέγχου εμπλέκονται.

Τα περισσότερα ψυχιατρικά φάρμακα επηρεάζουν τους νευροδιαβιβαστές, χημικούς αγγελιοφόρους, που βοηθούν στη ρύθμιση των λειτουργιών του εγκεφάλου (και του σώματος), όπως η σεροτονίνη, η ντοπαμίνη και η νοραδρεναλίνη, αλλά δεν είναι μέχρι σήμερα εντελώς κατανοητό για το πώς μπορεί να επηρεάσουν τις γνωσιακές λειτουργίες και το συναίσθημα. Για παράδειγμα, ο ρόλος των ευρέως χρησιμοποιούμενων αντικαταθλιπτικών φαρμάκων (που συνήθως επηρεάζουν τη σεροτονίνη στον εγκέφαλο) στον γνωστικό έλεγχο δεν είναι καλά κατανοητός και δεν είναι γνωστό εάν τα διεγερτικά του κεντρικού νευρικού συστήματος (που επηρεάζουν κυρίως την ντοπαμίνη και τη νοραδρεναλίνη στον εγκέφαλο), δηλαδή τα φάρμακα που χρησιμοποιούνται για το ADHD, βοηθούν σε αυτή τη λειτουργία.

Όταν η ψυχιατρική πράξη συνδυάζεται με τις νευροεπιστήμες τίθεται συχνά το ερώτημα: Με δεδομένο το υφιστάμενο επίπεδο γνώσης, είναι επαρκής ο επικρατής τρόπος σκέψης ή απαιτείται *αλλαγή παραδείγματος (paradigm shift)*; Σκοπός αυτής της διατριβής ήταν να μελετηθούν πτυχές του γνωστικού ελέγχου σε υγιή άτομα όσο και σε άτομα με διάγνωση ADHD. Εξετάσαμε πώς μπορεί να επηρεαστεί από διαφορετικά ψυχιατρικά φάρμακα και απλές ψυχολογικές παρεμβάσεις, όπως η εξάσκηση και η 'γνωστική αναδόμηση', μια τεχνική που βοηθάει να αλλάξουμε τη συναισθηματική μας εμπειρία τροποποιώντας τις ενστικτώδεις σκέψεις μας που επηρεάζουν αυτά τα συναισθήματα, όπως στο παραπάνω παράδειγμα. Αυτές οι μελέτες εξέτασαν όχι μόνο τις επιπτώσεις στη συμπεριφορά, αντικειμενική απόδοση και υποκειμενική εμπειρία, αλλά και τι συμβαίνει στον

εγκέφαλο και στο συμπαθητικό αυτόνομο νευρικό σύστημα, το σύστημα που αυτόματα και χωρίς συνειδητό έλεγχο ρυθμίζει τις λειτουργίες του σώματος όπως η αρτηριακή πίεση και ο ρυθμός της αναπνοής.

Αυτό που διαπιστώθηκε ήταν ότι μια μόνο δόση εσιταλοπράμης (escitalopram), ενός κοινού αντικαταθλιπτικού που χρειάζεται καθημερινή χορήγηση για εβδομάδες ώστε να έχει κλινικό αποτέλεσμα, οδήγησε σε μειωμένη εμπειρία αρνητικών συναισθημάτων σε υγιή άτομα όταν τους δείξαμε εικόνες με αρνητικό περιεχόμενο μόνο λίγες ώρες μετά. Αυτό δεν ήταν μόνο κάτι που περιέγραψαν οι εθελοντές που συμμετείχαν, αλλά παράλληλα μετρήσαμε μικρότερη διέγερση του αυτόνομου νευρικού τους συστήματος. Επίσης, όταν χορηγήθηκε μια δόση εσιταλοπράμη, παρατηρήθηκε μείωση της ενεργοποίησης του προμετωπιαίου φλοιού, μιας περιοχής του εγκεφάλου που προηγούμενες έρευνες είχαν συσχετίσει με τον γνωστικό έλεγχο. Παρόμοιο αποτέλεσμα μειωμένης συναισθηματικής εμπειρίας βρέθηκε όταν χορηγήθηκε αντ' αυτού μία δόση διεγερτικών, κυρίως μεθυλφαινιδάτη (κάτι που πιθανότατα να συμβαίνει μέσω διαφορετικών μηχανισμών).

Επιπλέον, εξετάσαμε τον τρόπο με τον οποίο οι ασθενείς με ADHD βιώνουν και ρυθμίζουν τα συναισθήματά τους, και διαπιστώσαμε ότι και οι δύο διαδικασίες διέφεραν σε σύγκριση με άτομα χωρίς ψυχιατρική διάγνωση. Οι ασθενείς με ADHD περιέγραψαν λιγότερο έντονα συναισθήματα κατά τη διάρκεια του πειράματος, αλλά και μικρότερη ικανότητα να τα ρυθμίσουν. Βρήκαμε επίσης διαφορές στον εγκέφαλό τους: όχι μόνο διαπιστώσαμε ότι ορισμένες περιοχές που σχετίζονται με την επεξεργασία συναισθημάτων ήταν λίγο μικρότερες κατά μέσο όρο, αλλά επίσης οι ασθενείς με ADHD απενεργοποίησαν με μικρότερη επιτυχία το γνωστό ως «δίκτυο περιπλανώμενης σκέψης» (‘default mode network’, ένα δίκτυο εγκεφαλικών περιοχών που συνήθως ενεργοποιείται όταν για παράδειγμα ονειροπολούμε ή έχουμε εσωτερικό διάλογο και απενεργοποιείται όταν χρειάζεται να συγκεντρωθούμε σε συγκεκριμένο έργο) όταν προσπαθούσαν να επιβάλουν γνωστικό έλεγχο. Σημαντικό είναι ότι δεν βρήκαμε ότι η φαρμακευτική αγωγή για το ADHD βοήθησε σε αυτό τον τομέα.

Το να αισθάνεσαι λιγότερο έντονα συναισθήματα μπορεί να είναι μια παρενέργεια ή ένα επιθυμητό αποτέλεσμα ανάλογα με το άτομο και τις περιστάσεις, αλλά στα πειράματά μας, αυτό το φαινόμενο αποδείχθηκε πλεονεκτικό στο πλαίσιο μιας εργασίας που απαιτεί έλεγχο των συναισθημάτων, όπου οι συμμετέχοντες είχαν καλύτερες επιδόσεις μετά την λήψη εσιταλοπράμης σε σύγκριση με εικονικό φάρμακο. Είναι πιθανό η μια δόση του αντικαταθλιπτικού να έκανε το αρνητικά αναδυόμενο συναισθηματικό περιεχόμενο λιγότερο έντονο και επομένως λιγότερο αποτελεσματικό στη διάσπαση της προσοχής. Είναι ενδιαφέρον ότι η εσιταλοπράμη δεν βελτίωσε την απόδοση όταν η απόσπαση της προσοχής δεν ήταν συναισθηματική. Είναι σημαντικό να αναφερθεί ότι οι ψυχολογικές και συμπεριφορικές παρεμβάσεις αποδείχθηκαν πολύ πιο αποτελεσματικές μέθοδοι βελτίωσης τόσο του συναισθηματικού όσο και του γνωστικού ελέγχου σε σύγκριση με τα φάρμακα, τουλάχιστον για τους συμμετέχοντες στη μελέτη.

Αυτά τα ευρήματα συμβάλλουν στη κατανόηση των γνωσιακών και συναισθηματικών διεργασιών που αποτελούν συστατικό σχεδόν όλων των ψυχιατρικών διαταραχών, ανεξάρτητα από τις τυπικές διαγνώσεις. Η βελτιωμένη γνώση σε αυτόν τον τομέα ελπίζουμε ότι θα οδηγήσει σε μια *αλλαγή παραδείγματος* στην ψυχιατρική πράξη, με προσέγγιση βασιζόμενη σε επιστημονικά δεδομένα και εστίαση σε αυτές τις διεργασίες (λειτουργίες γνωσιακές/ cognitive, συναισθηματικές/ emotional, (ψυχο)κινητικές/ motivational κτλ) αντί για αποκλειστικά τις κατηγορικές διαγνώσεις βασιζόμενες στα συμπτώματα (κατάθλιψη, αγχώδεις διαταραχές, ψυχωτικές διαταραχές κτλ) σύμφωνα με τον επικρατή τρόπο σκέψης και τα διεθνή διαγνωστικά συστήματα DSM (Diagnostic and Statistical Manual of Mental Disorders) και ICD (International Classification of Diseases). Αυτό για τον ασθενή μεταφράζεται σε μία πιο εξατομικευμένη, εξειδικευμένη, στοχευμένη και ολιστική προσέγγιση.

Popular science summary of the thesis, Swedish (Populärvetenskaplig sammanfattning av avhandlingen, Svenska)

Föreställ dig att medan du koncentrerar dig på att läsa den här texten börjar någon bredvid dig prata i telefon, om något intressant dessutom. Du får svårt att fokusera på vad du läser. Du blir också irriterad och till och med lite upprörd över detta högljudda samtal, ni befinner er trots allt på biblioteket! Din koncentration är kidnappad och du vill säga till, men det känns olämpligt så du lugnar dig själv med att anta att det måste vara ett viktigt samtal för personen i fråga och kommer ihåg att du också tagit emot viktiga samtal på biblioteket någon gång. Du andas ut och flyttar fokuset tillbaka till att läsa den här texten (som du verkligen vill läsa klart).

Bra jobbat! Du utövade kognitiv kontroll; avsiktligt och medvetet, och trots att det var med viss ansträngning lyckades du motstå distraktioner och olämpliga reaktioner, för att fokusera på uppgiften och göra det som var mer lämpligt socialt. Du kanske också har märkt att distraktioner kan vara av olika karaktär. Den aspekt av hjärnprocesserna där känslor är inblandade benämns ibland ‘het’ (eng ‘hot’) kognition, till exempel när du försöker låta bli och inte känna dig arg när en kollega tittar på sin mobil under din viktiga presentation, medan då känslor inte är inblandade, benämner man kognitionen ‘kall’ (eng ‘cold’), exempelvis när kognitiv kontroll krävs för att motstå att kolla din mobil under din kollegas presentation på jobbet.

Denna förmåga är avgörande både för god funktion och för mental hälsa. Kognitiv kontroll kan brista under vissa förhållanden för vem som helst, till exempel när vi är trötta, stressade, överväldigade, men ihållande nedsatt kognitiv kontroll och emotionell dysreglering är centrala i de flesta om inte alla psykiatriska diagnoser. ADHD är en av de diagnoser där det är alltmer allmänt godtaget att båda formerna av kognitiv kontroll kan påverkas.

De flesta psykiatriska mediciner påverkar signalsubstanser, kemiska budbärare som hjälper till att reglera hjärnans (och kroppens) funktioner, såsom serotonin, dopamin och noradrenalin, men hur dessa substanser kan påverka kognition och känslor är otillräckligt klarlagt. Exempelvis vet vi för lite om antidepressiva läkemedels (de flesta antidepressiva medel påverkar serotonin i hjärnan) effekt på emotion och kognitiv kontroll och huruvida centralstimulantia (en medicin som används vid ADHD och som främst påverkar dopamin och noradrenalin i hjärnan) är effektiva för att behandla problem med känslomässig dysreglering.

I min avhandling har jag undersökt aspekter av kognitiv kontroll hos friska deltagare och individer med ADHD diagnos. Detta gjordes genom att undersöka hur kognitiv kontroll kan påverkas av olika psykiatriska mediciner och enkla psykologiska interventioner, såsom övning och kognitiv omstrukturering, en teknik som kan hjälpa till att förändra ens känslomässiga upplevelse genom att justera de tankar som ger form till dessa känslor, som illustreras i exemplet ovan.

I mina studier har jag undersökt effekter av dessa interventioner på beteende, men också vad som händer i hjärnan och i det sympatiska autonoma nervsystemet, systemet som automatiskt och utan medveten kontroll reglerar kroppsfunktioner som blodtryck och andningshastighet.

Resultaten från olika studier visade att även en engångsdos av escitalopram, ett vanligt antidepressivt läkemedel, ledde till minskad upplevelse av negativa känslor hos friska individer: Dels rapporterade de detta subjektivt, men vi kunde samtidigt mäta en mindre aktivering av studiedeltagarnas autonoma nervsystem och en minskning av aktiveringen i prefrontala cortex, ett område i hjärnan som har förknippats med kognitiv kontroll. En liknande effekt av minskad emotionell upplevelse noterades när en dos centralstimulantia gavs i stället, även om mekanismen här troligen är en annan.

Vidare undersökte vi hur patienter med ADHD upplever respektive reglerar sina känslor. Vi fann att båda dessa processer var nedsatta jämfört med personer utan diagnos och att ADHD patienterna rapporterade mindre intensiva emotionella reaktioner på negativa bilder liksom mindre kapacitet att reglera dessa emotioner. Vi fann också skillnader när vi tittade på hjärnan: vissa områden som relateras till känslobearbetning var storleksmässigt lite mindre i genomsnitt hos patienterna som dessutom hade svårt att stänga av sitt 'standardnätverk' (eng 'default mode network'), som är ett nätverk av områden i hjärnan som aktiveras när man låter tankarna vandra spontant. Vi fann inte att ADHD medicinering förbättrade funktionen i dessa aspekter.

Att uppleva känslor mindre intensivt kan anses som en biverkning eller ett önskat resultat beroende på individen och omständigheterna. I våra experiment visade sig detta fenomen vara fördelaktigt för prestation i en uppgift som kräver kognitiv kontroll av känslor: deltagarna presterade bättre efter att de tagit en dos av escitalopram jämfört med placebo. Det är troligt att escitalopram gjorde upplevelsen av känslomässigt negativt innehåll mindre intensiv och därmed mindre distraherande. Intressant nog förbättrade inte escitalopram prestationen när distraktionen inte var av emotionell karaktär.

Viktigt är att beteendemässiga och psykologiska interventioner visade sig vara mer effektiva metoder för att förbättra kognitiv kontroll, jämfört med de farmakologiska, åtminstone under de specifika omständigheterna i studierna.

Avhandlingens resultat bidrar med en pusselbit kring förståelsen av de kognitiva och emotionella processer som ingår i alla psykiatriska störningar, oavsett diagnoskategori. Förhoppningsvis kommer förbättrad kunskap inom detta område att leda till ett paradigmskifte i psykiatrisk praxis och bidra till att formulera hypotesdrivna och vetenskapsorienterade arbetsteorier som kan vägleda behandlingen av psykiatriska patienter.

Abstract

Background:

Impairments in cognition are components of practically all psychiatric disorders and in that sense transdiagnostic factors. In both clinical and non-clinical populations, 'hot' and 'cold' cognitive control, i.e., in emotional context and non-emotional context, is strongly associated with daily functioning and physical and mental well-being. The paradigm shift that the National Institute of Mental Health (NIMH) Research Domain Criteria initiative (RDoC) has introduced, signifies that targeting the underlying biological and behavioural endophenotypes that determine mental health and illness might be more fruitful than simply focusing on symptom based diagnostic categories. Yet, little is known on how pharmacological interventions such as selective serotonin reuptake inhibitors (SSRI) and psychostimulants (CS), that are routinely used in everyday clinical praxis, affect cognitive and emotional processes beyond the symptoms they are supposed to treat.

Aim:

The aim of this thesis was to compare induction and regulation of fear and disgust in healthy subjects, and to investigate how SSRI affect these processes. This basic design was expanded to also include the effect of stimulant medication on the induction and regulation of negative emotions in healthy controls and patients with ADHD. A parallel aim was to compare pharmacological emotion regulation (SSRI and CS) with psychological emotion regulation (reappraisal) and emotion regulation with skills training/ exposure (task repetition).

Methods:

A multimodal approach was used to explore (i) subjective rating of emotion intensity and objective measures of performance at the behavioural level, (ii) neural underpinnings in the CNS with functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM) and (iii) physiological components of the sympathetic nervous system (electrodermal activity), which were all evaluated in the absence and presence of pharmacological and psychological interventions, during emotion induction, emotion regulation, cognitive Stroop and emotional Stroop paradigms.

Results:

Study I and **IV** demonstrated that emotion regulation with reappraisal is an effective strategy with robust effects on subjective emotional experience and electrodermal activity. **Study II** and **III** showed that task repetition improved performance during both cognitive and emotional Stroop tasks, and reduced electrodermal activity during cognitive Stroop, without significantly modifying emotion induction or emotion regulation.

Study II and **III** showed significant effects of single dose escitalopram in reducing subjective emotional experience, improving task performance during affective interference of an ongoing cognitive process, altering prefrontal activity in a task-specific manner, and blurring the differences in the electrodermal activity between fear and disgust seen at baseline. **Study IV** showed that single dose CS reduced emotion induction, and that emotion regulation with reappraisal was significantly more effective in reducing subjective emotional experience compared to pharmacological emotion regulation with CS.

Lastly, **Study IV** revealed aberrant emotion processing in patients with ADHD both at the behavioural and CNS levels, with patients reporting lower emotion induction and regulation scores, accompanied by less activation of dorsolateral prefrontal cortex, less deactivation of the default mode network and instead greater deactivation of the dorsal attention network, during emotion regulation compared to healthy controls. Structurally (VBM), less gray matter volume was found in limbic and paralimbic areas in patients with ADHD compared to healthy controls.

Conclusions and implications:

Dimensional approach using behavioural endophenotypes is a fruitful framework for studying normal physiology and diagnostic and treatment aspects of psychiatric disorders. In this thesis, it is demonstrated that emotional and non-emotional cognitive processes, although part of a continuum, likely respond differentially to psychological and pharmacological interventions and skills training with task repetition. Ultimately, improved knowledge in this field will help formulate hypothesis-driven and science-informed frameworks that will guide diagnosis and treatment plans, and usher a shift in psychiatric praxis.

List of scientific papers

I. **Myrto Sklivanioti Greenfield**, Yanlu Wang, Mussie Msghina
Similarities and differences in the induction and regulation of the negative emotions fear and disgust: A functional near infrared spectroscopy study.
Scandinavian Journal of Psychology (2022)

II. **Myrto Sklivanioti Greenfield**, Yanlu Wang, Mussie Msghina
Behavioural, cortical and autonomic effects of single-dose escitalopram on the induction and regulation of fear and disgust: Comparison with single-session psychological emotion regulation with reappraisal.
Frontiers in psychiatry (2023)

III. **Myrto Sklivanioti Greenfield**, Yanlu Wang, Lina Martinsson, Tie-Qiang Li, Mussie Msghina
Behavioural intervention with task repetition compared to pharmacological intervention with SSRI for enhancement of cognitive control in emotional and non-emotional settings.
Submitted

IV. **Myrto Sklivanioti Greenfield**, Yanlu Wang, Per Thunberg, Mussie Msghina
Emotion dysregulation in adult ADHD not reversed by stimulant medication.
Manuscript

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List of abbreviations

5-HT	5-hydroxytryptamine (serotonin)
α1-AR, α2A-AR	Alpha adrenergic receptors
aCC	Anterior cingulate cortex
ADHD	Attention Deficit Hyperactivity Disorder
ANS	Autonomic nervous system
BBB	Blood–brain barrier
BOLD	Blood oxygenation level dependent imaging
CNS	Central nervous system
CPT	Continuous performance task
CS	Stimulants, also often referred to as central stimulants or psychostimulants
D1R, D2R	Dopamine receptors
DA	Dopamine
DAT	Dopamine transporter
DLPFC	Dorsolateral PFC
DMPFC	Dorsomedial PFC
DR	Dorsal raphe
EDA	Electrodermal activity
EDR	Electrodermal response
EI	Emotion Induction
ER	Emotion Regulation
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
LC	Locus coeruleus
LPFC	Left lateral PFC
MPFC	Medial PFC
NA	Noradrenaline
NAc	Nucleus accumbens
NET	Noradrenaline transporter
Nic-α7R	Alpha-7 nicotinic (acetylcholine) receptor
NMDAR	NMDA glutamete receptor
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal cortex

PFC	Prefrontal cortex
RDoC	Research Domain Criteria Initiative
rIFJ	Right Inferior frontal junction
RPFC	Right lateral PFC
SERT	Serotonin transporter
SN	Substantia nigra
SSRI	Selective serotonin reuptake inhibitor
VBM	Voxel-based morphometry
VLPFC	Ventrolateral PFC
VMPFC	Ventromedial PFC
VTA	Ventral tegmental area

Introduction

The paradigm shift introduced by the Research Domain Criteria (RDoC) initiative (1) and other similar frameworks signifies that targeting specific biological and behavioural dimensions that comprise mental health and illness may be more fruitful than simply focusing on symptom based categorical diagnoses. Indeed, domains and constructs, such as emotion regulation and cognitive control, are core components of practically all psychiatric disorders, transdiagnostically. In the clinical setting, emotion dysregulation and aberrant cognitive functioning can be mitigated by pharmacological, psychological, skills training and psychosocial interventions, but none of these are 'one-size-fits-all' tools. Characterizing affective and cognitive domains and constructs and investigating which interventions can modify them best not only provides a 'window into the mind'(2), but also has real life applications that are highly relevant to clinical praxis.

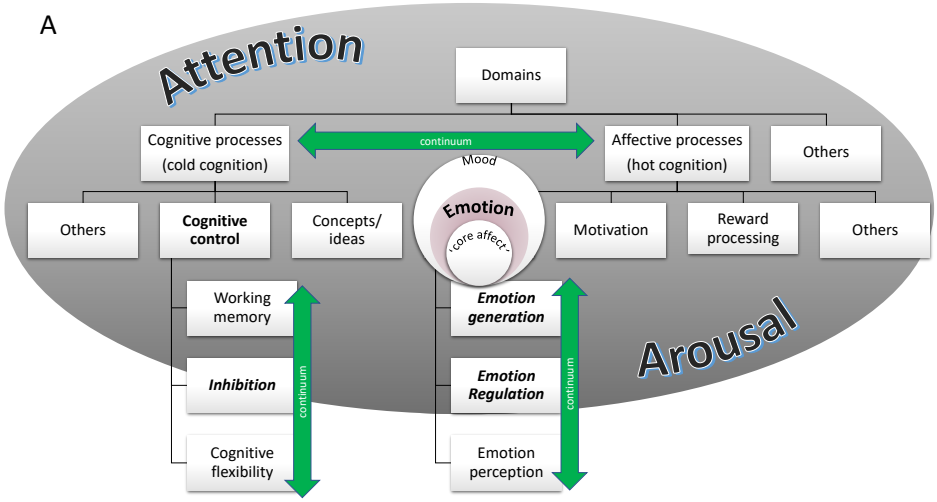
1 Literature review

1.1 Cognition

Cognitive neuroscience focuses on the biological basis of mental processes. Cognition can be approached by studying its neural correlates in the brain and the associated physiological manifestations in the periphery, but importantly, since 'behaviour is the macroscopic embodiment of brain activity' (3), measures of performance and subjective experience are also of paramount importance linking research insights to clinical applications.

There are different ways to conceptualize cognitive functions. A useful and pragmatic way is to organize them into 'hot', when emotional or motivational aspects are relevant, and 'cold' cognitive processes, when the latter is not the case (4, 5), *figure 1.1*.

Cognitive control, often also referred to as executive function, and emotion regulation are among the domains that are most relevant for human behaviour and central for the human experience. They are also fundamental psychopathological elements of psychiatric disorders such as depression (6-8), bipolar disorder (9, 10), schizophrenia (11) and anxiety disorders (12).



B	Cold cognition	Hot cognition
Examples of domains	Working memory Attentional control Cognitive flexibility Set shifting Error detection Performance monitoring	Emotion regulation Reward processing Delay discounting Social cognition Any domain of cold cognition with emotional or motivational elements
Examples of relevant tasks	Cognitive Stroop task n-back/ digit span AX-CPT Tower of London/ Stockings of Cambridge test Task-switching Attention shifting Conflincting task Verbal fluency	Emotion generation, regulation, perception tasks Iowa gambling task Theory of mind tasks eg false-belief task Any task forcold cognition with emotional or motivational elements
Neural correlates (with predominant functional specificity)	More lateral parts of the PFC , mainly DLPFC aCC Basal ganglia Hippocampus	More medial parts of the PFC eg OFC, MPFC and VLPFC Amygdala Insula Striatum
	• Place on a spectrum • Top-up and bottom-down aspects	

Figure 1.1 *(A) Domains and constructs in neuroscience research. Biased competition theory advocates the idea that every 'item' (sensory-driven stimuli and higher-order functions) competes for cortical representation and cognitive processing due to limited capacity (13-16) and attention (automatic or controlled) 'decides' which. Attention and arousal are overlapping constructs (see also figure 1.2). This categorization is practically useful, but artificial and probably inaccurate when it comes to biological systems that are parts of a continuum, overlap, affect, and modulate each other reciprocally. (B) 'Hot' and 'Cold' cognition, modified after Salehinejad, Ghanavati (5)*

1.1.1 Cognitive control

Cognitive control comprises of a set of mental processes that exert top-down control enabling goal-directed behaviour in demanding situations when automatic modulation is found to be suboptimal (17-20). Cognitive control is an umbrella term that includes a variety of subprocesses generally operationalized through some of its core functions: *response inhibition*, *working memory* and

cognitive flexibility. Executive function is the first thing to suffer under the detrimental effects of stress, insomnia, physical and mental illness, which can be seen at the functional and structural levels in prefrontal cortex and at the behavioural level in the form of impaired function and performance (17, 21-25).

Cognitive interference occurs when the processing of a task-irrelevant stimulus impedes the simultaneous processing of task-relevant processes (26). Inhibitory control entails the ability to override prepotent response tendencies in favor of what's more appropriate for the goal at hand (17). The concept of response inhibition incorporates both behavioural inhibition and interference control (15, 17). The Stroop task is an example of a paradigm that tests response inhibition and inference control.

1.1.2 Affective cognition

Emotion, the affective aspect of consciousness (27), provides an interface at which affective and cognitive processes are integrated to generate behaviour. Researchers in the field have been attempting to approach emotion by studying emotion generation, emotion perception, emotion expression, subjective experience and emotion regulation (28). 'Core affect', the most basic and fundamental form of emotional experience, is characterized by two orthogonal domain-general dimensions - valence and arousal (29-33). Although other dimensional models have been proposed (34-36), there is a general agreement on this framework within the scientific community.

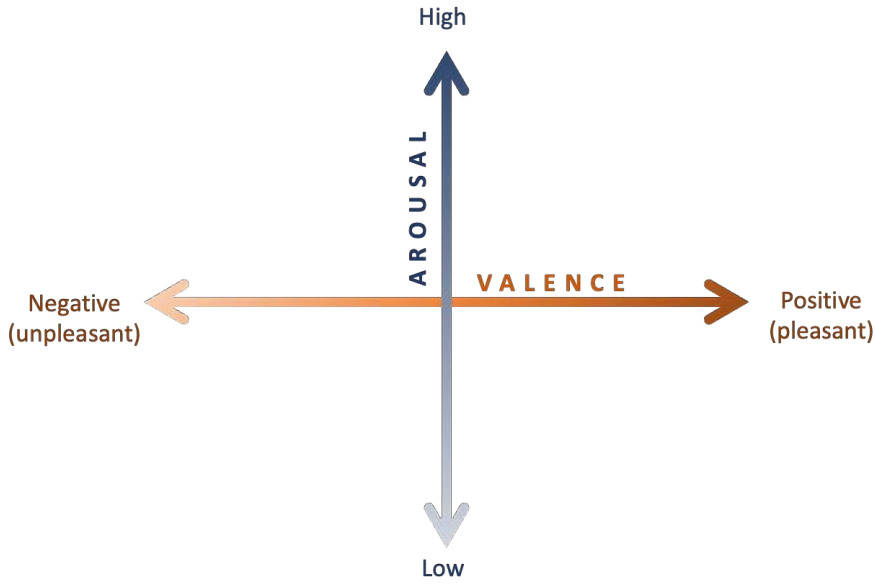


Figure 1.2 *'Core affect' is seen as an ongoing neurophysiological process defined by two dimensions, arousal (activation values) and valence (hedonic values). Valence is the property of an affective state distinguishing how positive/ attractive or negative/ unattractive it is experienced intrinsically, a property most likely emergent in a context-dependent and probabilistic whole-brain fashion (37, 38). Arousal on the other hand, can be described as a state of activation, vigilance or alertness presumed to be in response to sensory stimulation via the reticular activating system and involving physiological peripherical and CNS responsiveness (39, 40).*

When it comes to our understanding of emotion, however, it is still a hotly debated issue (32, 36, 41, 42). A century or so ago, Charles Darwin described emotion in evolutionary terms and highlighted the basic similarities in emotional behaviour among different species, including humans (43). According to the classical view of emotion, which still is popular among many today, a few basic emotions exist, each with characteristic biological signature, belonging to well-defined clusters of processes demarcated by physiological factors and served by distinct dedicated neural circuits (44-49). An alternative view is that emotion categories are culture-dependent and that instances of emotion emerge from the subjective experience of context-dependent processes of a brain that is constantly trying to give meaning to sensory events with the ultimate goal of serving homeostasis and allostasis (50, 51). Emotion experience, interpretation, and communication, thus, depend on individual characteristics (for example gender, social role, etc.), background (forming one's internal model of the world), umwelt and affective niche (what is relevant for the individual in her perceptual environment), priors (past experiences) and goals. Furthermore, in this context it has been proposed that emotion generation and emotion regulation are two sides of the same coin, engaging the same neural networks (37, 52) and experientially differing only in terms of whether one perceives agency over this experience or not (36).

Emotion is often operationalized as transient and prepotent response to salient external stimuli or internal mental representations (4, 53), with changes in experiential, behavioural and physiological systems (Gross 2011). Since emotion is important for guidance of behaviour and survival, another practical approach to conceptualize emotion has been through its functional features (12, 35, 41, 54, 55). For example, identification of threat is thought to activate survival mechanisms potentially contributing to the emergence of a conscious experience categorized as fear, which would then guide choice of a suitable behaviour from a wide repertoire of possible actions in model-free or model-based ways (12, 56). Disgust, on the other hand, is thought to have evolved from a phylogenetically primitive sensation of distaste (34, 57) and associated with disease and contamination (58). In this framework, categorizing an instance of emotion as 'fear' would guide behaviour differently than if it was labelled as 'disgust' (for example fight or flight response for fear and avoidance behaviour for disgust). Clinically, although fear has been put in the anxiety disorders' spectrum, recent research suggests that some anxiety disorders (e.g., spider phobia, contamination-related OCD, blood-injury-injection phobia) may also be associated with disgust (59-61).

1.1.2.1 Emotion regulation

Within the study of cognitive control, emotion regulation has received a lot of attention. Emotional content, especially that with negative valence, is almost always salient, receiving priority in processing and its flexible regulation being crucial for optimal mental health and adequate function (14, 22, 62, 63). Emotion regulation is of interest not only because it is useful to the study of how humans adaptively respond to affective events, but also because it is associated with a myriad of psychiatric diagnoses and as such is the target of many psychological therapy methods (6, 64-66).

Conceptually, cognitive control of emotion involves different types of appraisal processes that continuously assess the significance of stimuli to current goals, and it can be done at the cognitive, namely reappraisal, or behavioural level, namely suppression (4, 53, 67-70).

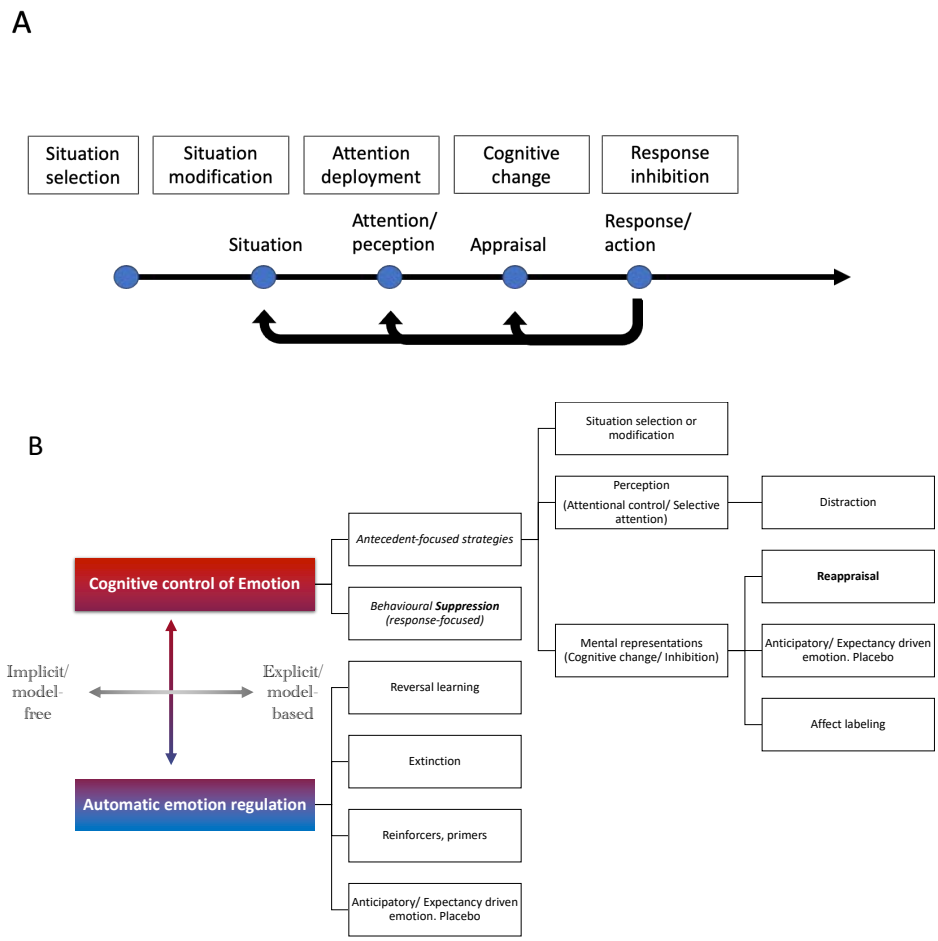


Figure 1.3 *(A) The process model of emotion regulation (68, 71) (B). Emotion regulation can be explicit or implicit regarding its goal, and willed (synonymous to effortful, cognitive or controlled) or automatic, depending on its nature. Two strategies that are often used, and have been therefore studied more, are cognitive reappraisal and suppression. Reappraisal is an antecedent-focused regulation of the attention or interpretation of emotion-eliciting situations – a strategy considered effective and more functional at least for moderate intensities of emotion. Inhibition at the behavioural level on the other hand is a response-focused regulatory strategy, consisting of suppression of expressive behaviour without affecting the subjective experience - a resource-demanding strategy with potential side effect further dysregulation of other cognitive and physiological processes. Figure 1.3B inspired by various publications including Diamond (17), Gross (68), (71), Braunstein, Gross (72), McRae and Gross (73).*

Emotion regulation can be applied voluntarily, by processes mediated by a lateral prefrontal cortex that is neocortical in origin and operates by a feedback mechanism, or automatically via a medial prefrontal cortex that is paleocortical in origin and operates through a feedforward mechanism (14). These regulatory systems integrate with subcortical regions and cortical association areas, modulating emotion and its effects on behaviour (69). When the goals of emotion regulation are explicit, this

process follows pre-determined rules (model-based regulation), but the bulk of everyday emotion regulation happens more crudely, automatically and without specific goals, based on direct feedback from the environment (model-free regulation) *(71).* Implicit emotion regulation can be achieved through different mechanisms, such as automatic control of attention, distraction or extinction (14, 72). Placebo has also been described as inducing automatic control of affect, albeit with varying degree of cognitive reappraisal taking place, and its pain-modulating and emotion regulating potential has been amply demonstrated (74-77).

1.2 Neural correlates of affective cognition

In the endeavor to model affective cognition including emotion regulation, Philips and colleagues (78) divided the controlling networks into a *ventral* (ventral PFC, aCC, OFC, amygdala, insula and striatum), responsible for identifying emotionally salient stimuli and generating emotional states, and *dorsal* affective systems (DLPFC, hippocampus) that implements cognitive control and voluntary regulation of emotional states. Later, they (69) revised and augmented their model, identifying a *medial* system (OFC, aCC, DMPFC) mediating automatic emotion regulation and a *lateral* system (DLPFC and VLPFC) exerting voluntary emotion regulation. From a different perspective, Ochsner and Gross (4, 79, 80) identify a subcortical *bottom-up* emotion appraisal network and a prefrontal *top-down* regulatory network. The *top-down* regulatory network in turn is further divided into a ventral part that exerts direct, *outcome-based* appraisal and a dorsal part related to *description-based* appraisal, leading to mental representation of affective states to make possible for reappraisal to regulate emotion.

1.2.1 Brain systems involved in emotion generation

Amygdala, traditionally relegated to the encoding of fear has had its role refined, implicating it in the detection of threat and coordination of response to danger (81). Beyond fear, further rigorous research has expanded amygdala's role in a variety of arousing stimuli of relevance to the organism's affective goals regardless of valence (82) and as such is central to the study of affective cognition (28).

Ventral striatum is involved in forming associations between stimuli and predictors of rewarding outcomes (72, 82).

Orbitofrontal PFC (OFC)/ Ventromedial PFC has been associated with assigning valuation by combining information from other cortical and subcortical areas so that this process becomes context and goal-informed (82).

Insula receives interoceptive signals from the internal milieu and negative affective experiences (71, 82, 83). Although there are findings implicating both amygdala and insula in negative emotions, a plethora of studies support some specificity for insula and disgust and for amygdala and fear (61), probably related to disgust having an intensive visceral component.

Hippocampus provides temporal and spatial context related to memory and can thus affect the appraisal of the situation and contribute to emotional experience and its regulation (71).

1.2.2 Brain systems involved in emotion regulation

The **dorsal anterior cingulate cortex (aCC)** is associated with performance monitoring and is implicated, among other things, in appraising ongoing emotional processes (71, 82).

The **prefrontal cortex** (**PFC)** is central to cognitive control of emotion, with its topographical organization determining which function is related to which neuroanatomic substrate. Separate brain networks with hubs in the PFC interact via local and global hierarchical networks (84). The PFC is

reciprocally connected with the ascending midbrain modulatory systems (85-88), so that the neural activity of the PFC gets distributed, with consequence for the activity pattern of various circuits of the brain (89, 90). On the rostral-caudal axis, it is thought that rostral areas get gradually more involved when cognitive tasks become increasingly abstract and demanding, and information processing in rostral areas both precedes and determines processing in caudal areas (85, 91). The functions of the PFC are also often studied along a dorsal - ventral axis. Dorsal and lateral areas preferentially receiving input from the external world (visual and auditory association cortices), with ventral and medial areas receiving input mainly arriving from the internal milieu, taste, smell, somatosensory and nociceptive information (85, 92, 93). Specifically, dorsomedial PFC is implicated in appraising affective states, DLPFC in selective attention and working memory, and VLPFC in response inhibition (82). The OFC has been implicated in assigning value to incoming stimuli, while the temporal lobe is thought to be involved in processing semantic and perceptual aspects of a stimulus (82). Ventral regions (including ventral aCC, ventromedial and ventrolateral PFC) serve as relay stations for 'bottom-up' emotion regulation (14, 94) and are thought to have a more 'intermediate' function, contributing to both emotion generation and regulation.

1.2.3 Intrinsic brain networks

A more recent framework, an alternative to associating specific brain areas with specific functions, is the change in the level of analysis to networks, namely discrete areas that show functional connectivity with each other. The Triple Network Model draws on how the interplay among the default mode network, the frontoparietal network and the salience network plays an important role in almost all cognitive functions.

1.2.3.1 Default mode network (DMN)

The DMN includes the medial PFC, posterior cingulate cortex and precuneus. It increases its activity during task-free conditions and during tasks that require autobiographical memory, prospective thinking and theory of mind. The DMN activity decreases when the individual is engaged in specific tasks, and as such is known as a task-negative network (95, 96).

1.2.3.2 Frontoparietal (or dorsal attention) network (FPN)

The FPN, as its name implies, consists of frontal (DLPFC) and parietal cortical areas that are activated during executive functions. Activity in FPN is negatively correlated with that in the DMN (96).

1.2.3.3 Salience network (SN)

The salience network includes the anterior insula and middorsal cingulate cortex. It has a role as an intermediate network affecting a dynamic switch between the DMN and FPN, and acts as a gatekeeper for salient stimuli to orchestrate activity in the DMN and FPN. Its function has been associated with affective processes (including reward, motivation, emotion, vigilance and pain) and homeostasis (96).

1.3 Aminergic neurotransmission

Monoamine transmitters, which include serotonin, dopamine and noradrenalin, have a number of common properties: they cannot cross the blood brain barrier, they are synthesized from amino acid precursors, are metabolized by monoamine oxidase (97) and with one notable exception they all exert their actions by binding to metabotropic receptors (98-100). Another shared element they have is that their cell bodies are located in small subcortical nuclei, while their axon arborizations diffusely innervate large target areas, in the majority of cases without making synaptic contact (100)

and thus, act mainly by volume transmission to modify more general states such as mood, attention, arousal (3, 100). Monoamine transporters are members of the same superfamily, and although they preferentially transport one kind of transmitter, they have ability to take up other transmitters as well (100). Most psychiatric drugs primarily act on aminergic transmitters.

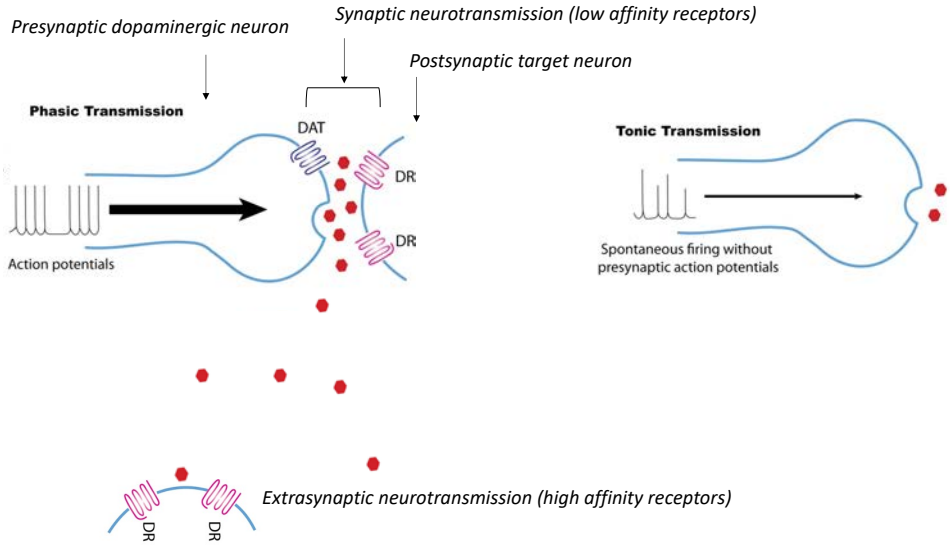
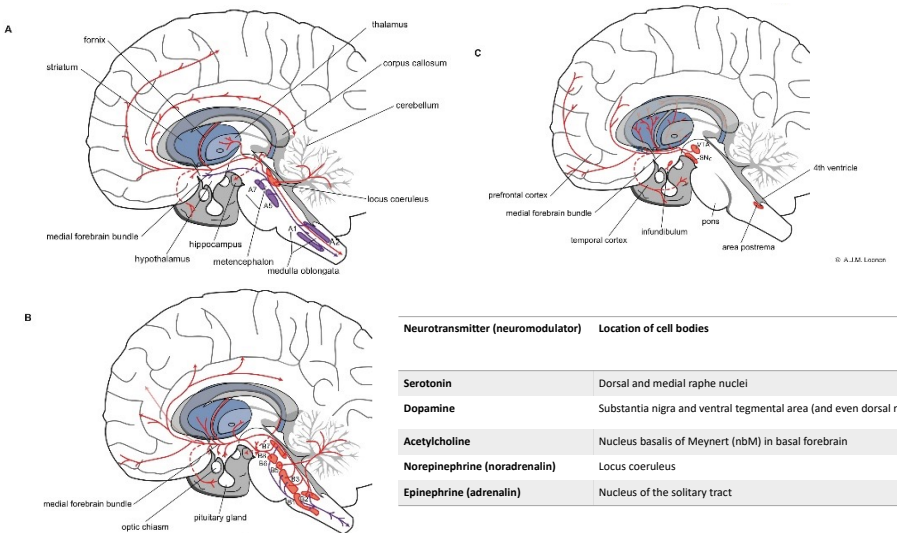


Figure 1.4. *Spontaneous (without presynaptic action potentials and regulation by other neurons, reuptake, or degradation) firing, that is slow and irregular, is responsible for the tonic neutransmission. Action potentials, on the other hand, lead to synchronized burst firing resulting in a fast and transient neurotransmitter release in the synaptic cleft (phasic neurotransmission). 'Wired' or synaptic transmission occurs when the transmitter is released into the synaptic gap and acts on postsynaptic low affinity receptors located in the synaptic gap, while non-synaptic, 'volume' communication occurs when the transmitter diffuses out of the synaptic gap or is released from a bouton without making synaptic contact and reaches its target non-synaptic (perisynaptic or extrasynaptic) receptors. Importantly, it has been speculated (mainly for dopamine but even other neurotransmitter) that the tonic levels affect phasic neurotransmission by altering their dynamic range (101-103). From Klein, Battagello (104), used with permission; modified according to Vizi, Fekete (100).*



Neurotransmitter (neuromodulator)	Location of cell bodies
Serotonin	Dorsal and medial raphe nuclei
Dopamine	Substantia nigra and ventral tegmental area (and even dorsal raphe)
Acetylcholine	Nucleus basalis of Meynert (nbM) in basal forebrain
Norepinephrine (noradrenalin)	Locus coeruleus
Epinephrine (adrenalin)	Nucleus of the solitary tract

Figure 1.5 *Three monoaminergic neurotransmitter systems: noradrenergic (A), serotonergic (B), and dopaminergic (C) neuropathways. Cell bodies are in the nuclei (red-filled shapes) positioned within the brainstem. Nerve fibers (red lines) terminate in the dorsal and ventral striata, amygdala, and frontotemporal cortex. There is a tight interconnection and reciprocal regulation among the monoaminergic systems. Modified with permission from prof. Dr. Anton JM. Loonen, University of Groningen.*

1.3.1 The serotonergic system

Serotonin is the most wide-spread neurotransmitter in the brain (105). Clusters of a few 100 000 serotonin-containing cell bodies, mainly restricted to the midline raphe nuclei, innervate nearly every area of the central nervous system (106). Conversely, midbrain 5-HT neurons receive input from, among others, medial PFC, lateral habenula and dorsal raphe GABA neurons (107). The large variety of serotonin receptors with dissimilar affinities respond differentially to distinct firing patterns of raphe nuclei (85, 108). Thus, serotonergic manipulations affect differentially cortical and subcortical areas, and in the PFC affect more ventral and medial areas compared to dorsolateral areas, which instead are more robustly affected by catecholaminergic transmission (85, 109-111).

Serotonin is considered to be an elusive transmitter (112) and according to Müller and Jacobs (113) ‘involved in everything, but responsible for nothing’. It has a role in sleep-wake cycle, appetite, sexual behaviour, mood and anxiety, reward, learning, memory, social behaviour and pain (27, 114-122). Serotonin’s multiple roles can be partly attributed to the fact that there are many different receptors with varying distribution in the brain (123), co-activation (124) and interaction with other neurotransmitters (125). Moreover, since only a small number of serotonin-synthesizing neurons in the brainstem innervate nearly the entire neuroaxis, the overall role of serotonin is thought to be quite general (3) (see also ‘Implications, personal reflections and future directions’).

1.3.1.1 Serotonin and affective cognition

The serotonergic system is the target of most antidepressants and theories about its role in mood disorders have been influential, although hotly debated (126). Serotonergic modulation of cognition and emotion in humans can be studied through acute or chronic effect of its uptake inhibitors (127,

128), acute depletion of its precursor tryptophan (ATD), and using agonists and antagonists at its various receptors.

Serotonin is thought to have differential effects on emotional processes, depending on the areas it regulates. Serotonergic modulation of subcortical areas, for example, affects motivational processes (103) and limbic reactivity, while its cortical effects supervise emotion regulation (103) and cognitive flexibility (129). ATD leads to perseverative deficits in reversal learning (110, 130, 131) and deficits in the OFC-related behavioural flexibility (132), without much effect on DLPFC-related functions. ATD reduces the effects of anxiety-related aversive stimuli and facilitates prediction of punishment without affecting reward prediction *per se* (103). ATD also accentuates the interference of negative emotional stimuli on cognitive processes (133, 134), while SSRI may increase sensitivity to emotionally salient negative feedback (135). Relevant to this is also the effect of serotonin on emotional bias in modulating learning (85, 112, 136-139).

Clinical studies with antidepressants implicate serotonin in depression and anxiety disorders. Although a clinical change usually requires repeated administration for several weeks, as early as hours after the first dose, measurable changes in emotional processing and brain activations can be seen (134, 140-156). Last but not least, borrowing from clinical insights, mild serotonergic syndrome is associated with increased anxiety and hypervigilance (157), and psychedelic agents have intense emotional components causing among other things increased sense of meaning/ salience (158, 159).

1.3.1.2 Serotonin transporter (SERT) and its selective inhibitors (SSRI)

The localization of the SERT is predominantly extrasynaptic and these non-synaptic transporters are the main targets of SSRI (100). Acute administration of SSRI blocks the serotonin transporter in axon terminals, increasing serotonin levels and duration of action in the synaptic cleft (160), although the net effect on serotonin concentrations in the projection areas is also regulated by activation of 5-HT auto-receptors (149, 161-164). Escitalopram is the most selective SSRI available (165) and a single-dose escitalopram is rapidly absorbed and reaches maximum plasma concentrations in approximately 3–4 hours (166). Clinically, SSRIs are used to treat depression, anxiety disorders and OCD, but the effect of acute and chronic administration of SSRI can vary, and at times even be opposite (167). Patients treated with SSRIs generally respond within 4-12 weeks after the start of treatment (168), but a substantial number report increased anxiety and blunted emotions as early side effects of treatment (169).

1.3.2 Catecholamines

Noradrenaline and dopamine are two of the best studied transmitters in the brain. Their release depends on the arousal state of the individual and their effects exhibit an inverted-U dose response relationship at many of their receptors (85, 170-173).

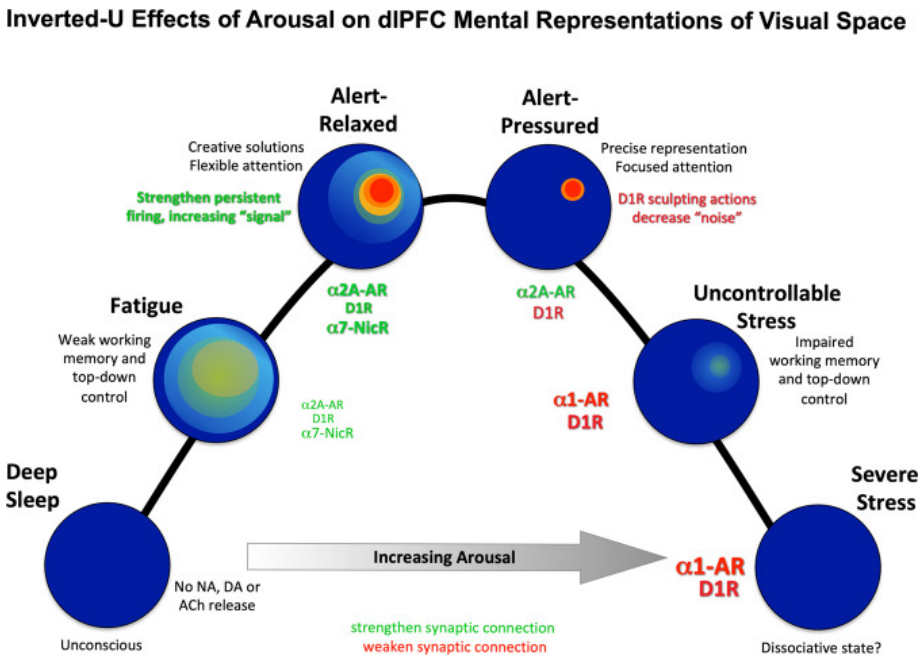


Figure 1.7 *Inverted U effects of the arousal modulators on network generation of mental representations of visual space held in working memory. During deep sleep, there is no release of acetylcholine, and minimal monoamine release, and thus glutamatergic circuits in layer III DLPFC have no NMDA-R neurotransmission, contributing to an unconscious state. In an awake, but less alert or fatigued state, cholinergic release allows NMDA-R transmission, but both connectivity and lateral inhibition are feeble leading to weak and diffuse representations. When arousal is optimal, Nic-α7R and α2A-AR neurotransmission is active leading to strong connectivity and stable representations. When even dopaminergic (D1R) stimulation increases to optimal levels (for example in the case of increased but controlled/ tolerable stress or pharmacologically), sculpting of 'noise' and improving the signal-to-noise ratio is possible, narrowing the representations held in working memory. However, when stress increases more than the optimal levels and becomes uncontrollable, high levels of D1R and α1-AR stimulation deteriorate signal-to-noise ratio and erode the representations. In this model it is speculated that extreme stress may disconnect DLPFC circuits sufficiently to create a dissociative state. Figure from Cools and Arnsten (85), used with permission.*

1.3.2.1 The dopaminergic system

A few decades ago, Goldman-Rakic (174) demonstrated the important role that dopamine (DA) plays in the PFC. Since then, several lines of evidence have demonstrated that DA, among other things, plays crucial roles in the physiology and pathology of executive functions by regulating the activity of pyramidal neurons that are involved in descending cognitive and limbic projections and implicated in many psychiatric disorders (21, 175). DA is thought to modulate the balance between PFC and striatal activity, the former promoting cognitive stability and the later flexibility (176). Subpopulations of DA neurons, so-called 'value' neurons, increase their firing to reward stimuli, while other populations, 'salience' neurons, increase their firing to salient events regardless of valence. These different DA neuron populations project to the PFC, with differing proportions in different subregions (177-180). DA in the OFC is involved in the process by which neutral stimuli, by being associated with reward,

take reinforcing properties. DA is necessary for processes requiring maintenance of information in the absence of stimuli, i.e., working memory, in the so-called 'delay active' neurons (85). Baseline working memory function has been identified as a proxy measure of baseline DA synthesis capacity (181, 182).

D1, the most prominent dopamine receptor subtype in pyramidal cells in the cortex (183), regulate signal-to-noise ratio and the function of 'delay neurons' (cells that maintain activity in the absence of sensory stimulus), thus these receptors are relevant to processes employing working memory and cognitive control. The relationship between D1R and performance depends on baseline cognitive capacity and follows an inverse-U formed curve. Previous studies have shown, for example, that dopamine agonists improve performance *only* in individuals with low baseline working memory, while worsening performance in those with higher baseline dopamine synthesis capacity (181, 184-190). These improvements are accompanied by reductions in DLPFC activity (191-194). According to the dual-state theory of prefrontal cortex dopamine function (195), moderate DA levels are associated with D1R-dominated state and distractor-resistant stabilization of working memory representations, while the D2R system has been hypothesized to be relate to flexible updating of working memory representations. PFC D2 receptors, concentrated on interneurons, are associated with regulating the firing of the so-called 'response' neurons, and distortions of their signaling might be related to psychotic phenomena, for example attributing thoughts and perception as not self-generated (85). D2 receptors have higher affinity for dopamine than D1 receptors, so it has been hypothesized that low affinity D1-receptors are activated by phasic synaptic events, whereas D2 receptors detect low levels of extrasynaptic dopamine (196).

The DA transporter (DAT) is responsible for clearing DA from extracellular space back into the dopaminergic neuron, by which it is exclusively expressed. DAT inhibitors include drugs such as methylphenidate and dexamphetamine (197, 198). Therapeutic doses of methylphenidate have been estimated to occupy >50% of striatal DAT (199). For comparison, cocaine shows higher occupancy around 75% (at reinforcing doses) and bupropion, a NET and DAT blocker that has indication as an antidepressant, has a DAT occupancy less than 25% (200, 201). The striatum has the highest levels of DAT, followed by basal ganglia, while, importantly, other regions of the dopaminergic circuit including the PFC have little or no DAT. The implication of this is that DAT can rapidly coordinate inputs to the striatum and outputs from the basal ganglia, but not cortical functions to the same extent (198).

1.3.2.1.1 Dopamine and affective cognition

Previous laboratory studies and clinical observations strongly implicate DA in the processing of natural rewards and drugs of abuse (196, 202). The work of Wolfram Schultz (203) has advanced our understanding of the role that DA plays in prediction of rewarding cues and reinforcement learning, demonstrating VTA neurons responding with phasic bursts to reward prediction errors. OFC is involved in representing stimulus-reward value, a process modulated by the dopaminergic system. Optimal levels of dopamine refine stimulus-rewards associations for which OFC and amygdala are important (132). It has been hypothesized that the dopaminergic effects on cognitive control are partly mediated by motivation and value-based processes in the striatum (204, 205). Dopamine has also a role in regulating fear conditioning and aversive learning via projections to the amygdala, medial PFC and striatum (206), and enhanced tonic DA levels enhances fear extinction (207).

1.3.2.2 The noradrengic system

The noradrenergic input to the brain comes from only a few dozen thousand neurons in the locus coeruleus (LC). Most inputs project broadly throughout the brain regulating arousal and attention, but

distinct subpopulations are connected to specific target areas serving distinct behavioural functions (206, 208). Noradrenaline (NA) is implicated in alertness and attention (209-211), working memory (211-216), impulsivity (130, 217-227) and cognitive flexibility (228-230). The balance between tonic and phasic NA activity regulates salience, anticipated reward or punishment (208), sustained attention (phasic mode) and distractibility (tonic mode) (173, 231). Transition between states by noradrenergic 'neural interruption' informs unpredicted change in the environment and prompting for a 'network reset' (232).

1.3.2.2.1 Noradrenaline and affective cognition

NA seems to play opposite roles in the PFC and subcortical areas (173, 233), with α1-AR stimulation impairing prefrontal and improving subcortical functions, and α2-AR stimulation having the opposite effect. NA's role in fear conditioning and fear extinction is also studied. Aversive events promote NA release in the amygdala modulating aversive memory acquisition and consolidation mechanisms, while blocking extinction learning. NA via different subpopulation of LC cells has opposite effect on the PFC, promoting fear extinction in an effect that varies with baseline levels of NA (206).

1.3.2.3 Stimulant medications

Central stimulants (CS) potentiate catecholaminergic neurotransmission by blocking NA (NET) and DA (DAT) transporters (234). NET can take up both NA and DA (235), thus methylphenidate and dexamphetamine increase NA and DA availability in the PFC (216, 236), while increasing DA levels in striatal areas (237). The net effect of methylphenidate leads therefore to increased cognitive stability (resisting distraction), but at the cost of cognitive flexibility (impaired updating) (238). Importantly, the effect of CS on cognition is state and task-dependent (234). The effect of CS on emotional processing is not well studied. Pharmacological studies suggest a role of NA in the formation of memories for emotional events and stimuli, with beta-blockers reducing recall of emotionally salient stimuli (239, 240) and suppressing amygdala during viewing of unpleasant stimuli (241). Clinically, ADHD treatment with CS seems to have positive effects on some aspects of dysregulated emotions (242).

1.4 Attention deficit/ hyperactivity disorder (ADHD)

Attention deficit/ hyperactivity disorder (ADHD) is a neurodevelopmental disorder with symptoms that arise in childhood but can persist in later life, affecting approximately 2.5-5% of the adult population (243-245). Its core symptoms include inattention, impulsiveness and/ or hyperactivity combined to form different subtypes according to both the DSM (246) and ICD diagnostic manuals (247). Neuroimaging studies have illustrated structural changes in ADHD, both in cortical and subcortical areas (248, 249). Mega-analyses of MRI data suggest that these structural changes are more prominent in children than adults (248-250). Functional studies have shown hyperconnectivity, or failure to deactivate, in the default-mode network (DMN) during rest (251) and cognitive tasks (252-254), with some evidence that CS may reverse this (255, 256). Other studies found abnormal reward processing that did not normalize with CS (257-259). Increased connectivity between ventral striatum and PFC in ADHD patients was associated with greater impulsivity (260). Most studies have been conducted in pediatric populations, which limits extrapolation of these results to adults given the temporal and developmental aspects of ADHD.

1.4.1 Emotion dysregulation in ADHD

Emotional dysregulation is being increasingly recognized as a core symptom in ADHD, with prevalence of roughly two third among adults with ADHD (242), and has been related not only to more severe ADHD, but also to higher risk for psychiatric comorbidity (245, 261-266). Adults with Previous studies have shown that CS and atomoxetine lead to only partial improvement on emotion dysregulation with smaller efficacy compared to their effect on core ADHD symptoms (267-271). CS can also increase irritability (272-274), making their effect on emotion dysregulation difficult to disentangle.

Emotion induction:

There is evidence that emotion induction may be altered in ADHD (267, 275), with some neuroimaging studies implicating amygdala and other limbic and paralimbic areas (276-278). Various studies have demonstrated a bias for negative valence (267, 275, 277, 279) and atypical fear processing in patients with ADHD (256, 280). In clinical research, ADHD is associated with aberrant emotion generation, with impulsive, fast-rising emotion reactivity and emotional lability (268), but experimental studies have revealed different facets of emotion induction impairment in ADHD. Recent studies (281, 282) demonstrated emotion recognition deficits with slower and less accurate response to emotional stimuli. Indeed, alexithymia is thought to occur at a higher prevalence among ADHD patients compared to the general population (283, 284). Implicit emotion regulation is also thought to be altered in ADHD (285), possibly being part of the observable phenotype related to emotional lability and hyperresponsivity in this patient group. Schulz, Krone (286) found that reduction in ADHD symptom caused by lisdexametamine was correlated altered functional connection of amygdala to inferior frontal regions.

Emotion regulation:

Adults with ADHD show impaired emotion regulation and a more frequent use of non-adaptive emotion regulation strategies, such as limited use of reappraisal and preferential use of suppression (279, 287, 288), which is correlated with reduced amygdala-prefrontal cortex connectivity (289). Additionally, a phenomenon of desynchrony between emotional experience and behaviour has been described, namely expression of behaviour that is disproportional in intensity and duration to the emotional experience (268). Previous research has also shed light on peripheral markers of emotion processing in patients with ADHD, identifying less adaptive and significantly elevated sympathetic and parasympathetic reactivity, likely related to emotion induction and emotion regulation processes, respectively (269, 290-292), as well as weaker coherence between facial expression and parasympathetic activation in response to emotional information (293).

2 Research aims

2.1 Overall aims

Multimodal treatment options, combining pharmacological, psychological, psychosocial intervention and skill training, are recommended for almost all psychiatric disorders. However, little is known about which aspects respond better to which types of intervention. The overall aim of this thesis was to probe aspects of affective cognition across different units of analysis (behavioural, central nervous system, autonomic nervous system) to study the:

- induction and regulation of two negative emotions, fear and disgust

- cognitive control of affective processes, and compare this with cognitive control of 'strictly cognitive' processes

- effect of different type of interventions - pharmacological, psychological and skills training with task repetition - on cognitive control in healthy subjects and patients with ADHD

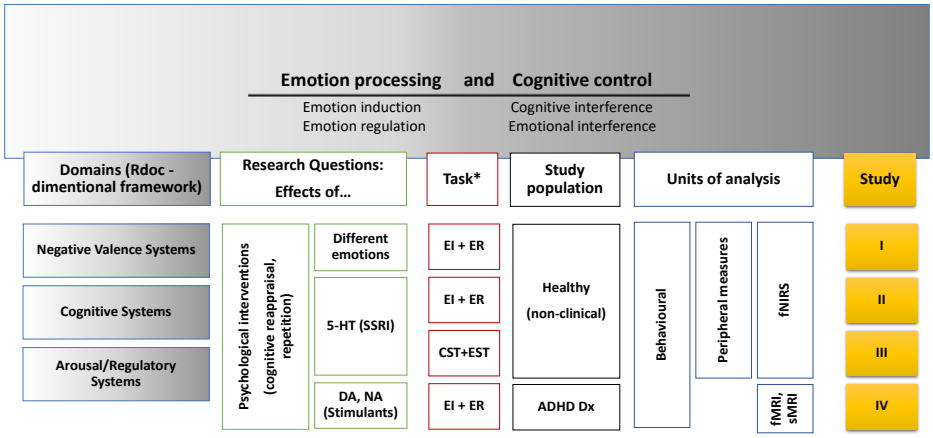
2.2 Specific research questions

- How do psychological interventions with reappraisal, pharmacological intervention with SSRI/ CS and skills training with task repetition affect emotion induction and emotion regulation in healthy individuals (Study I-II) and patients with ADHD (Study IV)?

- What are the similarities and differences in how the brain manages cognitive and affective interferences on an ongoing cognitive process, and how do pharmacological intervention with SSRI and skills training with task repetition modify this (Study III) in healthy individuals?

3 Materials and methods

3.1 Overall project



*EI+ER: emotion induction and regulation tasks, CST+EST=cognitive and emotional Stroop task

Figure 3.1. *The overall project design consisting of Studies I-IV*

Four different tasks (emotion induction, emotion regulation, cognitive Stroop, and emotional Stroop task) were employed to study psychiatric (ADHD) and non-clinical cohorts. Participants were recruited from a non-clinical population by advertisement in Psychiatry Southwest and Karolinska University Hospital, Huddinge Sweden (Study I-III) and from the local community and outpatient clinic at Örebro University Hospital, Örebro Sweden (Study IV).

3.2 Experimental design

3.2.1 Study I

The experimental design consisted of emotion induction and emotion regulation tasks of two different emotions, fear and disgust, using images taken from the International Affective Picture Series (IAPS). See *figure 3.2*.

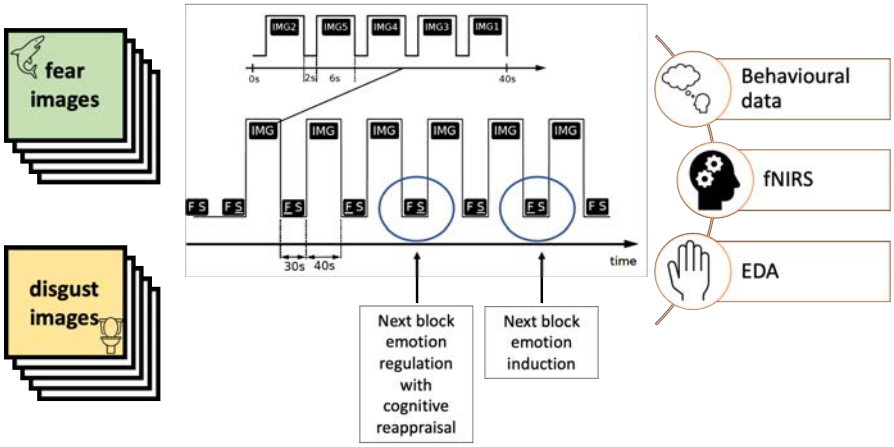


Figure 3.2. *Study design, Study I*

3.2.2 Study II, III

The design in Study II and III consisted of an experimental procedure that was repeated twice, i.e., before and 4 hours after pharmacological intervention with single dose 10 mg escitalopram or placebo. The experimental tasks in Study II were identical to those in Study I, i.e., emotion induction and emotion regulation tasks using emotive pictures from IAPS. In Study III, cognitive control of affective and cognitive interferences on an ongoing cognitive process was studied using cognitive and emotional Stroop task, see *figure 3.4* and *3.6*.

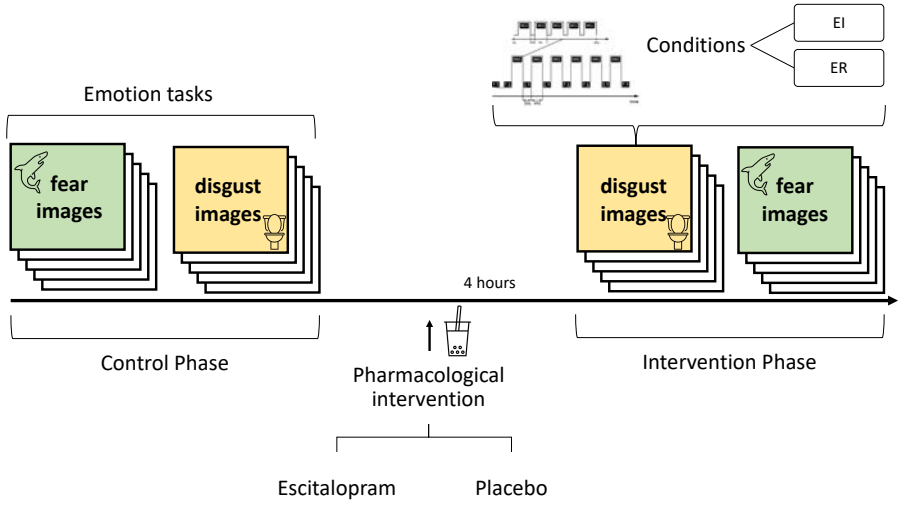


Figure 3.3. *Study design, Study II*

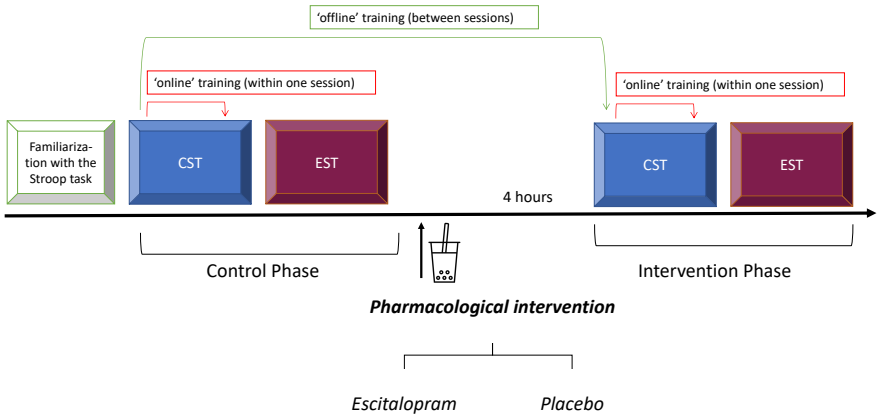


***Figure 3.4**. Study design, Study III*

3.2.3 Study IV

In Study IV, a single negative emotion (disgust) was studied before and 2 hours after ingestion of either 30 mg short-acting methylphenidate (T-Ritalina, healthy controls) or methylphenidate / lisdexamfetamine as selected and dose-optimized by the treating physician (ADHD patients), see *figure 3.5*. The task was otherwise the same as in Study I.

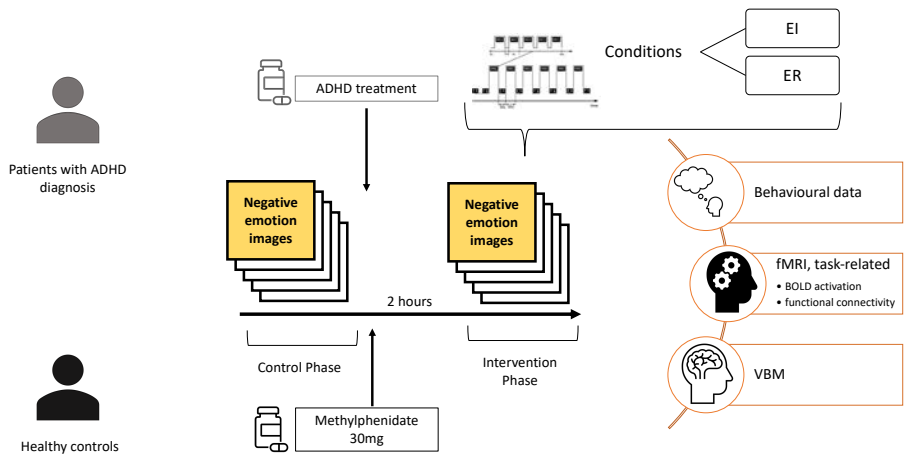


***Figure 3.5**. Study design, Study IV*

3.3 Tasks and behavioural measures

3.3.1 Emotion induction and emotion regulation tasks (Study I, II, IV)

The tasks consisted of blocks where five pictures were presented to generate emotions of fear and disgust. The International Affective Picture System (IAPS, Lang et al., 2008) was used as a source of standardized pictures. The participants were instructed to passively view the pictures during emotion induction (EI) and to actively down-regulate the generated emotion using reappraisal during emotion regulation (ER). The participants were asked to score emotion intensity for every image in a scale ranging from 1 to 9 during emotion induction and emotion regulation, where 1 represented lowest and 9 highest level of emotion intensity. They were also interviewed immediately after the end of the experiment about the specific strategy they used for emotion regulation. The mean score for the images was calculated to represent emotion rating for each condition (EI and ER). For Study I and Study II two negative emotions, fear and disgust, were studied, before and after SSRI medication or placebo. For Study IV, one negative emotion, disgust, was studied before and after CS medication. The tasks were implemented in E-Prime (version 2.1, http://www.pstnet.com/eprime.cfm).

3.3.2 The Stroop task (Study III)

An adapted version of the Color–Word interference task (26, 294) was used. Participants were presented with two rows of letters and instructed to determine, by button-press, if the color of the top row letter corresponded to the color name written at the bottom row. The experimental setup included a block design of two tasks: *cognitive Stroop (CST)* and *emotional Stroop task (EST)*. Each task consisted of four blocks, each block 30 seconds long and preceded and followed by a 30-second period of *Rest*. In each block, 15 trials were presented, randomized between congruent and incongruent trials for cognitive Stroop and neutral and emotionally charged words for the emotional Stroop, *figure 3.6*. Reaction time and accuracy were analysed as measures of performance. 'Online' practice was defined as real-time change in performance or electrodermal activity during an ongoing task. Delayed or 'offline' effect of task repetition was defined as change in performance, cortical or electrodermal activity four hours after the first session, *figure 3.4.*

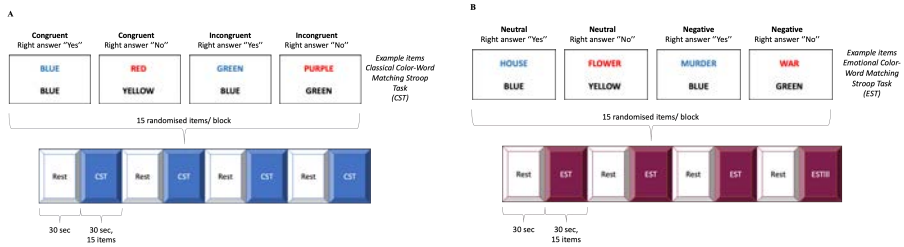


Figure 3.6 *Experimental procedure in Study III. (A) The Cognitive Stroop task, comprised of congruent and incongruent trials and interference was introduced when the color of the top word and the lexical information contained did not match (incongruent trials) (B) Emotional Stroop task, comprised of trials with neutral words and negatively charged word, where interference was introduced by using emotionally charged words with negative valence (negative trials).*

3.4 Measures of brain function and structure

3.4.1 Functional near infrared spectroscopy (fNIRS)

3.4.1.1 Background

Functional near infrared spectroscopy (fNIRS) is a neuroimaging method with superior ecological validity that allows more naturalistic experimental designs compared to other imaging methods. It is increasingly being used to probe cognitive and affective processes in cortical areas (295-300). fNIRS allows the determination of relative changes in the concentration of oxygenated (oxy-Hb) and deoxygenated Hb (deoxy-Hb) in areas of the cortex. Simultaneous functional magnetic resonance imaging (fMRI) and fNIRS recordings have shown that the blood oxygen level-dependent (BOLD) and fNIRS signals are strongly correlated to each other (301, 302). fNIRS has frequently been used to study neural underpinnings of emotion processes (94, 298, 300, 303-305).

3.4.1.2 fNIRS recordings and preprocessing

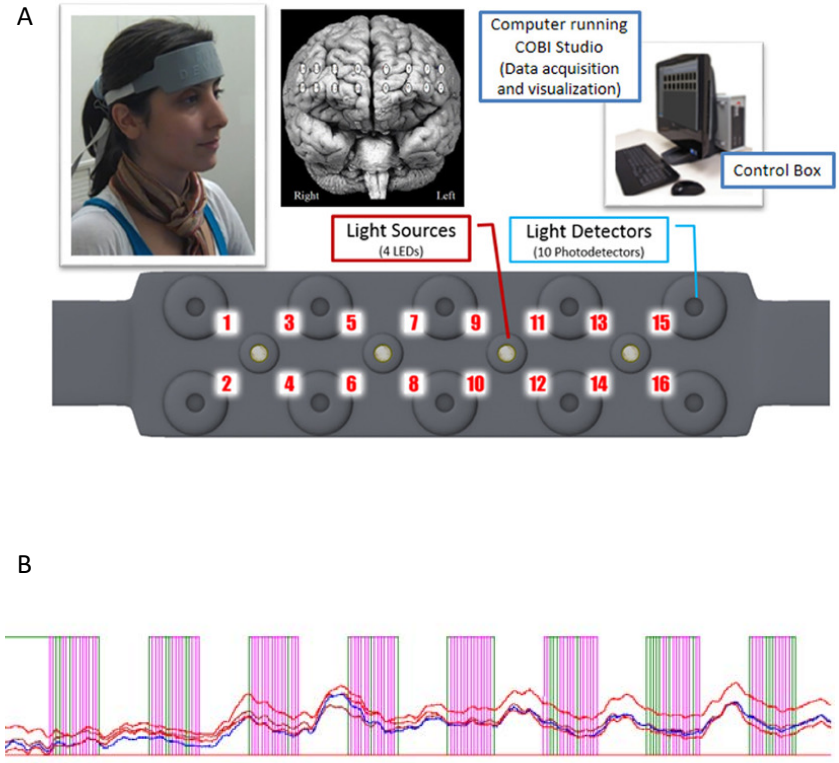


Figure 3.7*. (A) Sixteen channels recorded different parts of the prefrontal cortical mantle, mainly BA 9, 10, 45, 46 (306). The light sources emitted at two different wavelengths (730 and 850 nm) and the raw light intensity data was automatically converted to levels of oxygenated and deoxygenated hemoglobin utilizing the modified Beer-Lambert Law. Figure from Ayaz, Onaral (306), used with permission. (B) Raw fNIRS recordings, example with four channels*

A continuous wave fNIRS device consisting of a flexible headband holding light sources and detectors (fixed distributions), and a fNIR100 data acquisition box with a sampling rate of 2 Hz connected to a personal computer via an MP150 data acquisition and analysis system (Biopac Systems Inc, JOR AB Sweden) was used to measure the relative changes in the concentration of Oxy- and Deoxy-hemoglobin (Oxy-Hb, Deoxy-Hb). NIRS-SPM toolbox (307) was used to analyze mean Oxy-Hb concentration changes (ΔOxy-Hb), as it has been reported to provide greater signal-to noise ratio than Deoxy-Hb (301). The ΔOxy-Hb data were preprocessed to remove physiological noise and baseline drift.

3.4.2 Magnetic resonance imaging (MRI)

Neuroimaging data were collected using a GE Premiere 3 Tesla MRI scanner and three types of analyses were performed:

1) *Task-related BOLD activation*. We used fMRI-prep (308) (version 22.0.2) and AFNI (https://afni.nimh.nih.gov/, v23) programs to preprocess the raw data. Beta coefficients from the first-level statistical analysis using a general linear model (GLM) were used for group-level analysis.
2) *Task related functional connectivity*. Functional connectivity networks for the whole group were mapped with independent component analysis (ICA) using FSL's MELODIC pipeline. The resulting functional connectivity time courses and their corresponding spatial maps were then inferred onto each subject using a dual regression analysis method (309-312). Appropriate networks were manually selected through visual inspection for 2nd level analyses of the spatial inference maps and time courses.
3) *Voxel based morphometry (VBM):* FSL-VBM software (v1.1) was used to perform structural analysis on the T1-weighted structural MRI data (313). The preprocessing steps included brain extraction, tissue segmentation, spatial normalization to the MNI152NLin2009cAsym template, and modulation by the Jacobian determinant of the deformation field.

3.4.3 Measures of peripheral physiological activity (Electrodermal activity, EDA)

Raw data were preprocessed to remove artefacts and noise, and then they were decomposed into three components: tonic electrodermal signal, phasic electrodermal response and white Gaussian noise using a convex optimization approach (314). Finally, three variables were extracted: 1) mean electrodermal level (EDL, tonic), 2) mean phasic electrodermal response (EDR) magnitude and frequency.

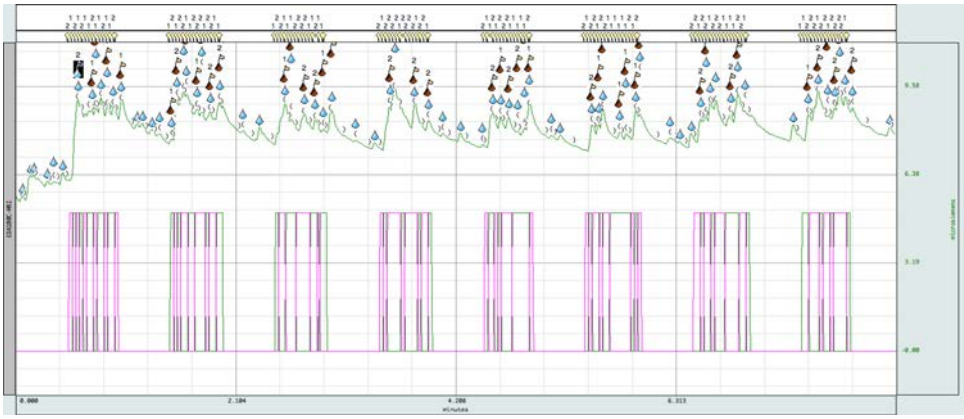


Figure 3.8 *Raw EDL and EDR data (higher green line) during a Stroop task (pink and green block in the bottom represent the blocks of stimuli). Flagged are the stimulus-induced phasic electrodermal responses (EDR).*

3.5 Pharmacological manipulations

Escitalopram (Study II and III) or methylphenidate/ lisdexamfetamine (Study IV) were used to probe effects of the monoamine transmitters serotonin and dopamine/ noradrenaline. No specific hypotheses or expectations relating to the possible effects of the psychoactive agents or placebo were discussed with the subjects. Measurements were done approximately 4 hours after ingestion of escitalopram and 1-2 hours after ingestion of CS, when maximum serum concentration is reached according to the pharmacokinetics of these drugs. At the end of the experiments, participants were asked to freely state any side effect they experienced (escitalopram) or fill a side-effect questionnaire (psychostimulants).

3.6 Statistical analysis

For data in Study I, II, III, as well as behavioural data in Study IV, a set of multilevel mixed-effects linear regression models were applied to the dependent measures of primary outcomes (behavioural measures, fNIRS and EDA data) and the Benjamini-Hochberg method was used to control for multiple testing.

4 Results

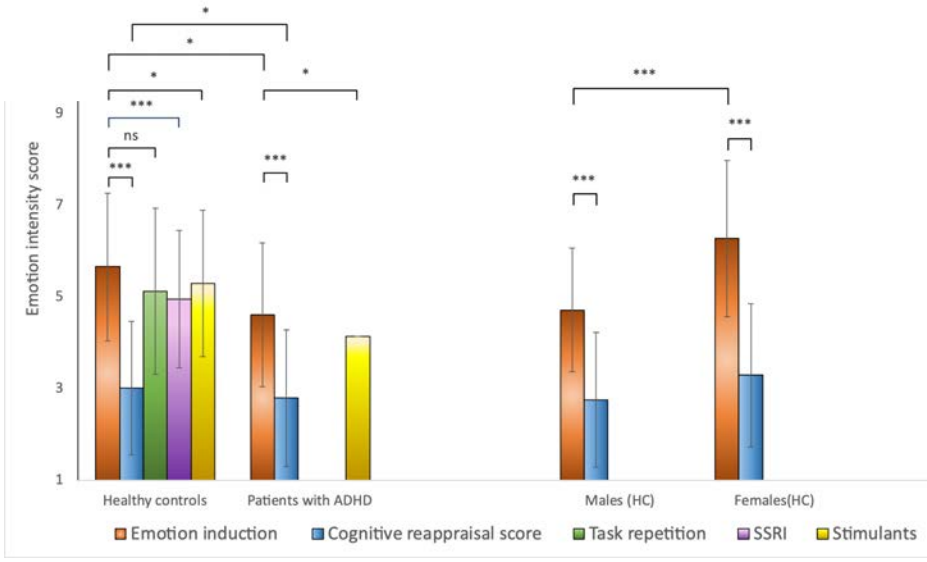


Figure 4.1 *Different parameters affecting subjective (negative emotion) intensity. Reappraisal reduced subjective emotion rating by 40-50% (Study I, IV). Task repetition had no significant effect on emotion induction or regulation (Study II). Patients with ADHD had 20% lower emotion rating scores compared to healthy controls (HC, Study IV). In healthy controls, acute administration of SSRI reduced emotion induction by about 12% (Study II), while acute administration of CS reduced emotion induction by roughly 7% (Study IV). Female participants had 25% higher emotion rating scores than male participants. Pooled data from fear and disgust and Study I, II and IV for HC shown in the graph.*

4.1 Comparison of fear and disgust during emotion induction (Study I and IV)

The pictures chosen to generate emotional experience of fear and disgust were relatively well calibrated and gave roughly similar subjective ratings in emotion intensity. Compared to males, female participants had higher emotion rating during emotion induction for both fear and disgust. During emotion induction, significant activations were seen in medial PFC for fear. For disgust, PFC activation was even more widespread covering almost all fNIRS channels. Comparing the two negative emotions directly, we found stronger activation for disgust in right lateral PFC during emotion induction. Regarding electrodermal response (EDR), we found no difference between task-evoked and spontaneous resting EDR during emotion induction for fear. For disgust, the frequency of task-evoked EDR was significantly lower and its magnitude significantly smaller compared to spontaneous resting EDR. When comparing the two basic emotions directly, fear had significantly higher task-evoked EDR frequency compared to disgust. Similar tendency was seen for EDR magnitude, which however didn't attain statistical significance.

4.2 Comparison of fear and disgust during emotion regulation (Study I and IV)

For fear, emotion regulation was more efficient the higher emotion rating was. No such variation in the efficiency of emotion regulation with emotion rating was seen for disgust. There was roughly 40-

50% reduction in emotion rating for fear and disgust with reappraisal, with no significant difference in this between the two negative emotions. Female participants had higher emotion regulation compared to males, but this did not attain statistical significance. There was no significant activation during emotion regulation in the fNIRS recordings for fear, while for disgust significant activation was seen in left lateral PFC. The frequency of phasic task-evoked EDR during emotion regulation was significantly lower for both negative emotions compared to rest.

4.3 Cognitive regulation of negative emotions under different conditions (Study I-II, IV)

As mentioned above, reappraisal reduced emotion induction scores by 40-50%. This was irrespective of the type of negative emotion tested (fear and disgust), gender (male and female), and population (healthy controls and ADHD patients) analyzed. Also, it was under all conditions significantly more efficacious than pharmacological emotion regulation with SSRI (Study II) and CS medication (Study IV), as described below. See also *figure 4.1.*

4.4 Effect of task repetition on negative emotions (Study II) and on cognitive control of affective and cognitive interferences (Study III)

Task repetition in the absence of active substance (placebo) did not significantly change emotion induction scores for fear and disgust (Study II). During both cognitive and emotional Stroop (Study III), task repetition (four hours later) in the absence of active substance (placebo) improved performance as measured by shorter reaction time ('offline' improvement). Task repetition also improved performance within each block, as well as between blocks within a session, in both cognitive and emotional Stroop ('online' improvement). fNIRS recordings in the PFC showed no significant change when task was repeated a second time four hours later (Study II and III). Task repetition had thus no significant effects on PFC, although at the same time it improved performance at the behavioural level. Task repetition four hours later did not have any significant effect on the frequency of task-evoked EDR, neither for the Stroop tasks (Study III) nor for emotion induction (Study II). In cognitive Stroop, however, EDR frequency decreased significantly with increasing block number within an ongoing session, which was not the case for emotional Stroop (Study III).

4.5 Emotion dysregulation in patients with ADHD (Study IV)

Compared to healthy controls, patients with ADHD had significantly lower emotion rating during emotion induction, and lower emotion regulation capacity regardless of their medication status. ADHD patients had no significantly greater activation during emotion regulation compared to emotion induction, while healthy controls activated more bilateral middle frontal gyrus during emotion regulation compared to emotion induction (*figure 4.2 B*). Compared to healthy controls, ADHD patients had greater activation in medial PFC and posterior cingulate cortex/ precuneus during emotion regulation, areas which are known to be part of the task-negative default-mode network (DMN) and which were significantly deactivated in healthy participants (*figure 4.2 C*). Instead, during the emotion regulation task, ADHD patients deactivated the cingulo-insular saliency network and the dorsal attention network (*figure 4.2 D*). Voxel based morphometry (VBM) showed that ADHD patients had significantly less gray matter volume in pertinent limbic and paralimbic areas compared to healthy controls and in specific right ventromedial PFC, left dorsal hippocampus and right fusiform gyrus.

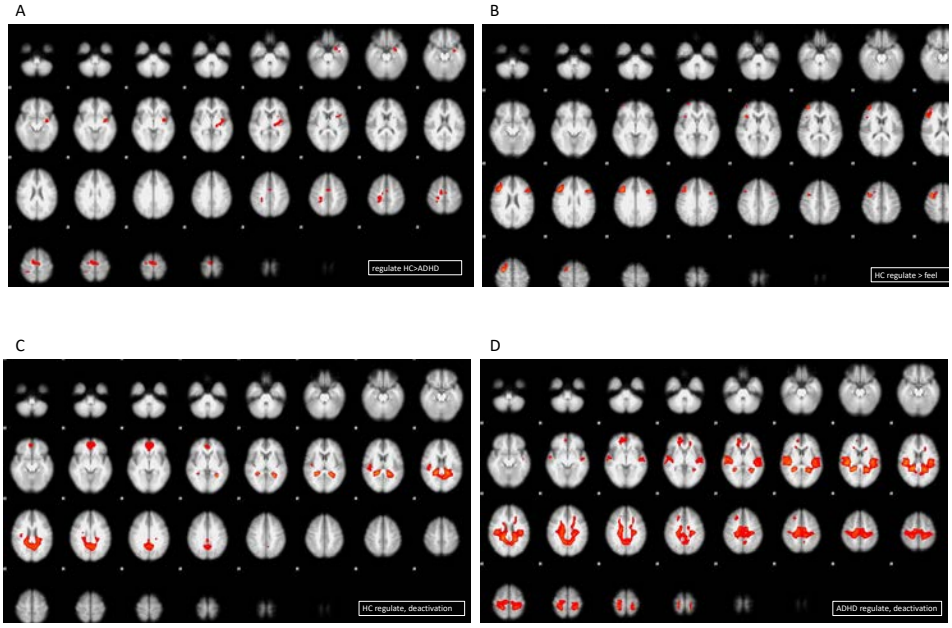


Figure 4.2 *Task-related BOLD activity in healthy control (HC) and patients with ADHD. (A) HC>ADHD during emotion regulation, (B) Emotion regulation>emotion induction in HC, (C) Deactivation of the default-mode network during emotion regulation in HC, (D) Deactivation of cingulo-insular saliency network and dorsal attention network during emotion regulation in patients with ADHD.*

4.6 Serotonergic modulation of cognitive control and emotional processes

4.6.1 Serotonergic modulation of emotion induction (Study II)

Emotion intensity was reduced by roughly 10% after acute ingestion of 10 mg escitalopram for both fear and disgust, with no significant difference in this between the two negative emotions. Regarding fNIRS, escitalopram increased activations in right lateral PFC for fear, and decreased it in left lateral and medial PFC for disgust. When the two negative emotions were directly compared to each other, escitalopram significantly increased activation for fear in right and left lateral PFC compared to disgust. In the absence of emotive stimuli, escitalopram increased spontaneous resting EDR frequency by roughly 30% for fear, but not for disgust. Escitalopram also reduced task-evoked EDR frequency for fear, but not for disgust. Placebo had no behavioural, cortical or peripheral effect during emotion induction.

4.6.2 Serotonergic modulation of emotion regulation (Study II)

Neither escitalopram nor placebo had any significant effect on emotion regulation with reappraisal for fear, although our hypothesis based on clinical experience was that escitalopram could somehow destabilize emotion regulation. Escitalopram reduced task-evoked EDR frequency for disgust, but not fear during emotion regulation, while placebo had no such effect. Emotion regulation with reappraisal was more effective than escitalopram in reducing emotion intensity for both fear and disgust. When psychological emotion regulation was compared with pharmacological emotion regulation with escitalopram, there was greater activation for fear in right lateral PFC during escitalopram, with no

PFC areas more active during psychological emotion regulation compared to escitalopram. For disgust, there were no significant differences in PFC activation when psychological and pharmacological regulations were compared to each other. There was no significant difference either in task-evoked EDR frequency when pharmacological emotion regulation with escitalopram was compared to psychological emotion regulation with reappraisal.

4.6.3 Serotonergic modulation of cognitive control on cognitive and affective interferences (Study III)

As mentioned in section 4.4, there was significant "offline" and "online" improvement in performance with task repetition. These were not modified by escitalopram during cognitive Stroop, while for emotional Stroop, there was an additional "offline" improvement in performance after escitalopram. Also, in each block, escitalopram had no significant effect on the first stimulus, but improved performance for subsequent stimuli in every block. Escitalopram, but not placebo, also reduced the occurrence of premature responses, defined as reaction time of 200 msec or less. During cognitive Stroop, escitalopram significantly reduced activation in dorsolateral and ventrolateral PFC, but not in medial PFC. During emotional Stroop, on the other hand, escitalopram reduced activation in ventrolateral and ventromedial, but not dorsolateral channels. Placebo had no such effect, neither during cognitive nor emotional Stroop.

4.7 Catecholaminergic modulation of emotional processes (Study IV)

In both healthy controls and ADHD patients, stimulant medication significantly reduced emotion induction compared to control conditions. As mentioned above, the lower emotion regulation scores that ADHD patients reported compared to healthy controls, was a deficit not normalized by stimulant medication. Psychological emotion regulation with reappraisal was significantly more effective than stimulant medication in reducing negative emotion intensity in both ADHD patients (mean difference 5.5, SE 2.17, $p= 0.011$) and healthy controls (mean difference 12.5, SE 2.27, $p< 0.001$ - these statistical p values are shown here as they are not taken up in the manuscript for Study IV).

5 Discussion

In relation to the research questions outlined in the introduction, in this section I discuss and put in context:

- emotion processes of two negative emotions (fear, disgust), in relation to different interventions (reappraisal, skills training with task repetition) in two different populations (healthy controls, ADHD patients). Results from all studies contribute to this part of discussion (5.1).

- the role of serotonin in emotion induction, emotion regulation, and cognitive control of cognitive and affective interferences, as revealed by a single dose of the SSRI escitalopram. Results from Study II and III are discussed in relation to this (5.2).

- the role of dopamine/ noradrenaline in emotion induction and regulation, as revealed by single dose CS medication. Results from Study IV are taken up in this section (5.3).

5.1 Emotion processing

5.1.1 Summary of main results

- Fear and disgust showed different activation patterns both in the central (CNS) and peripheral nervous systems (ANS) during emotion induction. Fear increased activation in medial PFC, whereas task-evoked electrodermal responses (EDR) were no different compared to spontaneous resting EDR. Disgust, on the other hand, induced a more widespread PFC activation and significantly reduced task-evoked EDR compared to resting EDR. Direct comparison of the two emotions revealed greater right lateral PFC activation and lower frequency of task-evoked EDR for disgust compared to fear.

- Emotion regulation with reappraisal was effective in reducing emotion intensity for both negative emotions. For fear, but not disgust, there was increased emotion regulation efficiency with higher emotion intensity. Emotion regulation abolished the cortical and peripheral differences between fear and disgust seen during emotion induction.

- Task repetition improved performance for both cognitive and emotional Stroop tasks, but did not affect emotion induction and emotion regulation. Performance during Stroop task improved both ‘online’, within an ongoing task, and ‘offline’, when the task was repeated four hours later, albeit without any concomitant change in PFC or electrodermal activity. Task-evoked EDR showed signs of habituation during the cognitive Stroop, but not the emotional Stroop task.

- Compared to healthy controls, patients with ADHD had (i) lower emotion induction and emotion regulation capacity, (ii) failed to successfully disengage the default mode network (DMN) to the same extent as healthy controls during task performance, (iii) deactivated instead cingulo-insular saliency network and dorsal attention network and (iv) had smaller gray matter volume in limbic and paralimbic areas.

5.1.2 Discussion of main results

The ability to exert voluntary control over emotional experience and the ensuing behaviour is crucial for goal-directed behaviour (4, 78, 315) and its dysregulation is associated with impairment in the clinical setting in (5) psychosis (316), depression (317), anxiety disorders (318) and ADHD (245) and increased vulnerability to physical and mental illness in the non-clinical population (319, 320). Dysregulation of specific emotions is thought to be implicated in specific psychiatric disorders, for example sadness is a core symptom in major depressive disorder, fear in paranoid schizophrenia and anxiety disorders, and disgust in obsessive compulsive disorder (321).

5.1.2.1 Emotional processing of different negative emotions

Previous studies have shown differences in the physiological responses fear and disgust elicit, such as acceleration of heart rate for fear and deceleration for disgust (45, 61, 322). In these studies, I hypothesized that participants would activate different central and peripheral processes relevant to a favoured action plan appropriate for respective emotion, namely a more sympathetic nervous system activation for fear that is congruent with 'fight or flight' response, and a more parasympathetic activation for disgust that is congruent with withdrawal and avoidance behaviour. Medial PFC (MPFC) is thought to be involved in cognitive aspects of emotional processing such as identification, attending to and appraisal of emotion (Phan et al., 2002), and is assumed to be engaged in this regardless of emotional valence. For disgust, which is thought to have evolved from the phylogenetically older sensation of distaste (34, 57), it was hypothesized that it would also induce emetic reactions (323) that would initiate automatic or effortful suppression of the motor response, and that this may activate ventrolateral PFC (VLPFC) including right inferior frontal junction (IFJ), an area known to play important roles in behavioural inhibition (324-327). Comparing the neuroimaging data of fear and disgust during emotion induction, there was indeed greater activation in right VLPFC for disgust compared to fear, which could be related to suppression of emetic responses. Significant differences between the two negative emotions were also found in the frequency of task-evoked EDR during emotion induction, probably reflecting a sympathetic dominance for fear and preferential parasympathetic activation during disgust.

To conclude this part of the discussion, irrespective of the current debate about the nature of emotions, whether they are evolutionarily hardwired or culturally learned and incorporated in the brain's internal model, classifying a stimulus as threat-related and fear-generating seems to be readily associated with relevant PFC areas and autonomic activation, whereas categorizing a stimulus as disease-/ contamination-related and disgust-generating elicits other central and peripheral responses.

5.1.2.2 Cognitive control, effects of psychological intervention and skills training

5.1.2.2.1 Cognitive emotion regulation with reappraisal

Cognitive control using reappraisal is an effective strategy in increasing or decreasing subjective rating of emotions (68, 79, 328). In both Study I and IV, it was found that effortful emotion regulation with reappraisal reduced the intensity of subjective experience of negative emotions by 40-50%. The healthy participants of Study I and IV, although from different regions and belonging to different socio-economic groups, showed similar magnitude of emotion regulation with reappraisal. In Study I, emotion regulation for fear was more efficient the higher the emotion rating was, while there was no such variation for disgust. This may indicate difference in the capacity or flexibility of emotion

regulation in fear and disgust, as it has indeed been reported that disgust may be more difficult to modulate cognitively (57, 329). A reflection of this is also seen in the clinical setting, where while Obsessive Compulsive (OCD) and anxiety disorders are both pharmacologically treated with antidepressants, OCD generally requires higher doses and takes longer time to treat compared to anxiety disorders (321). Also, psychotherapies facilitating cognitive restructuring are generally recommended for anxiety disorders, while exposure and response inhibition is recommended for OCD. These pharmacological and psychological treatment differences might reflect differences in the nature of these two basic emotions and the difference in regulation efficiency by reappraisal that was found.

Study I could also demonstrate that the robust differences in prefrontal and sympathetic activation patterns, seen during emotion induction between fear and disgust, disappeared upon successful emotion regulation with reappraisal. In fNIRS, we found less prefrontal activation during emotion regulation compared to emotion induction, an outcome that can appear to be odd when considering the classical notion of the PFC as regulating subcortical limbic areas. However, both increased and decreased PFC activations are expected when down-regulating emotions as shown by Ochsner, Bunge (79), who divided their results into PFC areas modulated by regulation (where activation decreases) and PFC areas activated by regulation (where activation increases), see also *figure 5.1*. We do not thus believe that all parts of PFC behave in the same direction; parts of PFC related to evaluation and automatic regulation of emotion may increase their activation during emotion induction and decrease their activation during successful regulation, while regulatory parts might operate in the opposite direction. Studies of emotion regulation on a larger time scale has also shown reduction of activation in prefrontal areas after accomplished emotion regulation (330). Our hypothesis was thus that *successful* emotion regulation may reflect reduced activation in many parts of PFC. Importantly, in this study, not only PFC, but also task-evoked EDR showed blunted activation during successful emotion regulation, supporting the above hypothesis.

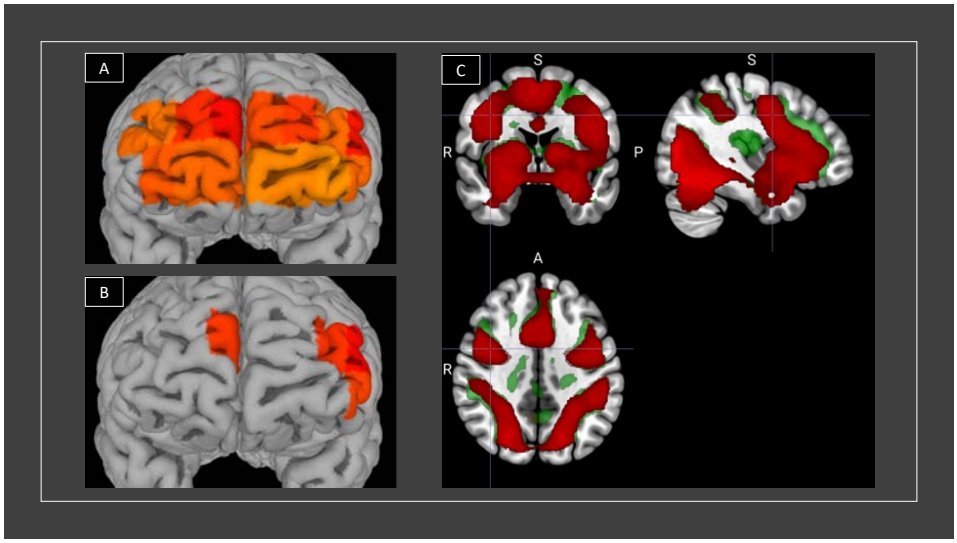


Figure 5.1 *(A-B) fNIRS (Study I) showing activation patterns during emotion induction (A) and emotion regulation (B) for disgust. (C) BOLD fMRI (Study IV) showing activation patterns during emotion induction (red) and emotion regulation (green) in healthy subjects demonstrating that multiple areas are active during both conditions. The relatively greater or smaller activity in one or the other condition likely varies depending on the experimental design.*

5.1.2.2.2 Effect of task repetition on cognitive control of cognitive and affective interferences

Cognitive control of cognitive and affective interferences was investigated in Study III using cognitive and emotional Stroop tasks. In these tasks, performance improved with task repetition both 'online' and 'offline'. Interestingly, the 'offline' improvement was not accompanied by any significant change in PFC or electrodermal activity. Also, 'online' performance improvement was seen alongside a habituation of phasic EDR in cognitive, but not emotional Stroop. Task repetition (placebo) was not associated with any significant change in any outcome measure in the emotion induction and emotion regulation tasks (Study II).

Combining these findings, one can draw the conclusion that task repetition, contrary to emotion regulation with reappraisal, does not effectively, in this time scale, modify subjective emotional experience or central and peripheral emotional processes. Additionally, as far as EDR goes, emotional distractions appear to be quite robust and not modifiable by task repetition in contrast to cognitive interference. Indeed, learning to ignore threatening cues would *not* be advantageous for survival in evolutionary terms, which likely makes negatively valenced affective stimuli more slowly adapting and habituating.

When differentiating 'hot' and 'cold' cognitive processes, it is important to mention that although it might be practically useful to study their content this way, it is unlikely that they are biologically distinct. An alternative way to conceptualize them is as parts of a continuum of processes that appraise and update perception and generate and regulate behaviour, which in turn updates the brain's representation of the internal and external world (36, 50, 68, 331-334). In other words, in real life, just as 'cold' cognition always has an affective 'colour', 'hot' cognition has also a 'cold' cognitive component that is modifiable by psychological and pharmacological modulations (see also discussion in *5.3*). This element was likely more evident in the emotional Stroop task (Study III), which regardless of the emotional character of the distractor, participants were still required to keep their attention on task and constantly make active choices. Thus, although impossible to know beyond doubt, it is reasonable to assume that at least some of the improvement in performance seen with practice may be due to improvement in this part of the cognitive domain for both Stroop tasks. In Study II, however, involving a less cognitively demanding task, task repetition in the placebo trials had no significant effect on emotion induction and regulation.

5.1.2.3 Emotion induction and regulation in ADHD

Emotion dysregulation is increasingly being acknowledged as a core feature of ADHD and is often associated with worse functional outcome and increased comorbidity (245, 268, 335). However, it is not well understood which aspects of emotion processing are most relevant for patients with ADHD, although 'explosive' reactive emotion, emotional lability and emotion dysregulation have been discussed as being relevant to the clinical presentation (268). In Study IV, patients with ADHD had both lower emotion induction and emotion regulation capacity. The latter is well in line with similar other studies, as well as clinical observations, that have found that patients with ADHD often have difficulties with emotion regulation and preferentially use suppression as emotion regulation strategy, with suboptimal outcome (336). ADHD patients have also been found to underutilize cognitive strategies such reappraisal, which come with greater processing cost but are more adaptive and efficient (245, 289). We also found that ADHD patients during emotion regulation fail to deactivate the default mode network (DMN) to the same extent as healthy controls. Instead, they deactivated the cingulo-insular saliency network and dorsal attention network indicating that they may be using different strategies, or nonspecialized compensatory areas, in regulating negative emotions. The

cingulo-insular network is thought to integrate sensory stimuli to emotional processes and implements switch between the task-negative DMN and task-positive frontoparietal cognitive network. Similar findings have previously been reported for non-emotional tasks (251, 337).

Regarding emotion induction, the results may initially appear to be paradoxical and not fully congruent with the fast and intensive emotional reactivity this patient group tend to display. One explanation could be that patients with ADHD have a high emotional baseline tonus and comparing to that they rate non-ecological emotional stimuli in the laboratory as blunt, and thus lower than healthy controls. However, other studies have found evidence for increased implicit emotion regulation (285) and impaired emotion recognition (281, 282) in this patient group that are congruent with the results of this study. Interestingly, desynchrony between subjective emotional experience and observed behaviour has also been described in ADHD (268), as well as alexithymia and inability to label emotions (283, 284). It is therefore likely that, at least in a subgroup of patients, the observed 'explosive' affect may not be a result of elevated emotion intensity, but a consequence of emotion dysregulation leading to maladaptive expressive behaviours. The latter is also partly supported by the structural findings in our sample. Recently published mega-analyses (248, 249) have reported both cortical and subcortical structural abnormalities in ADHD, although this was mainly in children and adolescents and less so in adult ADHD. However, large sample sizes, although they confer generalizability, may suffer from low levels of sample homogeneity, which can reduce power. In Study IV, reduced gray matter volume in limbic and paralimbic areas was found in patients with ADHD when compared to healthy controls, more specifically in right ventromedial PFC (VMPFC), left dorsal hippocampus and right fusiform gyrus. These areas have all been implicated in emotional processes and could therefore be contributing to the aberrant emotional processing we report in ADHD patients. Impairment of VMPFC function has been associated with problems in valuation, appraisal and sense-making of emotional experience (14, 338, 339), which could be relevant for the changes in reports of experience of negative emotions.

5.2 Serotonergic modulation of 'hot' and 'cold' cognition (Study II, III)

5.2.1 Summary of main results

Escitalopram

- increased affective tonus in the absence of emotive stimuli (spontaneous rest EDR) for fear, but not disgust
- reduced emotion rating for fear and disgust during emotion induction (flattened affect), but did not have any effect on the efficacy of emotion regulation with reappraisal
- reduced stimulus-evoked EDR frequency for fear, but not for disgust
- improved performance in emotional Stroop, but not cognitive Stroop, albeit without affecting the first stimulus in the block after each period of rest
- decreased fNIRS activations in left and medial PFC during emotion induction of disgust, but increased the activation of the right lateral PFC for fear

- reduced fNIRS activation in dorsal and lateral PFC during cognitive Stroop and in ventral and medial PFC during emotional Stroop
- reduced the occurrence of premature responses

5.2.2 Discussion of main results

Serotonergic neuromodulation is implicated in many processes including constraining impulsive choice and enabling waiting (119, 150, 340), limiting response to aversive emotional stimuli (119), decreasing vigilance (341-343), enhancing reversal learning and reducing perseverative behaviour and 'stimulus stickiness' (a tendency to make new choices depending on previously choices and models)(110, 111, 125, 344-347). It has also been speculated that SSRI might act by filtering aversive emotions from reaching conscious awareness (143) and in this way reduce cognitive processing of negative emotions (146, 161, 348). In these studies, it was indeed found that escitalopram reduced the impact of the negative emotions, as assessed by rating of subjective experience (Study II), objective performance (Study III), prefrontal activity (Study II, III) and sympathetic arousal (Study II). Qualitatively, the effects of pharmacological emotion regulation with escitalopram were all in the same direction as those of psychological emotion regulation with reappraisal, although more modest in size. Escitalopram decreased emotion intensity, shrank the emotional Stroop effect, altered the pattern of electrodermal responses, and reduced the prefrontal activity. There was, however, one notable exception to the latter with escitalopram *increasing* activity in right lateral PFC during fear. The reason why this was so, is unclear, but it could reflect activation of right IFJ to suppress emetic reactions that was a common side-effect of the SSRI. Study III helped disambiguate the specificity of the effects of escitalopram for emotional content, as escitalopram was not associated with any improvement in the cognitive Stroop task.

The observation that escitalopram had opposite effects on both prefrontal and sympathetic activity for fear and disgust supports the notion that some of its effects may be task-specific. Moreover, since SERT are located both in synaptic and extrasynaptic areas (100), SSRI can alter both the serotonin levels that drive the wired, synaptic transmission and the serotonin levels that are related to the slower and spatially diffuse extrasynaptic transmission. In the amygdala, for example, which is under strong serotonergic regulation and rich in SERT (123, 349) synaptic transmission seems to be more dominant, while extrasynaptic transmission is assumed to prevail in the PFC (123).

Some evidence supporting this claim was provided in Study III, namely the fact that during emotional Stroop, the first stimulus in each block was unaffected by escitalopram while subsequent stimuli were influenced. We hypothesised that if the effects of escitalopram were mediated by ambient changes in extrasynaptic serotonin levels, all stimuli would have been equally affected. If, however, the effect of serotonin on the emotional Stroop task was mediated by specific stimulus-evoked serotonin release at intrasynaptic receptors, then serotonin would have no effect on the first stimulus but would modulate subsequent stimuli, as was found. During cognitive Stroop, deactivation in right PFC was observed, mainly covering dorsolateral PFC and inferior frontal gyrus, two areas that are often activated during Stroop tasks (350). However, as mentioned above, this change in PFC activity was not associated with improved performance. It is possible that the changes in the PFC during cognitive Stroop were related to changes in extrasynaptic serotonin levels, compatible with previous studies suggesting that the prefrontal areas activated during cognitive tasks depend on the serotonergic tonus (351).

Lastly, escitalopram increased spontaneous resting EDR during the fear experiments. Persistence of emotional state due to inefficient recovery, also known as emotional inertia, is a well-characterized phenomenon (352-354). It is possible that the increase we saw in spontaneous resting EDR reflects either heightened general arousal or increased emotional inertia, with carry-over effects of fear when the emotive stimuli are no longer present. The latter is more likely, since increased general sympathetic arousal was not observed in relation to the disgust experiments or during the Stroop experiments.

5.3 Catecholaminergic manipulation of emotion processing (Study IV)

5.3.1 Summary of main results

Psychostimulants (CS)

- reduced the rating of emotion intensity during emotion induction in both healthy controls and ADHD patients
- were less potent in reducing emotion intensity than psychological emotion regulation with reappraisal, in both healthy controls and ADHD patients
- did not significantly affect the efficacy of psychological emotion regulation with reappraisal
- did not normalize the emotion induction and emotion regulation deficits seen in patients with ADHD compared to healthy controls as described in 5.1

5.3.2 Discussion of main results

Two findings regarding the effects of CS on emotion processing are important. First, CS reduced emotion induction both in healthy controls and ADHD patients. Some empirical and genetic studies have hinted that dopamine can modify emotion recognition (355), especially for disgust (356), but not much is known about dopamine's role on negative emotions. Both top-down and bottom-up mechanisms, involving for example increased prefrontal control on subcortical emotion generation areas and increased positive affect that can bias the negative emotional experience can be theorized to be behind the reduction in emotion rating scores caused by CS.

Secondly, in this cohort, CS did not significantly improve emotion regulation. Clinically, this is important because it implies that traditionally prescribed ADHD medications, although they substantially improve core ADHD symptoms, might not improve emotion regulation deficits per se when compared to healthy controls. Other studies have shown that pharmacological treatment for ADHD with CS or atomoxetine is associated with partial improvement in emotional dysregulation, and smaller effect size compared to the improvement in attention and hyperactivity (267-271). As previously mentioned, emotion processing has always components that are affected by 'cold' cognitive processes. For example, situation selection and attention, which are central in emotional processes, see *Figure 1.3* and (68), are likely to be affected by ADHD impairments related to impulsivity and inattention and as such be amenable to modification by stimulant medication. Nevertheless, accumulating evidence suggests that emotion dysregulation, even if not fully orthogonal, is distinct from the purely cognitive impairments seen in ADHD.

6 Summary and Conclusions

6.1 Overall conclusions

Overall, these studies add to our knowledge regarding the role of the ascending monoaminergic systems in cognition and emotion and how common psychiatric medications can affect these processes already a few hours after a single dose. More importantly, these studies contribute to the understanding that not all processes are amenable by all types of intervention. For example, affective cognition seems to be more modifiable by serotonergic intervention and psychological methods such as reappraisal, while cognitive processes in non-emotional settings may be more sensitive to catecholaminergic intervention and skills training with task repetition practice. Crucially, under all our experimental conditions, emotion regulation by single session psychological intervention was significantly more effective than pharmacological emotion regulation with single dose SSRI or CS.

6.2 Strengths and limitations

The major strength of the present studies is the multimodal approach with data gathering at the behavioural, central and peripheral nervous system level, and the symmetrical design in contrasting two different negative emotions, fear and disgust, and two categories of interference, cognitive and affective interference. This approach increases reliability of the results wherever there is internal consistency among the various methods, and the symmetrical design functions that for every outcome measure there is an active comparator. All studies also employed robust well-established paradigms to compare cognitive and emotional processes under physiological and pathological conditions, both at baseline and after manipulation with pharmacological and psychological probes. However, some limitations should be mentioned.

In Studies I, II and IV, two active conditions (emotion induction and regulation) were compared, but lack of an emotionally neutral condition is a limitation that restricts the conclusions that can be drawn. In Study IV, although there was an active comparator in the form of healthy individuals taking CS medication, there was no placebo group, which means that we cannot rule out the possibility that some of the changes seen were due to non-specific effects such as task repetition. In all studies, the sample sizes and the characteristics of the cohorts affect the generalizability of our findings and their extrapolation to clinical settings. Finally, for all studies, the experiments were performed under laboratory conditions where the emotive stimuli are static pictures or words on the screen of a computer, aspects that limit the generalizability to real-world conditions.

6.3 Ethical considerations

The four main requirements - the information, consent requirement, confidentiality and usage requirement - as set by the Swedish Research Council, are met in these studies that were performed after approval from the Swedish Ethical Review Authority. Some ethical considerations are however important to name:

- Patients are a vulnerable population and research including them always entails ethical dilemmas. Although participation in the study was completely voluntary, after informed consent and withdrawal of participation anytime was possible, it can be said that in some cases the patients may not always assert their autonomy and their right to self-determination, and may feel pressured to participate because they are being asked by healthcare professionals. Although ADHD diagnosis by itself is not considered to compromise capacity, severe deficits may however limit the ability to fully comprehend the consequences of participation.

- In the data analysis, we found some statistically non-significant results showing strong tendencies and we speculate that some may be due to lack of power despite our initial calculations. These were secondary or post-hoc outcome measures, but the correct calculation of power is important, because it means that resources and burden for the participants are utilized optimally so that the results can be statistically viable. However, we believe that we had done a correct power analysis because we were able to get statistically valid answers to our main questions.
- Healthy participants received an active substance (escitalopram or methylphenidate): although all participants were informed and consented to participate, and there is no reason to believed a single dose escitalopram or methylphenidate would produce any long-term harm, side effects such as headache, concentration difficulties, nausea and fatigue can be a problem.

7 Implications, personal reflections, and future directions

This chapter consists of a few reflections on clinical and theoretical implications of the findings, of how they fit in a broader context and of some insights I gained during these studies.

The main findings of these studies fit well with the clinical observations that treatment with SSRIs can result in 'flat affect', a terrible side effect as some patients describe it or a welcome relief of 'too intense' emotions as some others report.

Figure 7.1 *'Before I felt I was inside a maze, constantly facing walls and obstacles. When I took the medicine (viz. SSRI), I felt that there still was a maze, with all my difficult feelings, thoughts, and problems, but I was not inside anymore; instead, I was above, facing them from a safe distance so I could get perspective and in that way they became more manageable', description from anonymous patient Huddinge, 2017 during personal communication. Photo: "Longleat Maze" by joncandy is licensed under CC BY-SA 2.0.* *To view a copy of this license, visit https://creativecommons.org/licenses/by-sa/2.0/?ref=openverse.*

Given the potential for both negative and positive implications and the prevalence of this phenomenon, the reduced emotion intensity associated with SSRI is likely a more important and more central aspect than it has been given credit for and attention to so far, and therefore it ought to be addressed early in the course of treatment. This can be an even more crucial and complicating factor in some contexts. If the patient already suffers from alexithymia or poor 'emotional granularity', if the patient's reduced emotional reactivity is conflicting with the parental role (especially early postpartum), if the patient takes part in psychotherapy where emotions are in focus are a few examples. Not to be forgotten, evidence from Study IV suggests that other medications, such as stimulants, can also have the same net effects on emotions.

With regards to ADHD, emotion dysregulation seems to be a core issue. It is important to shed more light on this aspect and address not just its nature, but also its response to treatment, pharmacological and non-such, in both preclinical and clinical settings. Another timely matter stemming from these reflections, is a much larger one, namely the current use of categorical diagnoses with very limited dimensional approach. There is a plethora of empirical evidence supporting the notion that focusing on specific domains and dimensions that vary in a spectrum (rather than being binary) can be more pragmatic, have larger ecological validity and prove to be more fruitful for problem formulation and treatment plans, compared to categorical diagnoses. This is of course an issue heavily discussed in the research field, but its impact hasn't reached the 'critical mass' in the clinics, yet.

Another practical insight that I have gained from these studies is the significance of behavioural measures. Modern technological advances have done extraordinary contributions to the way we can see, measure and probe different aspects of psychiatric disorders, and that has offered new ways of thinking and understanding previously uncharted territory. However, often the appeal of colorful neuroimaging pictures and the objectivity of physiological measures can shy away the importance of measures of subjective experience or behavioural performance. It is essential though to remember that it is the latter that guides the interpretation of the former and allows for the mental leap towards the translational applications and clinical relevance.

A fascinating new approach that I came across a few years ago during this research project, is the framework of predictive coding. This way of thinking is a real paradigm shift from previous views, transforming the field of neuroscience and is likely going to inform more and more psychiatry in general (and my future research plans in specific!). Although this framework was not explicitly applied in the studies included in this thesis, it has affected my way of thinking and interpretations to a great extent. Specifically, in the context of serotonin, I have been finding the concept of the predictive brain exceptionally helpful to build for myself a 'scaffold' in order to grasp this neurotransmitter's elusive role: since only a small number of serotonin-synthesizing neurons in the brainstem innervate nearly the entire neuroaxis, the role of serotonin is thought to be quite general (3). The latter is supported by the fact that the majority of its neurotransmission is 'volume' rather than 'wired' (106), contributing to the conceptualization that the 5-HT system has more of an orchestrating role. Indeed, the DR activity reflects changes in the global reward state: general, average reward rate of a stimulus in an environment (357) and that it encodes for salient events regardless of their valence (358), although anxiety and stress are potent inducers of 5-HT release (129, 359). Association of serotonin with increased brain plasticity has also been demonstrated, perhaps most impressively as illustrated by Vetencourt and colleagues (360).
But how can this general role be accounting for so different phenomena such as sexual behaviour, anxiety, learning, impulsivity and mood?
A clue can come from the observation that the serotonergic activity is related to the experienced controllability of the environment (361) and under conditions of uncertainty, activation of the ascending serotonergic system is associated with increased learning and enhanced cognitive flexibility (362), whereas serotonin depletion is associated with stimulus-bound responding, preventing competing, task-irrelevant, salient stimuli from biasing responding (111).
Harnessing this interesting observation, different versions of a similar model (Carhart-Harris and Nutt (129), Belsky, Jonassaint (363), Branchi (364), Friston (365) among others),viewing the brain in Bayesian terms, suggest that serotonin signals uncertainty and unpredictability and thus promotes updating of the organisms internal models, increasing the weights of perceptual evidence and their prediction errors against the weights of priors (see *figure 7.2*). A way this could be mediated is through the serotonergic inhibitory action on the arousal of the cortex (366).

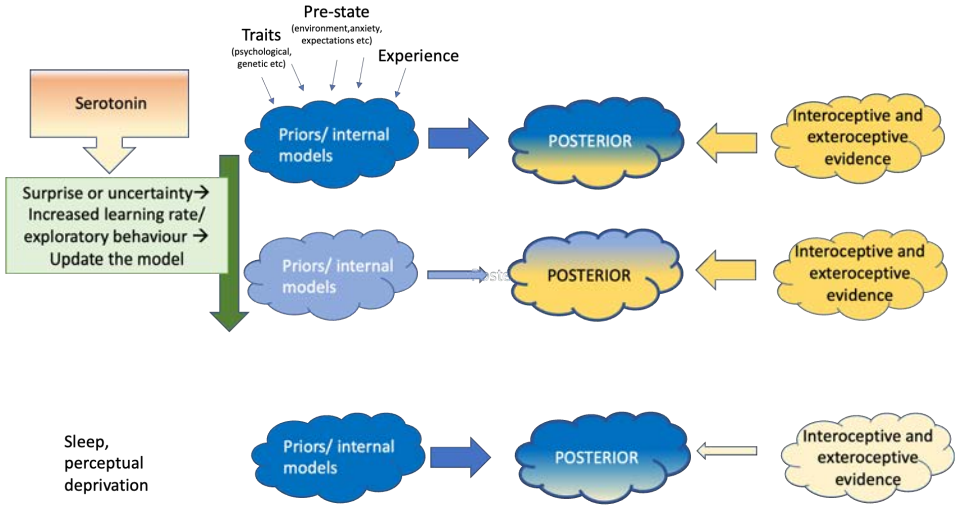


***Figure** 7.2 A theoretical, but promising framework capturing many serotonergic functions. Increases in serotonin associated with uncertainty and unreliability of the current generated predictions that prompts for an update of the internal model and increased influence of the prediction errors stemming from the internal and external milieu. In practice, this view could be accounting for phenomena related to serotonergic manipulations such as clinical effects (increased initial anxiety after initiating SSRI, symptomatology of serotonergic syndrome, psychedelic experiences and therapeutic effects) and experimental findings on reversal learning and perseverative behaviour (110, 111, 125, 344-347), learning regardless of valence (367), reduction of vigilance (341-343), role on interference (368), enabling of 'waiting' (119, 150, 340) and neural plasticity (360), likely mediated by cortical effects via 5-HT 2A receptors, but subcortical inhibitory effects via 5-HT 1A (129) might also be implicated. It is important to acknowledge that this is a framework rather than a falsifiable theory, at this stage, and that this model does not fully capture the complexity of the serotonergic system with distinct receptors(129), regions and temporal aspects (359) distinct of raphe 5-HT systems. Figure inspired and adapted from several publications including Carhart-Harris and Nutt (129), Walker, Mikheenko (132), Bigos, Pollock (147), Carhart-Harris (159), Belsky, Jonassaint (363), Branchi (364), Friston (365), Mainen (369).*

Finally, I have reflected a lot on the results of these studies, showing the robust and large effects of non-pharmacological interventions. It is often being dreamt of (or dreaded) that a mechanistic complete understanding of the brain will be achieved. The journey is breathtaking, but we are far from such a destination. However, it is assumed that the closer we get there, the more likely it becomes that the remission of ailments and diseases will be possible via a mechanistic approach with designed and tailor-made, precise pharmacotherapy that can target the desired receptors or systems. Not suggesting that one can predict what the future holds when it comes to revolutionary treatments and biomedical advancements, but an insight I believe I have gained from both performing these studies and reading the relevant literature is that although, psychiatric medication can indeed improve some aspects of cognition (in the context of mental health or illness) and with indeed a positive overall global effect, there are two caveats that follow. The first is that it comes with an inflexible cost: optimizing one function that is desirable in a context will likely result with a less optimal state for another function or different context. The second is that although medication may be helping or necessary for many conditions, the need for and importance of a biopsychosocial, holistic perspective will not disappear –

just as the science of quantum physics does not make classical mechanics obsolete! Psychological and sociological approaches will still be necessary to understand the fellow human in suffering, and relevant interventions such as psychoeducation, psychotherapy, physical and mental training, and social support will likely have a great (if not greater) impact in one's function, and quality of life. Given my personal interest in the brain, pharmacology, neuroimaging and neuroscience in general, that is a humbling insight ought to be remembered and defended.

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9 References

1. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. The American Journal of Psychiatry. 2010;167:748-51.
2. Wentura D. Cognition and emotion: on paradigms and metaphors. Cognition and emotion. 2019;33(1):85-93.
3. Andrade R, Beck SG. CHAPTER 2.5 - Cellular Effects of Serotonin in the CNS. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 219-31.
4. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005;9(5):242-9.
5. Salehinejad MA, Ghanavati E, Rashid MHA, Nitsche MA. Hot and cold executive functions in the brain: A prefrontal-cingular network. Brain Neurosci Adv. 2021;5:23982128211007769.
6. Beck AT. The current state of cognitive therapy: a 40-year retrospective. Arch Gen Psychiatry. 2005;62(9):953-9.
7. Huang Y-L, Chen S-H, Tseng H-H. Attachment avoidance and fearful prosodic emotion recognition predict depression maintenance. Psychiatry Research. 2019;272:649-54.
8. Gaddy MA, Ingram RE. A meta-analytic review of mood-congruent implicit memory in depressed mood. Clin Psychol Rev. 2014;34(5):402-16.
9. Mao M, Chen G, Feng K, Xu D, Hua X, Shan C, et al. Characteristics of prefrontal activity during emotional and cognitive processing in patients with bipolar disorder: A multi-channel functional near-infrared spectroscopy study. Front Neurosci. 2022;16:946543.
10. Lima IMM, Peckham AD, Johnson SL. Cognitive deficits in bipolar disorders: Implications for emotion. Clin Psychol Rev. 2018;59:126-36.
11. Phillips LK, Seidman LJ. Emotion processing in persons at risk for schizophrenia. Schizophr Bull. 2008;34(5):888-903.
12. Mobbs D, Headley DB, Ding W, Dayan P. Space, Time, and Fear: Survival Computations along Defensive Circuits. Trends Cogn Sci. 2020;24(3):228-41.
13. Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci. 1995;18:193-222.
14. Fitzgerald JM, Kinney KL, Phan KL, Klumpp H. Distinct neural engagement during implicit and explicit regulation of negative stimuli. Neuropsychologia. 2018.
15. Lavie N. Distracted and confused?: selective attention under load. Trends Cogn Sci. 2005;9(2):75-82.
16. Lavie N, Lin Z, Zokaei N, Thoma V. The role of perceptual load in object recognition. J Exp Psychol Hum Percept Perform. 2009;35(5):1346-58.
17. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68.
18. Espy KA. Using developmental, cognitive, and neuroscience approaches to understand executive control in young children. Dev Neuropsychol. 2004;26(1):379-84.
19. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167-202.
20. Rahm C, Liberg B, Kristoffersen-Wiberg M, Aspelin P, Msghina M. Differential Effects of Single-Dose Escitalopram on Cognitive and Affective Interference during Stroop Task. Front Psychiatry. 2014;5:21.
21. Arnsten AF. Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci. 1998;2(11):436-47.
22. Banich MT, Mackiewicz KL, Depue BE, Whitmer AJ, Miller GA, Heller W. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. Neurosci Biobehav Rev. 2009;33(5):613-30.
23. Liston C, McEwen BS, Casey BJ. Psychosocial stress reversibly disrupts prefrontal processing and attentional control. Proc Natl Acad Sci U S A. 2009;106(3):912-7.
24. von Hecker U, Meiser T. Defocused attention in depressed mood: evidence from source monitoring. Emotion (Washington, DC). 2005;5(4):456-63.
25. Glausier JR, Lewis DA. Mapping pathologic circuitry in schizophrenia. Handbook of clinical neurology. 2018;150:389-417.

26. Zysset S, Muller K, Lohmann G, von Cramon DY. Color-word matching stroop task: separating interference and response conflict. NeuroImage. 2001;13(1):29-36.
27. Hensler JG. CHAPTER 3.5 - Serotonin in Mood and Emotion. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 367-78.
28. Elliott R, Zahn R, Deakin JF, Anderson IM. Affective cognition and its disruption in mood disorders. Neuropsychopharmacology. 2011;36(1):153-82.
29. Anderson DJ, Adolphs R. A framework for studying emotions across species. Cell. 2014;157(1):187-200.
30. Russell JA. A circumplex model of affect. Journal of personality and social psychology. 1980;39(6):1161-78.
31. Barrett LF, Mesquita B, Ochsner KN, Gross JJ. The Experience of Emotion. Annual review of psychology. 2007;58(1):373-403.
32. Mobbs D, Adolphs R, Fanselow MS, Barrett LF, LeDoux JE, Ressler K, et al. Viewpoints: Approaches to defining and investigating fear. Nat Neurosci. 2019;22(8):1205-16.
33. Russell JA. Core affect and the psychological construction of emotion. Psychol Rev. 2003;110(1):145-72.
34. Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. Nature reviews Neuroscience. 2001;2(5):352-63.
35. Adolphs R. How should neuroscience study emotions? by distinguishing emotion states, concepts, and experiences. Social cognitive and affective neuroscience. 2017;12(1):24-31.
36. Gross JJ, Barrett LF. Emotion Generation and Emotion Regulation: One or Two Depends on Your Point of View. Emot Rev. 2011;3(1):8-16.
37. Elizabeth Clark-Polner TDW, Ajay B. Satpute, & Lisa Feldman Barrett. Handbook of emotions, chapter 8. In: Lisa Feldman Barrett ML, and Jeannette M. Haviland-Jones, editor. Handbook of emotions2016. p. 146-65.
38. Barrett LF, Adolphs R, Marsella S, Martinez AM, Pollak SD. Emotional Expressions Reconsidered: Challenges to Inferring Emotion From Human Facial Movements. Psychol Sci Public Interest. 2019;20(1):1-68.
39. Arnsten AF. Catecholamine influences on dorsolateral prefrontal cortical networks. Biological psychiatry. 2011;69(12):e89-99.
40. Kuhbandner C, Zehetleitner M. Dissociable effects of valence and arousal in adaptive executive control. PLoS One. 2011;6(12):e29287.
41. Adolphs R, Mlodinow L, Barrett LF. What is an emotion? Current biology. 2019;29(20):R1060-R4.
42. Clore GL, Ortony A. Psychological Construction in the OCC Model of Emotion. Emotion Review. 2013;5(4):335-43.
43. Darwin C. The Expression of the Emotions in Man and Animals: John Murray; 1872.
44. Ekman P. An argument for basic emotions. Cognition and Emotion. 1992;6(3-4):169-200.
45. Ekman P, Levenson RW, Friesen WV. Autonomic nervous system activity distinguishes among emotions. Science. 1983;221(4616):1208-10.
46. Panksepp J. Affective Neuroscience : The Foundations of Human and Animal Emotions. New York, UNITED STATES: Oxford University Press, Incorporated; 2004.
47. Buck R. The biological affects: a typology. Psychol Rev. 1999;106(2):301-36.
48. Damasio A, Grof P. The feeling of what happens: body and emotion in the making of consciousness. SAGE PUBLICATIONS, INC; 2002. p. 276.
49. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155-84.
50. Barrett LF. The theory of constructed emotion: an active inference account of interoception and categorization. Soc Cogn Affect Neurosci. 2017;12(1):1-23.
51. LeDoux JE. Thoughtful feelings. Curr Biol. 2020;30(11):R619-r23.
52. Gross JJ. Handbook of emotion regulation. Second edition. ed. New York: The Guilford Press; 2014.
53. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biological psychiatry. 2005;57(3):210-9.
54. Barrett LF. Emotions Are Real. Emotion (Washington, DC). 2012;12(3):413-29.

55. Fanselow MS, Lester LS. A functional behavioristic approach to aversively motivated behavior: Predatory imminence as a determinant of the topography of defensive behavior. Evolution and learning. Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc; 1988. p. 185-212.
56. LeDoux JE. Coming to terms with fear. Proc Natl Acad Sci U S A. 2014;111(8):2871-8.
57. Rozin P, Fallon AE. A perspective on disgust. Psychol Rev. 1987;94(1):23-41.
58. Anderson, Rutherford. Cognitive Reorganization during Pregnancy and the Postpartum Period: An Evolutionary Perspective. Evolutionary psychology. 2012;10(4):147470491201000-687.
59. Lang PJ, Davis M, Ohman A. Fear and anxiety: animal models and human cognitive psychophysiology. Journal of affective disorders. 2000;61(3):137-59.
60. Woody SR, Teachman BA. Intersection of Disgust and Fear: Normative and Pathological Views. Clinical Psychology: Science and Practice. 2000;7(3):291-311.
61. Cisler JM, Olatunji BO, Lohr JM. Disgust, fear, and the anxiety disorders: a critical review. Clin Psychol Rev. 2009;29(1):34-46.
62. Pessoa L, Ungerleider LG. Neuroimaging studies of attention and the processing of emotion-laden stimuli. Prog Brain Res. 2004;144:171-82.
63. Troy AS, Wilhelm FH, Shallcross AJ, Mauss IB. Seeing the silver lining: cognitive reappraisal ability moderates the relationship between stress and depressive symptoms. Emotion (Washington, DC). 2010;10(6):783-95.
64. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, et al. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb Cortex. 2014;24(11):2981-90.
65. Bateman A, Fonagy P. Mentalization based treatment for borderline personality disorder. World Psychiatry. 2010;9(1):11-5.
66. Lynch TR, Trost WT, Salsman N, Linehan MM. Dialectical behavior therapy for borderline personality disorder. Annu Rev Clin Psychol. 2007;3:181-205.
67. Nelson BD, Fitzgerald DA, Klumpp H, Shankman SA, Phan KL. Prefrontal engagement by cognitive reappraisal of negative faces. Behavioural brain research. 2015;279:218-25.
68. Gross JJ. Emotion Regulation: Current Status and Future Prospects. Psychological Inquiry. 2015;26(1):1-26.
69. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry. 2008;13(9):829, 33-57.
70. Gyurak A, Gross JJ, Etkin A. Explicit and implicit emotion regulation: a dual-process framework. Cogn Emot. 2011;25(3):400-12.
71. Etkin A, Büchel C, Gross JJ. The neural bases of emotion regulation. Nat Rev Neurosci. 2015;16(11):693-700.
72. Braunstein LM, Gross JJ, Ochsner KN. Explicit and implicit emotion regulation: a multi-level framework. Soc Cogn Affect Neurosci. 2017;12(10):1545-57.
73. McRae K, Gross JJ. Emotion Regulation. Emotion (Washington, DC). 2020;20(1):1-9.
74. Evers EA, F vdV, Jolles J, N D, J S. The effect of acute tryptophan depletion on performance and the BOLD response during a Stroop task in healthy first-degree relatives of patients with unipolar depression. Psychiatry Res. 2009;173(1):52-8.
75. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing--induced expectations of anxiety relief activate a generalized modulatory network. Neuron. 2005;46(6):957-69.
76. Schienle A, Ubel S, Wabnegger A. When opposites lead to the same: a direct comparison of explicit and implicit disgust regulation via fMRI. Soc Cogn Affect Neurosci. 2017;12(3):445-51.
77. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. Lancet. 1978;2(8091):654-7.
78. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biological psychiatry. 2003;54(5):504-14.

79. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002;14(8):1215-29.
80. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage. 2004;23(2):483-99.
81. Phan KL, Wager TD, Taylor SF, Liberzon I. Functional neuroimaging studies of human emotions. CNS spectrums. 2004;9(4):258-66.
82. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2012;1251:E1-24.
83. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage. 2002;16(2):331-48.
84. Badre D, Nee DE. Frontal Cortex and the Hierarchical Control of Behavior. Trends Cogn Sci. 2018;22(2):170-88.
85. Cools R, Arnsten AFT. Neuromodulation of prefrontal cortex cognitive function in primates: the powerful roles of monoamines and acetylcholine. Neuropsychopharmacology. 2022;47(1):309-28.
86. Arnsten AF, Goldman-Rakic PS. Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. Brain research. 1984;306(1-2):9-18.
87. Chiba T, Kayahara T, Nakano K. Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, Macaca fuscata. Brain research. 2001;888(1):83-101.
88. Frankle WG, Laruelle M, Haber SN. Prefrontal cortical projections to the midbrain in primates: evidence for a sparse connection. Neuropsychopharmacology. 2006;31(8):1627-36.
89. Panichello MF, Buschman TJ. Shared mechanisms underlie the control of working memory and attention. Nature (London). 2021;592(7855):601-5.
90. Suzuki M, Gottlieb J. Distinct neural mechanisms of distractor suppression in the frontal and parietal lobe. Nat Neurosci. 2013;16(1):98-104.
91. Schumacher FK, Schumacher LV, Amtage F, Horn A, Egger K, Piroth T, et al. The rostro-caudal gradient in the prefrontal cortex and its modulation by subthalamic deep brain stimulation in Parkinson's disease. Scientific Reports. 2021;11(1):2138.
92. Ongür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000;10(3):206-19.
93. Goldman-Rakic PS. Topography of cognition: parallel distributed networks in primate association cortex. Annu Rev Neurosci. 1988;11:137-56.
94. Tupak SV, Dresler T, Guhn A, Ehlis AC, Fallgatter AJ, Pauli P, et al. Implicit emotion regulation in the presence of threat: neural and autonomic correlates. NeuroImage. 2014;85 Pt 1:372-9.
95. Raichle ME. The brain's default mode network. Annu Rev Neurosci. 2015;38:433-47.
96. Schimmelpfennig J, Topczewski J, Zajkowski W, Jankowiak-Siuda K. The role of the salience network in cognitive and affective deficits. Frontiers in human neuroscience. 2023;17:1133367.
97. Stahl SM, editor 13 – Platelets as Pharmacologic Models for the Receptors and Biochemistry of Monoaminergic Neurons1985.
98. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev. 2011;63(1):182-217.
99. Bockaert J, Claeysen S, Dumuis A, Marin P. CHAPTER 1.5 - Classification and Signaling Characteristics of 5-HT Receptors. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 103-21.
100. Vizi ES, Fekete A, Karoly R, Mike A. Non-synaptic receptors and transporters involved in brain functions and targets of drug treatment. Br J Pharmacol. 2010;160(4):785-809.
101. Frank MJ, Seeberger LC, O'Reilly R C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science. 2004;306(5703):1940-3.
102. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991;41(1):1-24.

103. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci. 2008;12(1):31-40.
104. Klein MO, Battagello DS, Cardoso AR, Hauser DN, Bittencourt JC, Correa RG. Dopamine: Functions, Signaling, and Association with Neurological Diseases. Cell Mol Neurobiol. 2019;39(1):31-59.
105. Whitaker-Azmitia PM. CHAPTER 3.1 - Serotonin and Development**This chapter is dedicated to Dr Jean Lauder, on the occasion of her retirement. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 309-23.
106. Hensler JG. Serotonergic modulation of the limbic system. Neuroscience and biobehavioral reviews. 2006;30(2):203-14.
107. Hornung J-P. CHAPTER 1.3 - The Neuronatomy of the Serotonergic System. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 51-64.
108. Peroutka SJ, Lebovitz RM, Snyder SH. Two distinct central serotonin receptors with different physiological functions. Science. 1981;212(4496):827-9.
109. Brozoski TJ, Brown RM, Rosvold HE, Goldman PS. Cognitive Deficit Caused by Regional Depletion of Dopamine in Prefrontal Cortex of Rhesus Monkey. Science (American Association for the Advancement of Science). 1979;205(4409):929-32.
110. Clarke HF, Walker SC, Crofts HS, Dalley JW, Robbins TW, Roberts AC. Prefrontal Serotonin Depletion Affects Reversal Learning But Not Attentional Set Shifting. The Journal of neuroscience. 2005;25(2):532-8.
111. Walker SC, Robbins TW, Roberts AC. Differential Contributions of Dopamine and Serotonin to Orbitofrontal Cortex Function in the Marmoset. Cerebral cortex (New York, NY 1991). 2008;19(4):889-98.
112. Dayan P, Huys QJM. Serotonin in Affective Control. Annual review of neuroscience. 2009;32(1):95-126.
113. Müller CP, Jacobs BL. Preface. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. xi-xii.
114. Uphouse L, Guptarak J. CHAPTER 3.4 - Serotonin and Sexual Behavior. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 347-65.
115. Lowry CA, Hale MW. CHAPTER 3.6 - Serotonin and the Neurobiology of Anxious States. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 379-97.
116. Carey RJ. CHAPTER 3.2 - Serotonin and Basal Sensory–Motor Control. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 325-30.
117. Lee MD, Clifton PG. CHAPTER 3.3 - Role of the Serotonergic System in Appetite and Ingestion Control. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 331-45.
118. McBride WJ. CHAPTER 3.7 - Role of Serotonin in Brain Reward and Regulation of Alcohol Drinking Behavior. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 399-414.
119. Robbins TW, Crockett MJ. CHAPTER 3.8 - Role of Central Serotonin in Impulsivity and Compulsivity: Comparative Studies in Experimental Animals and Humans. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 415-27.
120. Cassel J-C. CHAPTER 3.9 - Experimental Studies on the Role(s) of Serotonin in Learning and Memory Functions. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 429-47.
121. Duman EA, Canli T. CHAPTER 3.10 - Social Behavior and Serotonin. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 449-56.
122. Sommer C. CHAPTER 3.11 - Serotonin in Pain and Pain Control. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 457-71.
123. Beliveau V, Ganz M, Feng L, Ozenne B, Højgaard L, Fisher PM, et al. A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. J Neurosci. 2017;37(1):120-8.
124. Jacobs BL, Fornal CA. CHAPTER 2.1 - Activity of Brain Serotonergic Neurons in Relation to Physiology and Behavior. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 153-62.

125. Roberts C, Sahakian BJ, Robbins TW. Psychological mechanisms and functions of 5-HT and SSRIs in potential therapeutic change: Lessons from the serotonergic modulation of action selection, learning, affect, and social cognition. Neurosci Biobehav Rev. 2020;119:138-67.
126. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular psychiatry. 2022.
127. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. British journal of psychiatry. 2009;195(2):102-8.
128. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant Drug Treatment Modifies the Neural Processing of Nonconscious Threat Cues. Biological psychiatry (1969). 2006;59(9):816-20.
129. Carhart-Harris RL, Nutt DJ. Serotonin and brain function: a tale of two receptors. Journal of Psychopharmacology. 2017;31(9):1091-120.
130. Chamberlain SR, Müller U, Robbins TW, Sahakian BJ. Neuropharmacological modulation of cognition. Curr Opin Neurol. 2006;19(6):607-12.
131. Evers EAT, Cools R, Clark L, van der Veen FM, Jolles J, Sahakian BJ, et al. Serotonergic Modulation of Prefrontal Cortex during Negative Feedback in Probabilistic Reversal Learning. Neuropsychopharmacology. 2005;30(6):1138-47.
132. Walker SC, Mikheenko YP, Argyle LD, Robbins TW, Roberts AC. Selective prefrontal serotonin depletion impairs acquisition of a detour-reaching task. The European journal of neuroscience. 2006;23(11):3119-23.
133. Evers EA, Tillie DE, van der Veen FM, Lieben CK, Jolles J, Deutz NE, et al. Effects of a novel method of acute tryptophan depletion on plasma tryptophan and cognitive performance in healthy volunteers. Psychopharmacology. 2005;178(1):92-9.
134. Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology. 2002;163(1):42-53.
135. Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science. 2006;311(5762):861-3.
136. Meyniel F, Goodwin GM, Deakin JW, Klinge C, MacFadyen C, Milligan H, et al. A specific role for serotonin in overcoming effort cost. Elife. 2016;5.
137. Crockett MJ, Cools R. Serotonin and aversive processing in affective and social decision-making. Current Opinion in Behavioral Sciences. 2015;5:64-70.
138. Cools R, Nakamura K, Daw ND. Serotonin and dopamine: unifying affective, activational, and decision functions. Neuropsychopharmacology. 2011;36(1):98-113.
139. Crockett MJ, Clark L, Robbins TW. Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. J Neurosci. 2009;29(38):11993-9.
140. Anderson IM, Del-Ben CM, McKie S, Richardson P, Williams SR, Elliott R, et al. Citalopram modulation of neuronal responses to aversive face emotions: a functional MRI study. Neuroreport. 2007;18(13):1351-5.
141. Bhagwagar Z, Cowen PJ, Goodwin GM, Harmer CJ. Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. Am J Psychiatry. 2004;161(1):166-8.
142. Harmer CJ, Bhagwagar Z, Perrett DI, Völlm BA, Cowen PJ, Goodwin GM. Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology. 2003;28(1):148-52.
143. Del-Ben CM, Deakin JF, McKie S, Delvai NA, Williams SR, Elliott R, et al. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology. 2005;30(9):1724-34.
144. Browning M, Reid C, Cowen PJ, Goodwin GM, Harmer CJ. A single dose of citalopram increases fear recognition in healthy subjects. J Psychopharmacol. 2007;21(7):684-90.
145. Brühl AB, Kaffenberger T, Herwig U. Serotonergic and noradrenergic modulation of emotion processing by single dose antidepressants. Neuropsychopharmacology. 2010;35(2):521-33.

146. Lochner C, Simmons C, Kidd M, Chamberlain SR, Fineberg NA, van Honk J, et al. Differential effects of escitalopram challenge on disgust processing in obsessive-compulsive disorder. Behavioural brain research. 2012;226(1):274-80.
147. Bigos KL, Pollock BG, Aizenstein HJ, Fisher PM, Bies RR, Hariri AR. Acute 5-HT Reuptake Blockade Potentiates Human Amygdala Reactivity. Neuropsychopharmacology (New York, NY). 2008;33(13):3221-5.
148. Grillon C, Levenson J, Pine DS. A Single Dose of the Selective Serotonin Reuptake Inhibitor Citalopram Exacerbates Anxiety in Humans: A Fear-Potentiated Startle Study. Neuropsychopharmacology (New York, NY). 2007;32(1):225-31.
149. Selvaraj S, Walker C, Arnone D, Cao B, Faulkner P, Cowen PJ, et al. Effect of Citalopram on Emotion Processing in Humans: A Combined 5-HT1A [11C]CUMI-101 PET and Functional MRI Study. Neuropsychopharmacology (New York, NY). 2017;43(3):655-64.
150. Skandali N, Rowe JB, Voon V, Deakin JB, Cardinal RN, Cormack F, et al. Dissociable effects of acute SSRI (escitalopram) on executive, learning and emotional functions in healthy humans. Neuropsychopharmacology. 2018;43(13):2645-51.
151. Grady CL, Siebner HR, Hornboll B, Macoveanu J, Paulson OB, Knudsen GM. Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. Eur Neuropsychopharmacol. 2013;23(5):368-78.
152. Kemp AH, Nathan PJ. Acute augmentation of serotonin suppresses cardiovascular responses to emotional valence. Int J Neuropsychopharmacol. 2004;7(1):65-70.
153. Ma Y, Li B, Wang C, Zhang W, Rao Y, Han S. Allelic variation in 5-HTTLPR and the effects of citalopram on the emotional neural network. The British journal of psychiatry : the journal of mental science. 2015;206(5):385-92.
154. Outhred T, Das P, Felmingham KL, Bryant RA, Nathan PJ, Malhi GS, et al. Impact of acute administration of escitalopram on the processing of emotional and neutral images: a randomized crossover fMRI study of healthy women. J Psychiatry Neurosci. 2014;39(4):267-75.
155. Outhred T, Das P, Felmingham KL, Bryant RA, Nathan PJ, Malhi GS, et al. Facilitation of emotion regulation with a single dose of escitalopram: A randomized fMRI study. Psychiatry Res. 2015;233(3):451-7.
156. Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, et al. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. NeuroImage. 2005;27(4):991-1001.
157. Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. Int J Tryptophan Res. 2019;12:1178646919873925.
158. Halberstadt AL, Nichols DE. CHAPTER 4.7 - Serotonin and Serotonin Receptors in Hallucinogen Action. In: Müller CP, Jacobs BL, editors. Handbook of Behavioral Neuroscience. 21: Elsevier; 2010. p. 621-36.
159. Carhart-Harris RL. How do psychedelics work? Curr Opin Psychiatry. 2019;32(1):16-21.
160. Sánchez C, Bergqvist PBF, Brennum LT, Gupta S, Hogg S, Larsen A, et al. Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. Psychopharmacology. 2003;167(4):353-62.
161. Wolf D, Klasen M, Eisner P, Zepf FD, Zvyagintsev M, Palomero-Gallagher N, et al. Central serotonin modulates neural responses to virtual violent actions in emotion regulation networks. Brain Struct Funct. 2018;223(7):3327-45.
162. Arnone D, Wise T, Walker C, Cowen PJ, Howes O, Selvaraj S. The effects of serotonin modulation on medial prefrontal connectivity strength and stability: A pharmacological fMRI study with citalopram. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):152-9.
163. Nord M, Finnema SJ, Halldin C, Farde L. Effect of a single dose of escitalopram on serotonin concentration in the non-human and human primate brain. Int J Neuropsychopharmacol. 2013;16(7):1577-86.
164. Bosker FJ, Cremers TI, Jongsma ME, Westerink BH, Wikström HV, den Boer JA. Acute and chronic effects of citalopram on postsynaptic 5-hydroxytryptamine(1A) receptor-mediated feedback: a microdialysis study in the amygdala. J Neurochem. 2001;76(6):1645-53.
165. Aronson S, Delgado P. Escitalopram. Drugs Today (Barc). 2004;40(2):121-31.

166. Rao N. The clinical pharmacokinetics of escitalopram. Clin Pharmacokinet. 2007;46(4):281-90.
167. Anderson IM, McKie S, Elliott R, Williams SR, Deakin JF. Assessing human 5-HT function in vivo with pharmacoMRI. Neuropharmacology. 2008;55(6):1029-37.
168. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.
169. Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. Biological psychiatry (1969). 1998;44(9):812-24.
170. Vijayraghavan S, Major AJ, Everling S. Dopamine D1 and D2 Receptors Make Dissociable Contributions to Dorsolateral Prefrontal Cortical Regulation of Rule-Guided Oculomotor Behavior. Cell Rep. 2016;16(3):805-16.
171. Vijayraghavan S, Major AJ, Everling S. Neuromodulation of Prefrontal Cortex in Non-Human Primates by Dopaminergic Receptors during Rule-Guided Flexible Behavior and Cognitive Control. Front Neural Circuits. 2017;11:91.
172. Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, et al. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell. 2007;129(2):397-410.
173. Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu Rev Neurosci. 2009;32:267-87.
174. Goldman-Rakic PS. Circuitry of Primate Prefrontal Cortex and Regulation of Behavior by Representational Memory. Hoboken, NJ, USA: John Wiley & Sons, Inc; 2011. p. 373-417.
175. Del Arco A, Mora F. Neurotransmitters and prefrontal cortex-limbic system interactions: implications for plasticity and psychiatric disorders. J Neural Transm (Vienna). 2009;116(8):941-52.
176. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biological psychiatry. 2011;69(12):e113-25.
177. Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci. 1993;13(3):900-13.
178. Matsumoto M, Hikosaka O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature. 2009;459(7248):837-41.
179. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 2010;68(5):815-34.
180. Kodama T, Hikosaka K, Honda Y, Kojima T, Watanabe M. Higher dopamine release induced by less rather than more preferred reward during a working memory task in the primate prefrontal cortex. Behavioural brain research. 2014;266:104-7.
181. Soutschek A, Kozak R, de Martinis N, Howe W, Burke CJ, Fehr E, et al. Activation of D1 receptors affects human reactivity and flexibility to valued cues. Neuropsychopharmacology. 2020;45(5):780-5.
182. Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M. Working memory capacity predicts dopamine synthesis capacity in the human striatum. J Neurosci. 2008;28(5):1208-12.
183. Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P. Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]SCH23390. Neuroscience. 1991;40(3):657-71.
184. Cools R, Sheridan M, Jacobs E, D'Esposito M. Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. J Neurosci. 2007;27(20):5506-14.
185. Gibbs SE, D'Esposito M. Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. Cogn Affect Behav Neurosci. 2005;5(2):212-21.
186. Kimberg DY, D'Esposito M, Farah MJ. Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport. 1997;8(16):3581-5.

187. Mehta MA, Goodyer IM, Sahakian BJ. Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. J Child Psychol Psychiatry. 2004;45(2):293-305.
188. Wallace DL, Vytlacil JJ, Nomura EM, Gibbs SE, D'Esposito M. The dopamine agonist bromocriptine differentially affects fronto-striatal functional connectivity during working memory. Frontiers in human neuroscience. 2011;5:32.
189. van der Schaaf ME, van Schouwenburg MR, Geurts DE, Schellekens AF, Buitelaar JK, Verkes RJ, et al. Establishing the dopamine dependency of human striatal signals during reward and punishment reversal learning. Cereb Cortex. 2014;24(3):633-42.
190. Frank MJ, O'Reilly RC. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci. 2006;120(3):497-517.
191. Furman DJ, Zhang Z, Chatham CH, Good M, Badre D, Hsu M, et al. Augmenting Frontal Dopamine Tone Enhances Maintenance over Gating Processes in Working Memory. J Cogn Neurosci. 2021;33(9):1753-65.
192. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 2003;100(10):6186-91.
193. Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain. 2002;125(Pt 3):584-94.
194. Landau SM, Lal R, O'Neil JP, Baker S, Jagust WJ. Striatal dopamine and working memory. Cereb Cortex. 2009;19(2):445-54.
195. Durstewitz D, Seamans JK. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. Biological psychiatry. 2008;64(9):739-49.
196. Baik J-H. Dopamine Signaling in reward-related behaviors. Frontiers in Neural Circuits. 2013;7.
197. Schmitt KC, Zhen J, Kharkar P, Mishra M, Chen N, Dutta AK, et al. Interaction of cocaine-, benztropine-, and GBR12909-like compounds with wild-type and mutant human dopamine transporters: molecular features that differentially determine antagonist-binding properties. J Neurochem. 2008;107(4):928-40.
198. Varrone A, Halldin C. Chapter Nine - Human Brain Imaging of Dopamine Transporters. In: Seeman P, Madras B, editors. Imaging of the Human Brain in Health and Disease. Boston: Academic Press; 2014. p. 203-40.
199. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry. 1998;155(10):1325-31.
200. Meyer JH, Goulding VS, Wilson AA, Hussey D, Christensen BK, Houle S. Bupropion occupancy of the dopamine transporter is low during clinical treatment. Psychopharmacologia. 2002;163(1):102-5.
201. Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B. In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. Biological psychiatry (1969). 2003;54(8):800-5.
202. Fisher H, Aron A, Brown LL. Romantic love: an fMRI study of a neural mechanism for mate choice. J Comp Neurol. 2005;493(1):58-62.
203. Schultz W, Dayan P, Montague PR. A Neural Substrate of Prediction and Reward. Science (American Association for the Advancement of Science). 1997;275(5306):1593-9.
204. Cools R, Froböse M, Aarts E, Hofmans L. Dopamine and the motivation of cognitive control. Handbook of clinical neurology. 2019;163:123-43.
205. Braver TS, Krug MK, Chiew KS, Kool W, Westbrook JA, Clement NJ, et al. Mechanisms of motivation-cognition interaction: challenges and opportunities. Cogn Affect Behav Neurosci. 2014;14(2):443-72.
206. Likhtik E, Johansen JP. Neuromodulation in circuits of aversive emotional learning. Nat Neurosci. 2019;22(10):1586-97.

207. Haaker J, Gaburro S, Sah A, Gartmann N, Lonsdorf TB, Meier K, et al. Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear. Proc Natl Acad Sci U S A. 2013;110(26):E2428-36.
208. Holland N, Robbins TW, Rowe JB. The role of noradrenaline in cognition and cognitive disorders. Brain. 2021;144(8):2243-56.
209. Rowe JB, Saunders JR, Durantou F, Robbins TW. Systemic idazoxan impairs performance in a non-reversal shift test: implications for the role of the central noradrenergic systems in selective attention. J Psychopharmacol. 1996;10(3):188-94.
210. Brown SB, Tona KD, van Noorden MS, Giltay EJ, van der Wee NJ, Nieuwenhuis S. Noradrenergic and cholinergic effects on speed and sensitivity measures of phasic alerting. Behav Neurosci. 2015;129(1):42-9.
211. Coull JT, Middleton HC, Robbins TW, Sahakian BJ. Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology. 1995;120(3):322-32.
212. Arnsten AF, Goldman-Rakic PS. Analysis of alpha-2 adrenergic agonist effects on the delayed nonmatch-to-sample performance of aged rhesus monkeys. Neurobiol Aging. 1990;11(6):583-90.
213. Arnsten AF, Goldman-Rakic PS. Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science. 1985;230(4731):1273-6.
214. Pu X, Ma Y, Cai J. A study on the effect of lesions of area 7 of the parietal cortex on the short-term visual spatial memory of rhesus monkeys (Macaca mulatta). Brain research. 1993;600(2):187-92.
215. Mair RG, McEntee WJ. Cognitive enhancement in Korsakoff's psychosis by clonidine: a comparison with L-dopa and ephedrine. Psychopharmacology. 1986;88(3):374-80.
216. Gamo NJ, Wang M, Arnsten AF. Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. J Am Acad Child Adolesc Psychiatry. 2010;49(10):1011-23.
217. Kumar U, Medel-Matus JS, Redwine HM, Shin D, Hensler JG, Sankar R, et al. Effects of selective serotonin and norepinephrine reuptake inhibitors on depressive- and impulsive-like behaviors and on monoamine transmission in experimental temporal lobe epilepsy. Epilepsia. 2016;57(3):506-15.
218. Liu YP, Huang TS, Tung CS, Lin CC. Effects of atomoxetine on attention and impulsivity in the five-choice serial reaction time task in rats with lesions of dorsal noradrenergic ascending bundle. Prog Neuropsychopharmacol Biol Psychiatry. 2015;56:81-90.
219. Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology. 2008;199(3):439-56.
220. Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. Brain. 2014;137(Pt 7):1986-97.
221. Rae CL, Nombela C, Rodríguez PV, Ye Z, Hughes LE, Jones PS, et al. Atomoxetine restores the response inhibition network in Parkinson's disease. Brain. 2016;139(Pt 8):2235-48.
222. Borchert RJ, Rittman T, Passamonti L, Ye Z, Sami S, Jones SP, et al. Atomoxetine Enhances Connectivity of Prefrontal Networks in Parkinson's Disease. Neuropsychopharmacology. 2016;41(8):2188.
223. Graf H, Abler B, Freudenmann R, Beschoner P, Schaeffeler E, Spitzer M, et al. Neural correlates of error monitoring modulated by atomoxetine in healthy volunteers. Biological psychiatry. 2011;69(9):890-7.
224. Chamberlain SR, Hampshire A, Müller U, Rubia K, Del Campo N, Craig K, et al. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biological psychiatry. 2009;65(7):550-5.
225. Hauser TU, Moutoussis M, Purg N, Dayan P, Dolan RJ. Beta-Blocker Propranolol Modulates Decision Urgency During Sequential Information Gathering. J Neurosci. 2018;38(32):7170-8.
226. Whelan R, Conrod PJ, Poline JB, Lourdusamy A, Banaschewski T, Barker GJ, et al. Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat Neurosci. 2012;15(6):920-5.

227. Hesse S, Müller U, Rullmann M, Luthardt J, Bresch A, Becker GA, et al. The association between in vivo central noradrenaline transporter availability and trait impulsivity. Psychiatry Res Neuroimaging. 2017;267:9-14.
228. Newman LA, Darling J, McGaughy J. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology. 2008;200(1):39-50.
229. Cain RE, Wasserman MC, Waterhouse BD, McGaughy JA. Atomoxetine facilitates attentional set shifting in adolescent rats. Dev Cogn Neurosci. 2011;1(4):552-9.
230. Middleton HC, Sharma A, Agouzoul D, Sahakian BJ, Robbins TW. Idazoxan potentiates rather than antagonizes some of the cognitive effects of clonidine. Psychopharmacology. 1999;145(4):401-11.
231. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28:403-50.
232. Dayan P, Yu AJ. Phasic norepinephrine: a neural interrupt signal for unexpected events. Network. 2006;17(4):335-50.
233. Ramos BP, Arnsten AF. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol Ther. 2007;113(3):523-36.
234. Robbins TW. Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp Brain Res. 2000;133(1):130-8.
235. Morón JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci. 2002;22(2):389-95.
236. Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AF, Kelley AE, Schmeichel B, et al. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biological psychiatry. 2006;60(10):1111-20.
237. Volkow ND, Wang G-J, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic Doses of Oral Methylphenidate Significantly Increase Extracellular Dopamine in the Human Brain. The Journal of neuroscience. 2001;21(2):121-RC.
238. Fallon SJ, van der Schaaf ME, Ter Huurne N, Cools R. The Neurocognitive Cost of Enhancing Cognition with Methylphenidate: Improved Distractor Resistance but Impaired Updating. J Cogn Neurosci. 2017;29(4):652-63.
239. Chamberlain SR, Müller U, Blackwell AD, Robbins TW, Sahakian BJ. Noradrenergic modulation of working memory and emotional memory in humans. Psychopharmacology. 2006;188(4):397-407.
240. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci. 2004;27:1-28.
241. van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijer JP, et al. Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. NeuroImage. 2005;24(3):898-909.
242. Retz W, Stieglitz RD, Corbisiero S, Retz-Junginger P, Rösler M. Emotional dysregulation in adult ADHD: What is the empirical evidence? Expert Rev Neurother. 2012;12(10):1241-51.
243. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. The British journal of psychiatry : the journal of mental science. 2009;194(3):204-11.
244. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. Atten Defic Hyperact Disord. 2017;9(1):47-65.
245. Soler-Gutiérrez AM, Pérez-González JC, Mayas J. Evidence of emotion dysregulation as a core symptom of adult ADHD: A systematic review. PLoS One. 2023;18(1):e0280131.
246. APA. Diagnostic and statistical manual of mental disorders : DSM-5-tr. 5th ed. Washington, DC: American Psychiatric Association Publishing.; 2022.
247. ICD. International Classification of Diseases. 11th Revision ed2022 February 2022.

248. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017;4(4):310-9.
249. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, et al. Brain Imaging of the Cortex in ADHD: A Coordinated Analysis of Large-Scale Clinical and Population-Based Samples. Am J Psychiatry. 2019;176(7):531-42.
250. Sato JR, Hoexter MQ, Castellanos XF, Rohde LA. Abnormal brain connectivity patterns in adults with ADHD: a coherence study. PLoS One. 2012;7(9):e45671.
251. McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, et al. Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. JAMA Psychiatry. 2013;70(12):1329-37.
252. Wolf RC, Plichta MM, Sambataro F, Fallgatter AJ, Jacob C, Lesch KP, et al. Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Human brain mapping. 2009;30(7):2252-66.
253. Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ. Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Human brain mapping. 2010;31(2):287-99.
254. Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(4):356-67.
255. Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, et al. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. Am J Psychiatry. 2009;166(11):1286-94.
256. Posner J, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50(8):828-37.e3.
257. Stoy M, Schlagenhauf F, Schlochtermeier L, Wrase J, Knutson B, Lehmkuhl U, et al. Reward processing in male adults with childhood ADHD--a comparison between drug-naïve and methylphenidate-treated subjects. Psychopharmacology. 2011;215(3):467-81.
258. Ströhle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, et al. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. NeuroImage. 2008;39(3):966-72.
259. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biological psychiatry. 2007;61(5):720-4.
260. Costa Dias TG, Wilson VB, Bathula DR, Iyer SP, Mills KL, Thurlow BL, et al. Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2013;23(1):33-45.
261. Rosello B, Berenguer C, Raga JM, Baixauli I, Miranda A. Executive functions, effortful control, and emotional lability in adults with ADHD. implications for functional outcomes. Psychiatry Res. 2020;293:113375.
262. Mayer JS, Brandt GA, Medda J, Basten U, Grimm O, Reif A, et al. Depressive symptoms in youth with ADHD: the role of impairments in cognitive emotion regulation. Eur Arch Psychiatry Clin Neurosci. 2022;272(5):793-806.
263. Welkie J, Babinski DE, Neely KA. Sex and Emotion Regulation Difficulties Contribute to Depression in Young Adults With Attention-Deficit/Hyperactivity Disorder. Psychol Rep. 2021;124(2):596-610.
264. Sanabra M, Gómez-Hinojosa T, Grau N, Alda JA. Deficient Emotional Self-Regulation and Sleep Problems in ADHD with and without Pharmacological Treatment. J Atten Disord. 2022;26(3):426-33.
265. Frick MA, Darling Rasmussen P, Brocki KC. Can attachment predict core and comorbid symptoms of attention-deficit/hyperactivity disorder beyond executive functions and emotion regulation? Br J Clin Psychol. 2022;61(1):93-111.

266. Surman CB, Biederman J, Spencer T, Miller CA, McDermott KM, Faraone SV. Understanding deficient emotional self-regulation in adults with attention deficit hyperactivity disorder: a controlled study. Atten Defic Hyperact Disord. 2013;5(3):273-81.
267. Williams LM, Hermens DF, Palmer D, Kohn M, Clarke S, Keage H, et al. Misinterpreting emotional expressions in attention-deficit/hyperactivity disorder: evidence for a neural marker and stimulant effects. Biological psychiatry. 2008;63(10):917-26.
268. Faraone SV, Rostain AL, Blader J, Busch B, Childress AC, Connor DF, et al. Practitioner Review: Emotional dysregulation in attention-deficit/hyperactivity disorder - implications for clinical recognition and intervention. J Child Psychol Psychiatry. 2019;60(2):133-50.
269. Conzelmann A, Woidich E, Mucha RF, Weyers P, Jacob CP, Lesch KP, et al. Methylphenidate normalizes emotional processing in adult patients with attention-deficit/hyperactivity disorder: preliminary findings. Brain research. 2011;1381:159-66.
270. Rösler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World J Biol Psychiatry. 2010;11(5):709-18.
271. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry. 2007;68(1):93-101.
272. Manos MJ, Brams M, Childress AC, Findling RL, López FA, Jensen PS. Changes in emotions related to medication used to treat ADHD. Part I: literature review. J Atten Disord. 2011;15(2):101-12.
273. Childress AC, Arnold V, Adeyi B, Dirks B, Babcock T, Scheckner B, et al. The effects of lisdexamfetamine dimesylate on emotional lability in children 6 to 12 years of age with ADHD in a double-blind placebo-controlled trial. J Atten Disord. 2014;18(2):123-32.
274. Childress AC, Sallee FR. Emotional Lability in Patients with Attention-Deficit/Hyperactivity Disorder: Impact of Pharmacotherapy. CNS Drugs. 2015;29(8):683-93.
275. Du J, Li J, Wang Y, Jiang Q, Livesley WJ, Jang KL, et al. Event-related potentials in adolescents with combined ADHD and CD disorder: a single stimulus paradigm. Brain and cognition. 2006;60(1):70-5.
276. Schulz KP, Bédard AC, Fan J, Clerkin SM, Dima D, Newcorn JH, et al. Emotional bias of cognitive control in adults with childhood attention-deficit/hyperactivity disorder. NeuroImage Clinical. 2014;5:1-9.
277. Tajima-Pozo K, Yus M, Ruiz-Manrique G, Lewczuk A, Arrazola J, Montañes-Rada F. Amygdala Abnormalities in Adults With ADHD. J Atten Disord. 2018;22(7):671-8.
278. Viering T, Hoekstra PJ, Philipsen A, Naaijen J, Dietrich A, Hartman CA, et al. Functional network topology of the right insula affects emotion dysregulation in hyperactive-impulsive attention-deficit/hyperactivity disorder. Sci Rep. 2021;11(1):15045.
279. Musser ED, Galloway-Long HS, Frick PJ, Nigg JT. Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(2):163-71.e2.
280. Spencer AE, Marin MF, Milad MR, Spencer TJ, Bogucki OE, Pope AL, et al. Abnormal fear circuitry in Attention Deficit Hyperactivity Disorder: A controlled magnetic resonance imaging study. Psychiatry Res Neuroimaging. 2017;262:55-62.
281. Viering T, Naaijen J, van Rooij D, Thiel C, Philipsen A, Dietrich A, et al. Amygdala reactivity and ventromedial prefrontal cortex coupling in the processing of emotional face stimuli in attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry. 2022;31(12):1895-907.
282. Zuberer A, Schwarz L, Kreifelts B, Wildgruber D, Erb M, Fallgatter A, et al. Neural Basis of Impaired Emotion Recognition in Adult Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2022;7(7):680-7.
283. Edel MA, Rudel A, Hubert C, Scheele D, Brüne M, Juckel G, et al. Alexithymia, emotion processing and social anxiety in adults with ADHD. Eur J Med Res. 2010;15(9):403-9.
284. Kiraz S, Sertçelik S, Erdoğan Taycan S. The Relationship Between Alexithymia and Impulsiveness in Adult Attention Deficit and Hyperactivity Disorder. Turk Psikiyatri Derg. 2021;32(2):109-17.

285. Materna L, Wiesner CD, Shushakova A, Trieloff J, Weber N, Engell A, et al. Adult patients with ADHD differ from healthy controls in implicit, but not explicit, emotion regulation. J Psychiatry Neurosci. 2019;44(5):340-9.
286. Schulz KP, Krone B, Adler LA, Bédard AV, Duhoux S, Pedraza J, et al. Lisdexamfetamine Targets Amygdala Mechanisms That Bias Cognitive Control in Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018;3(8):686-93.
287. Roberts W, Milich, R., & Barkley, R. A. Primary symptoms, diagnostic criteria, subtyping, and prevalence of ADHD. In: Barkley RA, editor. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment The Guilford Press; 2015. p. 51–80.
288. Hagstrøm J, Maigaard K, Pagsberg AK, Skov L, Plessen KJ, Vangkilde S. Reappraisal is an effective emotion regulation strategy in children with Tourette syndrome and ADHD. J Behav Ther Exp Psychiatry. 2020;68:101541.
289. Liu Q, Chen W, Preece DA, Xu D, Li H, Liu N, et al. Emotion dysregulation in adults with ADHD: The role of cognitive reappraisal and expressive suppression. Journal of affective disorders. 2022;319:267-76.
290. Morris SSJ, Musser ED, Tenenbaum RB, Ward AR, Martinez J, Raiker JS, et al. Emotion Regulation via the Autonomic Nervous System in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): Replication and Extension. J Abnorm Child Psychol. 2020;48(3):361-73.
291. Musser ED, Backs RW, Schmitt CF, Ablow JC, Measelle JR, Nigg JT. Emotion regulation via the autonomic nervous system in children with attention-deficit/hyperactivity disorder (ADHD). J Abnorm Child Psychol. 2011;39(6):841-52.
292. Walcott CM, Landau S. The relation between disinhibition and emotion regulation in boys with attention deficit hyperactivity disorder. J Clin Child Adolesc Psychol. 2004;33(4):772-82.
293. Musser ED, Nigg JT. Emotion Dysregulation Across Emotion Systems in Attention Deficit/Hyperactivity Disorder. J Clin Child Adolesc Psychol. 2019;48(1):153-65.
294. Treisman A, Fearnley S. The Stroop Test: Selective Attention to Colours and Words. Nature (London). 1969;222(5192):437-9.
295. Herrmann MJ, Ehlis AC, Fallgatter AJ. Prefrontal activation through task requirements of emotional induction measured with NIRS. Biological psychology. 2003;64(3):255-63.
296. Herrmann MJ, Huter T, Plichta MM, Ehlis AC, Alpers GW, Muhlberger A, et al. Enhancement of activity of the primary visual cortex during processing of emotional stimuli as measured with event-related functional near-infrared spectroscopy and event-related potentials. Human brain mapping. 2008;29(1):28-35.
297. Doi H, Nishitani S, Shinohara K. NIRS as a tool for assaying emotional function in the prefrontal cortex. Frontiers in human neuroscience. 2013;7:770.
298. Hoshi Y, Huang J, Kohri S, Iguchi Y, Naya M, Okamoto T, et al. Recognition of human emotions from cerebral blood flow changes in the frontal region: a study with event-related near-infrared spectroscopy. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2011;21(2):e94-101.
299. Yang H, Zhou Z, Liu Y, Ruan Z, Gong H, Luo Q, et al. Gender difference in hemodynamic responses of prefrontal area to emotional stress by near-infrared spectroscopy. Behavioural brain research. 2007;178(1):172-6.
300. Crum Ii JE. Future Applications of Real-World Neuroimaging to Clinical Psychology. Psychological reports. 2020:33294120926669-.
301. Strangman G, Culver JP, Thompson JH, Boas DA. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. NeuroImage. 2002;17(2):719-31.
302. Cui X, Bray S, Bryant DM, Glover GH, Reiss AL. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. NeuroImage. 2011;54(4):2808-21.
303. Everhart DE, Harrison DW. Facial affect perception in anxious and nonanxious men without depression. Psychobiology. 2000;28(1):90-8.
304. Tanida M, Katsuyama M, Sakatani K. Relation between mental stress-induced prefrontal cortex activity and skin conditions: a near-infrared spectroscopy study. Brain research. 2007;1184:210-6.

305. Balconi M, Grippa E, Vanutelli ME. What hemodynamic (fNIRS), electrophysiological (EEG) and autonomic integrated measures can tell us about emotional processing. Brain and cognition. 2015;95:67-76.
306. Ayaz H, Onaral B, Izzetoglu K, Shewokis P, McKendrick R, Parasuraman R. Continuous monitoring of brain dynamics with functional near infrared spectroscopy as a tool for neuroergonomic research: empirical examples and a technological development. Frontiers in human neuroscience. 2013;7(871).
307. Tak S, Uga M, Flandin G, Dan I, Penny WD. Sensor space group analysis for fNIRS data. J Neurosci Methods. 2016;264:103-12.
308. Esteban O, Ciric R, Finc K, Blair RW, Markiewicz CJ, Moodie CA, et al. Analysis of task-based functional MRI data preprocessed with fMRIPrep. Nat Protoc. 2020;15(7):2186-202.
309. Nickerson LD, Smith SM, Öngür D, Beckmann CF. Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. Front Neurosci. 2017;11:115.
310. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. NeuroImage. 2012;62(2):782-90.
311. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage. 2004;23 Suppl 1:S208-19.
312. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, et al. Bayesian analysis of neuroimaging data in FSL. NeuroImage. 2009;45(1 Suppl):S173-86.
313. Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, et al. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain. 2007;130(Pt 9):2375-86.
314. Greco A, Valenza G, Lanata A, Scilingo EP, Citi L. cvxEDA: A Convex Optimization Approach to Electrodermal Activity Processing. IEEE Trans Biomed Eng. 2016;63(4):797-804.
315. Gross JJ. The emerging field of emotion regulation: An integrative review. Review of General Psychology. 1998;2(3)(Special Issue: New Directions in Research on Emotion):271-99.
316. Weiss EM, Golaszewski S, Mottaghy FM, Hofer A, Hausmann A, Kemmler G, et al. Brain activation patterns during a selective attention test—a functional MRI study in healthy volunteers and patients with schizophrenia. Psychiatry research. 2003;123(1):1-15.
317. Wagner G, Sinsel E, Sobanski T, Köhler S, Marinou V, Mentzel H-J, et al. Cortical Inefficiency in Patients with Unipolar Depression: An Event-Related fMRI Study with the Stroop Task. Biological psychiatry (1969). 2006;59(10):958-65.
318. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. A functional MRI comparison of patients with obsessive–compulsive disorder and normal controls during a Chinese character Stroop task. Psychiatry research. 2005;139(2):101-14.
319. Feldman Barrett L, Tugade MM, Engle RW. Individual Differences in Working Memory Capacity and Dual-Process Theories of the Mind. Psychological bulletin. 2004;130(4):553-73.
320. Gray JR. Integration of Emotion and Cognitive Control. Current directions in psychological science : a journal of the American Psychological Society. 2004;13(2):46-8.
321. Bhikram T, Abi-Jaoude E, Sandor P. OCD: obsessive-compulsive … disgust? The role of disgust in obsessive-compulsive disorder. Journal of psychiatry & neuroscience : JPN. 2017;42(5):300-6.
322. Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology. 1993;30(3):261-73.
323. Skolnick AJ. Gender differences when touching something gross: unpleasant? No. Disgusting? Yes! J Gen Psychol. 2013;140(2):144-57.
324. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004;8(4):170-7.
325. Swick D, Ashley V, Turken AU. Left inferior frontal gyrus is critical for response inhibition. BMC neuroscience. 2008;9:102.
326. Bari A, Robbins TW. Inhibition and impulsivity: behavioral and neural basis of response control. Progress in neurobiology. 2013;108:44-79.

327. Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. The European journal of neuroscience. 1998;10(3):1209-13.
328. Gross JJ. Emotion Regulation: Taking Stock and Moving Forward. Emotion (Washington, DC). 2013;13(3):359-65.
329. Sheppes G, Meiran N. Better late than never? On the dynamics of online regulation of sadness using distraction and cognitive reappraisal. Pers Soc Psychol Bull. 2007;33(11):1518-32.
330. Beauregard M. Functional neuroimaging studies of the effects of psychotherapy. Dialogues Clin Neurosci. 2014;16(1):75-81.
331. Barrett LF. The Future of Psychology: Connecting Mind to Brain. Perspect Psychol Sci. 2009;4(4):326-39.
332. Pessoa L. Understanding emotion with brain networks. Curr Opin Behav Sci. 2018;19:19-25.
333. Pessoa L. On the relationship between emotion and cognition. Nat Rev Neurosci. 2008;9(2):148-58.
334. Pessoa L. The cognitive-emotional brain: From interactions to integration. Cambridge, MA, US: MIT Press; 2013. xii, 320-xii, p.
335. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014;171(3):276-93.
336. Cutuli D. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front Syst Neurosci. 2014;8:175.
337. Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Human brain mapping. 2010;31(6):904-16.
338. Motzkin JC, Philippi CL, Wolf RC, Baskaya MK, Koenigs M. Ventromedial Prefrontal Cortex Is Critical for the Regulation of Amygdala Activity in Humans. Biological psychiatry (1969). 2015;77(3):276-84.
339. Damasio AR. REVIEW ■ : Toward a Neurobiology of Emotion and Feeling: Operational Concepts and Hypotheses. The Neuroscientist. 1995;1(1):19-25.
340. Ye Z, Altena E, Nombela C, Housden CR, Maxwell H, Rittman T, et al. Selective serotonin reuptake inhibition modulates response inhibition in Parkinson's disease. Brain. 2014;137(Pt 4):1145-55.
341. O'Hanlon JF, Robbe HWJ, Vermeeren A, Van Leeuwen C, Danjou PE. Venlafaxine's effects on healthy volunteers' driving, psychomotor, and vigilance performance during 15-day fixed and incremental dosing regimens. Journal of clinical psychopharmacology. 1998;18(3):212-21.
342. Schmitt JA, Ramaekers JG, Kruizinga MJ, van Boxtel MP, Vuurman EF, Riedel WJ. Additional dopamine reuptake inhibition attenuates vigilance impairment induced by serotonin reuptake inhibition in man. J Psychopharmacol. 2002;16(3):207-14.
343. Ramaekers JG, Muntjewerff ND, O' Hanlon J. A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. British journal of clinical pharmacology. 1995;39(4):397-404.
344. Brown HD, Amodeo DA, Sweeney JA, Ragozzino ME. The selective serotonin reuptake inhibitor, escitalopram, enhances inhibition of prepotent responding and spatial reversal learning. Journal of Psychopharmacology. 2012;26(11):1443-55.
345. Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion. Science. 2004;304(5672):878-80.
346. Kanen JW, Ersche KD, Fineberg NA, Robbins TW, Cardinal RN. Computational modelling reveals contrasting effects on reinforcement learning and cognitive flexibility in stimulant use disorder and obsessive-compulsive disorder: remediating effects of dopaminergic D2/3 receptor agents. Psychopharmacology. 2019;236(8):2337-58.
347. Rygula R, Clarke HF, Cardinal RN, Cockcroft GJ, Xia J, Dalley JW, et al. Role of Central Serotonin in Anticipation of Rewarding and Punishing Outcomes: Effects of Selective Amygdala or Orbitofrontal 5-HT Depletion. Cerebral Cortex. 2014;25(9):3064-76.
348. Murphy SE, Norbury R, O'Sullivan U, Cowen PJ, Harmer CJ. Effect of a single dose of citalopram on amygdala response to emotional faces. The British journal of psychiatry : the journal of mental science. 2009;194(6):535-40.

349. Freedman LJ, Shi C. Monoaminergic innervation of the macaque extended amygdala. Neuroscience. 2001;104(4):1067-84.
350. Levy BJ, Wagner AD. Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. Ann N Y Acad Sci. 2011;1224(1):40-62.
351. Cano-Colino M, Almeida R, Gomez-Cabrero D, Artigas F, Compte A. Serotonin regulates performance nonmonotonically in a spatial working memory network. Cerebral cortex (New York, NY 1991). 2014;24(9):2449-63.
352. Kuppens P, Allen NB, Sheeber LB. Emotional inertia and psychological maladjustment. Psychol Sci. 2010;21(7):984-91.
353. Baez-Lugo S, Deza-Araujo YI, Maradan C, Collette F, Lutz A, Marchant NL, et al. Exposure to negative socio-emotional events induces sustained alteration of resting-state brain networks in older adults. Nature Aging. 2023;3(1):105-20.
354. Waugh CE, Hamilton JP, Gotlib IH. The neural temporal dynamics of the intensity of emotional experience. NeuroImage. 2010;49(2):1699-707.
355. Péron J, Grandjean D, Drapier S, Vérin M. Effect of dopamine therapy on nonverbal affect burst recognition in Parkinson's disease. PLoS One. 2014;9(3):e90092.
356. Zhu B, Chen C, Moyzis RK, Dong Q, Chen C, He Q, et al. Genetic variations in the dopamine system and facial expression recognition in healthy chinese college students. Neuropsychobiology. 2012;65(2):83-9.
357. Wittmann MK, Fouragnan E, Folloni D, Klein-Flügge MC, Chau BKH, Khamassi M, et al. Global reward state affects learning and activity in raphe nucleus and anterior insula in monkeys. Nat Commun. 2020;11(1):3771.
358. Hayashi K, Nakao K, Nakamura K. Appetitive and aversive information coding in the primate dorsal raphé nucleus. J Neurosci. 2015;35(15):6195-208.
359. Forster GL, Feng N, Watt MJ, Korzan WJ, Mouw NJ, Summers CH, et al. Corticotropin-releasing factor in the dorsal raphe elicits temporally distinct serotonergic responses in the limbic system in relation to fear behavior. Neuroscience. 2006;141(2):1047-55.
360. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science. 2008;320(5874):385-8.
361. Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci. 2005;8(3):365-71.
362. Matias S, Lottem E, Dugué GP, Mainen ZF. Activity patterns of serotonin neurons underlying cognitive flexibility. Elife. 2017;6.
363. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry. 2009;14(8):746-54.
364. Branchi I. The double edged sword of neural plasticity: increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. Psychoneuroendocrinology. 2011;36(3):339-51.
365. Friston K. The free-energy principle: a unified brain theory? Nat Rev Neurosci. 2010;11(2):127-38.
366. Robbins TW. Arousal systems and attentional processes. Biological psychology. 1997;45(1-3):57-71.
367. Scholl J, Kolling N, Nelissen N, Browning M, Rushworth MF, Harmer CJ. Beyond negative valence: 2-week administration of a serotonergic antidepressant enhances both reward and effort learning signals. PLoS Biol. 2017;15(2):e2000756.
368. Scholes KE, Harrison BJ, O'Neill BV, Leung S, Croft RJ, Pipingas A, et al. Acute serotonin and dopamine depletion improves attentional control: findings from the stroop task. Neuropsychopharmacology. 2007;32(7):1600-10.
369. "Serotonin: from neural circuits to adaptive behavior" [Internet]. 2017. Available from: www.fens.org/Training/FENS-Schools/Video-Educational-Material/.