Contributions of Human Prefrontal Cortex to the Recogitation of Thought

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Declaration

I, James Ernest Crum II, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Publications

The following publications were produced from work undertaken as part of this thesis:

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Abstract

Human beings have a unique ability to not only verbally articulate past and present experiences, as well as potential future ones, but also evaluate the mental representations of such things. Some evaluations do little good, in that they poorly reflect facts, create needless emotional distress, and contribute to the obstruction of personal goals, whereas some evaluations are the converse: They are grounded in logic, empiricism, and pragmatism and, therefore, are functional rather than dysfunctional. The aim of non-pharmacological mental health interventions is to revise dysfunctional thoughts into more adaptive, healthier ones; however, the neurocognitive mechanisms driving cognitive change have hitherto remained unclear. Therefore, this thesis examines the role of the prefrontal cortex (PFC) in this aspect of human higher cognition using the relatively new method of functional near-infrared spectroscopy (fNIRS). Chapter 1 advances *recogitation* as the mental ability on which cognitive restructuring largely depends, concluding that, as a cognitive task, it is a form of open-ended human problem-solving that uses metacognitive and reasoning faculties. Because these faculties share similar executive resources, Chapter 2 discusses the systems in the brain involved in controlled information processing, specifically the nature of executive functions and their neural bases. Chapter 3 builds on these ideas to propose an information-processing model of recogitation, which predicts the roles of different subsystems localized within the PFC and elsewhere in the context of emotion regulation. This chapter also highlights several theoretical and empirical challenges to investigating this neurocognitive theory and proposes some solutions, such as to use experimental designs that are more ecologically valid. Chapter 4 focuses on a neuroimaging method that is best suited to investigating questions of spatial localization in ecological experiments, namely functional near-infrared spectroscopy (fNIRS). Chapter 5 then

demonstrates a novel approach to investigating the neural bases of interpersonal interactions in clinical settings using fNIRS. Chapter 6 explores physical activity as a ‘bottom-up’ approach to upregulating the PFC, in that it might help clinical populations with executive deficits to regulate their mental health from the ‘top-down’. Chapter 7 addresses some of the methodological issues of investigating clinical interactions and physical activity in more naturalistic settings by assessing an approach to recovering functional events from observed brain data. Chapter 8 draws several conclusions about the role of the PFC in improving psychological as well as physiological well-being, particularly that rostral PFC is inextricably involved in the cognitive effort to modulate dysfunctional thoughts, and proposes some important future directions for ecological research in cognitive neuroscience; for example, psychotherapy is perhaps too physically stagnant, so integrating exercise into treatment environments might boost the effectiveness of intervention strategies.

Impact statement

This work has several theoretical, methodological, and practical implications that could impact research in clinical cognitive neuroscience and strategies in clinical institutions. Experiments that place greater emphasis on being representative of the real-world situations in which people behave and adapt have the advantage of capturing a more diverse set of phenomena, including those which are not so easily observed in traditional laboratory environments. For example, ecological validity can be increased by adopting a multi-person neuroscience approach by which live interactions between two or more people are observed. Assessing the intra- and inter-brain dynamics supporting interpersonal interactions in clinical situations might help to reveal the neurocognitive mechanisms underlying treatment effects, such as changes in outcome measures in mental health interventions. Outside of academia, such observations could impact professional practice and translate into a better understanding of what clinical strategies should be developed or adapted to optimize the effectiveness of clinician-client interactions. This would help to accelerate the closing of the 'theory-practice' gap between clinical researchers and practitioners. In addition, future research that extends the present work on interrelations between physical activity and cognitive functioning can take the step from basic to applied research in investigating the feasibility and efficacy of integrating physical activity into some treatment environments. These clinical implications should extend across different types of clinical and non-clinical populations, which could ultimately impact public health at an international level.

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To Andrew Freeman, LISW

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PART I

THEORETICAL UNDERPINNINGS

Chapter 1: On the Recogitation of Thought

1.1 Introduction

The human mind is exceptional in its capacity to think carefully, or cogitate, about the perceptions and sensations it encounters in everyday life as well as the things that are not encountered, but self-generated (i.e., stimulus-independent thought). For example, planning a novel sequence of behavioral actions to achieve a goal-related outcome is a ‘thinking’ task that calls for cognitive functions such as attention to be directed toward both types of representation, such as features of the problem and future intentions that might solve it. Chess is a concrete example of such a mental task (De Groot, 1965). To find the best move, a player needs to consider exogenous parameters of the board, such as the opponent’s position in relation to one’s own, and endogenous, self-generated information, such as future moves based on a hypothetical contingency. Sometimes certain problems arise in everyday life that task the mind with determining something from information that is purely endogenous in nature—for instance, what a future visit to a novel environment might be like—and sometimes the mind is itself the object of endogenous thought. These situations are ‘metacognitive’ in the sense that people are aware of properties of the mind and can evaluate them in different ways. Continuing with the example of chess, an estimation of one’s skill at anticipating opponents’ moves is a metacognitive judgment.

The ability to detect and assess one’s judgements, beliefs, or desires (i.e., propositional attitudes) becomes quite useful when people have the goal to maintain accurate and adaptive representations of the self, others, and world. Having this general, long-term goal makes sense given the innate fallibility of the human mind; fortunately, the mind is also corrigible and, therefore, plastic enough to enact rudimentary modifications to propositional attitudes that are encoded in long-term memory (e.g., semantic networks). The present chapter advances the hypothesis that a metacognitive procedure supports these cognitive modifications, namely a procedure or mental effort that reconsiders the validity of thought: recogitation (*re-* + *cog-* +*agitare*: to again-jointly-turn over). At the level of commonsense-psychological explanation, recogitation is a means of revising propositional attitudes to foster more rational, adaptive beliefs about the self, others, and world, resonating with philosophical ideas such as transvaluation (Nietzsche, 1878/1924) and critical rationalism (Popper, 1956/2002). However, little is understood at the levels of information processing and the brain of its cognitive and functional underpinnings. Therefore, the present chapter draws from clinical psychology to lay the conceptual groundwork for cognitive theorizing in information-processing terms. That is, the real-world situations in which recogitation and its connection to well-being are perhaps best exemplified are clinical ones, and it is these situations from which we stand to learn the most.

1.2 Foundations of human normativity and its dysfunction

To think of the world, self, and others not only as they are but as they ought to be is a core feature of the human psychological constitution (normativity). Convention has maintained that the principal element of the human mind is intelligence, but others have recently advanced that the basic ability to imagine the future (i.e., prospection) is most definitive (Seligman, Railton, Baumeister, & Sripada, 2016): People are *Homo prospectus* rather than *Homo sapiens.* On this view, human beings are unique in their ability to simulate future states (Schacter & Addis, 2007; Schacter, Norman, & Koutstaal, 1998), form specific plans and contingencies to realize them (Shallice, 1988), and multitask over long periods of time to satisfy goal states (Burgess, 2000). Whatever is most definitive about the human mind, both prospection and intelligence are both probably the result of proportional changes in brain areas such as the frontal lobes and hippocampal formation (Goldberg, 2001), and they are predicated on the same sense of psychological normativity. For example, prospection is normative in the sense that its cognitive functions work together to satisfy active goals states—states to which it is believed that thought and action ought to be dedicated.

In other words, a definitive feature of the organization of mind is that it consists of basic operations for processing information (e.g., Kant, 1787/2007; see Ariew & Watkins, 2009 for an anthology): Rather than passively recording and storing information, these functions actively transform it in favor of goal states (Shallice & Cooper, 2011). At a higher level of psychological explanation, this *active* thinking represents a directedness of processing that is largely captured in the notion of *intentionality* (Brentano, 1874/1973), a property inherent to the everyday propositional attitudes that human beings adopt about the world, self, and others (Churchland & Churchland, 2013). People's intentionality is shared in many situations: in environments wherein two or more autonomous agents "…influence each other by modulating a bidirectional information exchange in real time and by co-regulating implicit and explicit aspects of their social behavior" (Crivelli & Balconi, 2017). Such a collective intention, as an emergent property of the inter-strategic plans of conspecifics (Searle, 1990), forms the essence of dynamic social cooperation; however, social understanding and interaction extend beyond shared intentionality, since some interactions are devoid of this sense of coordination and, therefore, the rudiments of social engagement are likely the mechanisms uniquely dedicated to general interactive situations (e.g., Di Paolo & De Jaegher, 2012) and the general-purpose mechanisms applied to them (e.g., Baron-Cohen, 1995). Thus, the normative orientation of human thought is captured by the concepts of active thought and intentionality at different levels of explanation.

Sometimes the evaluations and interpretations people generate about goal-relevant stimuli (e.g., beliefs, appraisals) are inaccurate—a mental fallibility of human beings. The inaccuracies of these propositions constitute reasons in favor of revision. For example, empirical facts constitute practical reasons in favor of both wanting a particular state of affairs to occur and to act in ways that realize it; if there are reasons to warrant a revision in only a belief and not also a concomitant action, such reasons are *epistemic* (Parfit, 2011). So, the evidence indicative of a belief being true is a reason to adopt it, and it should be renounced if reasons count in favor of falsehood. Take this simple example: That Earth has the objective property of being an irregularly shaped ellipsoid is an epistemic reason to revise any belief to the contrary. Here is a slightly more complex and timelier example that is tied to well-being: Amid a global pandemic, that wearing masks over one's mouth and nose markedly prevents one from transmitting viruses to others is a sufficient reason to adhere to policies requiring them. However, if it is also true that doing this will not detract from one's well-being, but a person falsely believes that, for instance, wearing a mask means inhaling dangerous amounts of carbon dioxide, then the individual holds the erroneous belief that one is faced with a case of the dualism of practical reason (Sidgwick, 1874/2012): a dilemma in which one is faced with choosing what is good for the self over that of others, or vice versa. However, because the well-being of others is not preserved at the cost of one's own, there is most reason to renounce this view. Another example is that physical activity protects against neurological and epigenetic diatheses, as well as the pernicious effects of a sedentary lifestyle, and improves cognitive functions and mood (see C. Di Liegro, Schiera, Proia, & I. Di Liegro, 2019) are reasons against believing that exercise is a waste of time.

Sometimes the normative propositions people generate about the self, others, and world are so inaccurate—so ungrounded in reason, logic, empiricism, and pragmatism—that they have deleterious effects on mental health and, therefore, are objects of cognitive change in clinical psychology. The role of cognition in emotion and mental health is one of the oldest subjects of discussion in psychology, tracing as far back as ancient Greek philosophers such as Epictetus in 108$_{\text{AD}}$, and was a topic around which there was considerable debate in the 20th century (see Lazarus, 1999, for review). An early example during this epoch of a model propounding the mediating role of cognition is the *stimulus-organism-response* model of William James' protégé, Robert Woodworth (1918), but it was not until around the advent of what many consider the so-called 'Cognitive Revolution' during the mid-20th century that more explicit cognitive mediation models describing affective responding were formally developed. For example, clinical psychology has long appreciated cognitive mediation in models of the pathogenesis of psychopathological symptoms (see Hergenhahn & Henley, 2014, for a review of this history), with Albert Ellis' (1958, 1962) *activating event-belief-consequence* (ABC) model of emotional distress.

According to this framework, emotional responses are largely the consequence of cognitive evaluations (i.e., appraisals; see Scherer, Schorr, & Johnstone, 2001, for review), which are a particular class of propositional attitude (Bermúdez, 2005). Appraisals are comprised of a descriptive component that represents features of goal-(in)congruent stimuli (i.e., schema). They also have a normative component that represents the perceived significance of this information to one's personal well-being (Lazarus & Smith, 1988): an affective valuation. Interactions between these factors typically promote adaptive and appropriate thinking, feeling, and behaving within the common range of human functioning; however, when cognitive appraisals engender maladaptive behavior and negative emotional distress, as well as future goal obstruction, they are designated as dysfunctional (David, Lynn, & Ellis, 2010). Theories of emotion generally accord to what has been termed the basic *modal model* of emotion, according to which emotional responses are part of a cyclic sequence: the *situation-attention-appraisal-*

response sequence (Figure 1.1; Ochsner & Gross, 2014); this model and future box- and –arrow diagrams are shown using the COGENT formalism (Figure 1.2; see Shallice & Cooper, 2011).

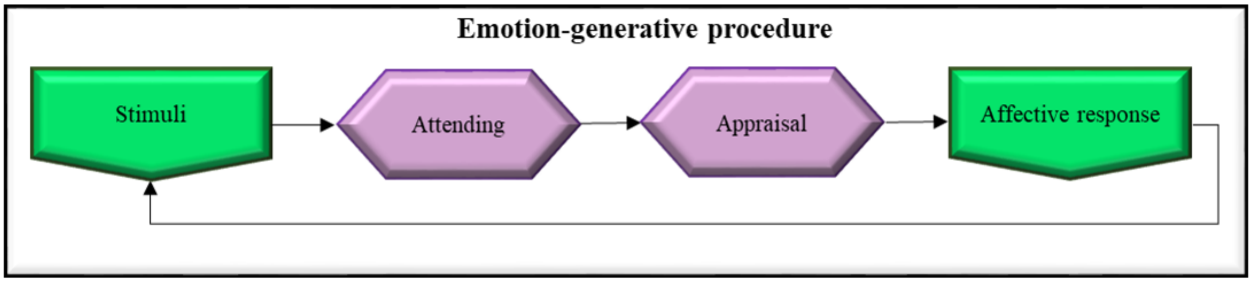
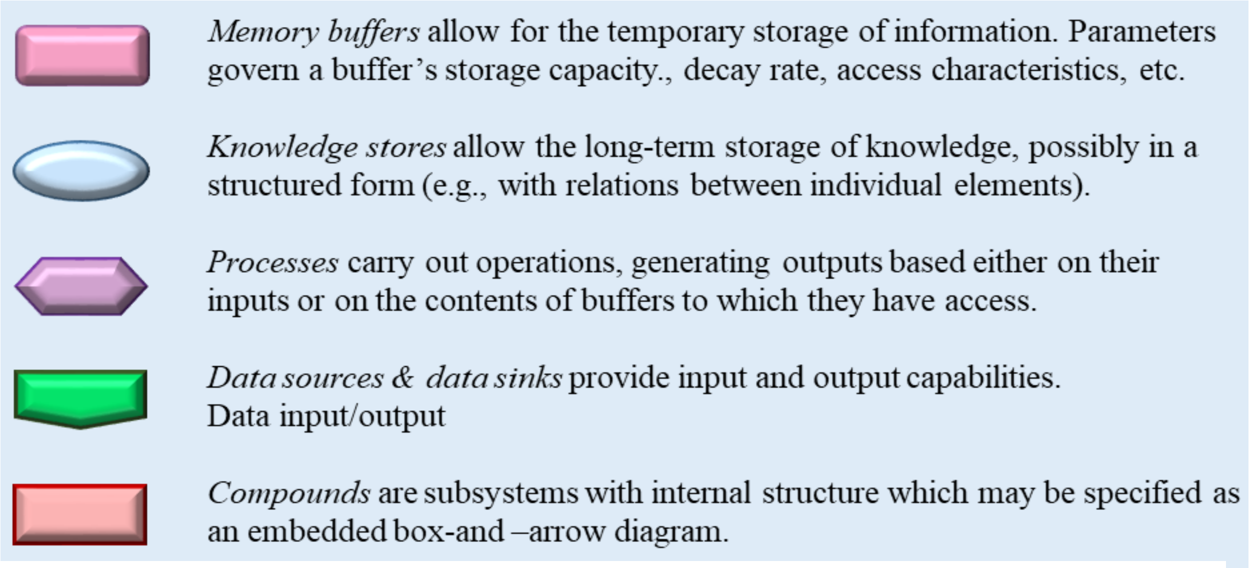


Figure 1.1 The modal model of emotion generation (see Gross, 2014).



Memory buffers allow for the temporary storage of information. Parameters govern a buffer's storage capacity., decay rate, access characteristics, etc.

Knowledge stores allow the long-term storage of knowledge, possibly in a structured form (e.g., with relations between individual elements).

Processes carry out operations, generating outputs based either on their inputs or on the contents of buffers to which they have access.

Data sources & data sinks provide input and output capabilities.
Data input/output

Compounds are subsystems with internal structure which may be specified as an embedded box-and –arrow diagram.

Figure 1.2 Box- and -arrow diagram key based on the COGENT formalism. Adapted from "*On the Organisation of Mind*," by Shallice and Cooper, 2011, p. 500, with permission from Oxford University Press.

Although there are several theoretical frameworks within appraisal theory (e.g., Lazarus, 2001; Roseman, 2001; Scherer, 2001), there are core principles on which all systems of appraisal converge (Scherer et al., 2001). Namely, they postulate that appraisals differentiate emotions: Distinct patterns of appraisal engender qualitatively different emotions and predict variance in the dynamics—the intensity, frequency, and duration—of particular emotions. In addition, it is maintained that appraisal has evolved to facilitate adaptive responding, is involved in both conscious and unconscious information processing, and is universal across cultures. So, cognition is contemporarily understood as a necessary mediator of the emotion-generative process, including those emotions which people would rather not experience—those which detract from psychological well-being.

However, it is worth noting that although dysfunctional appraisals are those tending to promote emotional distress and maladaptive behavior, they are not inherently etiopathogenic; otherwise, 99% of people would have psychopathological conditions. Conventionally, clinicians employ nomothetic strategies to identify the class of psychopathology into which clients' presenting problems fall, with this type of diagnostic strategy aiming to categorically classify psychopathological symptoms (Barlow, Durand, Lalumiere, & Hofmann, 2021). For example, formal nosological systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the International Classification of Diseases (ICD-10) are widely used by mental health professionals to diagnose and treat psychopathological conditions (American Psychiatric Association [APA], 2013; World Health Organization, 1993). These systems are largely categorical, meaning in the strictest sense that a person is either mentally disturbed or not; that is, a mental disorder is either present or absent (Kecmanovic, 2012). But these systems also contain some dimensional elements, in that some diagnostic criteria are quantifiable in terms of an interval level of measurement; cognitive, emotive, behavioral, and physiological responses are indexed by scales of frequency, intensity, and duration. For instance, the Beck Depression Inventory is a widely used self-report measure in clinical practice to index dysfunctional schema about the self and world (Beck, Steer, & Brown, 1996; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). In recent years, there has been a push for incorporating more dimensional features into the formal nosology, and for even adopting a predominantly dimensional approach (see Brown & Barlow, 2005, for review). In addition to the collection of psychometric data, computational, multifactorial approaches to psychopathology in cognitive neuroscientific research are becoming increasingly popular (see Heinz, 2017, for review) and powerful in their aim to improve the reliability and validity of diagnostic classification by providing important, idiographic information about individuals that might better account for within-category heterogeneity (Kecmanovic, 2012).

Importantly, psychopathologists have traditionally posited mental disorders as etiologically disparate, such that they have distinct causative factors (e.g., Kraepelin, 1913), but this is not as ostensibly clear as 20th century theoreticians once thought. Contemporary clinical psychological research has amassed a multitude of interdisciplinary investigations of different classes of data which together suggest the idea that the same etiopathogenic mechanisms can interact to produce different or the same disorders (see Barlow et al., 2021, for review). In fact, such mechanisms are not largely thought of as being inherently etiopathogenic because they necessarily depend on these interactions to yield psychopathological symptoms. Therefore, they are more readily considered as *vulnerability* factors in diathesis-stress models, according to which disease symptoms are the product of a diathesis or diatheses interacting with environmental factor(s). Such models are widely used in medicine and are not unique to psychopathology. This approach to understanding the etiopathogenesis of psychopathological symptoms can conceptually encompass categories of disorder whose core diatheses are understood as largely genetic and neurobiological, such as neurodevelopmental and neurocognitive diseases. For example, although impairments under these categories might manifest socially, cognitively, and so forth, they do not reduce to them etiologically, but to the interaction of neurobiological and genetic vulnerability factors with ecological ones (e.g., Liu, Jiao, & Shen, 2018; Siu & Weksberg, 2017).

However, vulnerability factors consist not only of low-level, biological phenomena but also of phenomena at higher levels of scientific explanation: cognitive, social, ecological, and so forth (e.g., Os, Kenis, & Rutten, 2010); conversely, factors relating to mental health that cultivate it or hinder its onset, severity, or course are referred to as prophylactic or protective factors. Factors that are cognitive in nature receive their greatest emphasis in the cognitive-vulnerability models of the theories of cognitive-behavioral therapy (CBT)-based forms of psychotherapy (Beck, 1963, 1976; Beck, 2011; Ellis, 1994; Ellis & Dryden, 2007; David et al., 2010). Although CBT-based schools of psychotherapy differ relative to one another on the nature of the dysfunctional cognitive operations underpinning emotional distress and particular types of mental illness and, therefore, also on the appropriate objects of cognitive change, there are a number of rudimentary principles on which they agree (Crum, 2019). Namely, they differ from older schools of psychotherapy (e.g., psychoanalysis [Freud, 1917/1963], person-centered therapy [Rogers, 1942], etc.) in their de-emphasis of the past and adoption of an active-directive method of restructuring patients’ thoughts (see Austad, 2009 for a history of psychotherapy; see also Hofmann, 2014; Kuehlwein & Rosen, 1993). More specifically, they accord to not only the principle of cognitive mediation (i.e., active thinking) but also the principle of cognitive penetrability (Bermúdez, 2005). This is the idea that dysfunctional appraisals are modifiable by the same principles underpinning neurobiological change: activity-dependent, plasticity mechanisms (i.e., long-term potentiation; see Baudry & Davis, 1997).

Classical CBT-based forms of psychotherapy theoretically diverge at this point, in that cognitive therapy (CT) (Beck, 1976) maintains that the core dysfunctional cognitive-vulnerability factor is the depreciation of self-worth (e.g., worthlessness and helplessness schema) whereas rational-emotive behavior therapy (REBT) holds that it is the demandingness of irrational appraisals that drives the intensity, frequency, and duration of their emotive corollaries (Ellis, Ellis, 1987, 2003). Interestingly, the evidence seems to be accruing in favor Ellis' postulation (e.g., Buschmann et al., 2018; DiLorenzo, David, & Montgomery, 2007, 2011; Hyland, Shevlin, Adamson, & Boduszek, 2013, 2014; see David, Schnur & Belloiu, 2002; see also Hyland & Boduszek, 2012). Whatever the most critical object of cognitive change to cultivate mental health, all dysfunctional cognitions tend to share the feature of being absolutistic, erroneous, and inflexible and, therefore, of not being readily amenable to skepticism and incredulity. That is, they have an extreme, normative propositional nature towards the self, others, or the world that some event or situation *ought* not to be goal incongruent. This inordinate exhibition of intentionality is perhaps key to better understanding problems of emotion dysregulation and maladaptive behavior, particularly its mutability. The following section considers such cognitive change in mental health interventions, particularly the application of cognitive restructuring strategies (mechanisms *of* change) to dysfunctional appraisals (mechanisms *for* change).

1.3 From clinical practice to cognitive theorizing

The many initiatives and movements away from mental health stigma in recent years have been exceedingly impactful, with more people on average reaching out for help (Schnyder et al. 2017). In addition to receiving face-to-face assistance from clinicians, many are using internet-based interventions of well-established psychotherapies such as cognitive behavioral therapy (iCBT), with several reviews and meta-analyses suggesting effectiveness for reducing mild to moderate psychopathological symptoms (Andersson & Cuijpers, 2009; Andrews et al.

2018; Cuijpers et al. 2009; Ebert et al. 2015; Heber et al. 2017; D. Richards, & T. Richards, 2012; Richards, Enrique, Palacios, & Duffy, 2018; Williams, Blackwell, Mackenzie, Holmes, & Andrews, 2013). Mental health interventions are an important resource for people because familial, societal, and evolutionary influences feed a propensity in most human beings to sometimes have irrational, unhelpful thoughts which make self-regulation difficult (Lazarus & Folkman, 1984). These interventions create an ideal naturalistic situation in which these irrational thoughts are explicitly and interpersonally disputed on their epistemic merits, but what are the conditions of cognitive change in these clinical settings?

As conceptualized in the present exemplar of CBT theory, it is clear from the outset that there are probably a number of factors involved in treating dysfunctional cognitive operations; there is likely not a single, necessary condition. The relative criticality of these factors to the process of psychotherapeutic change, particularly cognitive change, largely depends on the form of CBT under consideration: Different schools of CBT postulate different mechanisms of change (see Austad, 2009; Kuehlwein & Rosen, 1993, for reviews) and differ by their object to modify the function or content of these mechanisms (see Herbert & Cardaciotto, 2005, for review). Therefore, the question posed above might indeed seem relative to the form of CBT under consideration, but there are some ideas regarding cognitive change to which almost all CBT-based treatments accord (Hofmann, 2014). There is a rudimentary emphasis in general CBT theory on the aforementioned ideas that certain types of cognition, such as appraisals and schemas, influence the expression of emotional distress and maladaptive behavior (i.e., cognitive mediation) and that dysfunctional types are corrigible (i.e., cognitive penetrability) through therapist-led efforts that target the dysfunctional cognitions engendering emotional distress and maladaptive behavior (i.e., cognitive restructuring) (Clark, 2014; Clen, Mennin, & Fresco, 2013).

These efforts typically consist of verbal intervention strategies. Often these consist of a Socratic procedure for conceptually disputing propositions (Beal, Kopec, & DiGiuseppe, 1996; Ellis & Dryden, 2007).

In addition, having clients discern that their beliefs, emotions, and behaviors all relate in basic and complex ways is crucial to facilitating opportunities to achieve cognitive change (A. T. Beck, 1976; J. S. Beck, 1995; Clark, 1995; David et al., 2010; Ellis, 1994). Cultivating this insight—that is, the principle of cognitive mediation—in clients has been referred to as establishing the *b-c connection* in clinical practice (belief-consequence connection; Dryden, 2006). The idea behind establishing this connection in clients and why it is important to progress in CBT is that dysfunctional cognitions are more susceptible to modification when individuals are aware of the interrelationships between their thinking, feeling, and behaving—when they can actively identify their beliefs about goal-incongruent events. Interestingly, thinking about one's or others' thinking in this way is likely served by some metacognitive, mentalizing subsystem (Wells & Purdon, 1999). However, establishing this insight in practice can often be problematic. For instance, clients typically agree, after some resistance, with the general idea that people have influence over the regulation of their emotions; however, seldom do they succeed in applying this understanding to future, novel events (Ellis & Dryden, 2007). To help individuals acknowledge more responsibility for their states of functioning, therapists are frequently tasked with having to inculcate, and re-inculcate, individuals with the b-c connection (Ellis, 2002). In these situations, it becomes requisite to challenge clients' beliefs about how emotions and behaviors are engendered in human beings, and there are a number of strategies by which to carry out this type of disputation. For example, Dryden (2006) explicated that it is frequently useful to appeal to the idea that there would be a complete lack of variance in how people emotionally respond to things if thought and beliefs held no influence over emotional distress. This logic is typically helpful, with clients eventually learning to identify and articulate the thoughts they have about goal-related things.

So, there are conceptual differences between leading forms of psychotherapy such as CBT-based schools of treatment, but most accord to the idea that helping clients develop insight into the ways in which their thinking influences their emotions and behaviors is crucial to the process of cognitive restructuring (Hofmann, 2014; see Clark, 2014, for review). Clinical practitioners help clients to identify beliefs about stressful environmental events, to distinguish the irrational from rational aspects of the beliefs, and to challenge the irrational ones empirically, logically, and pragmatically. Consequently, clients renounce their erroneous evaluations and form rational ones, which facilitates emotional and behavioral responding that is more functional (David, Szentagotai, Eva, & Macavei, 2005). Post-treatment independence and aptitude in using these intervention strategies ultimately combats the human proclivity to self-generate and uncritically adopt tenuous thoughts—ideas that do little good towards having an equanimity of mind. However, the information-processing systems supporting these strategies in the brain remain unclear, but the clinical interpersonal interactions in which they are typically used are a major clue; this is likely the facet of treatment in which much cognitive change is achieved at the level of information processing.

Similar to the ability of cognitive neuropsychology to deduce aspects of the nature of cognitive functions and their spatial localizations from the brain lesions impairing them (Shallice, 1988), clinical psychological theory and observations in practice offer not in-themselves a scientific method of deduction but a window into a cognitive neuroscientific task analysis: an analysis of the potential mechanisms by which the mind reasons about thoughts to affect unhealthy emotional responses and motivate adaptive behavior. As with any task in which people engage in everyday life, tasks are situations that place certain demands for people to think and act in certain ways. Clinical situations involving mental health interventions typically represent an environment in which there are at least two individuals: a client and clinician. Such a pair of people, or dyad, does not involve phenomena dissimilar to the many other interpersonal interactions in everyday life that are outside the context of psychotherapy. More specifically, the behavioral functions which occur in these situations are almost always shared between the dyad and across situations of social engagement: verbal communication, eye-gaze, and facial gestures, and sometimes emotional responses and motor gestures with hands, arms, legs, and so forth. Importantly, a sense of normativity pervades clinical interpersonal interactions, particularly the dialectical nature of the verbal communication that drives treatment in non-pharmacological interventions. This type of discourse has long been appreciated in philosophy (see Cohen, Curd, & Reeve, 2016, for an anthology), as well as clinical psychology, jurisprudence, and politics.

So, verbal communication is the chief means of facilitating treatment: The aim of the clinician’s dialog is to influence in highly specific ways the information processing of the client. First, clients express to clinicians a number of statements in light recent crises (i.e., goal-incongruent events), reflecting specific dysfunctional cognitive schemas and appraisals and, in turn, clinicians employ various adaptive strategies by which to verbally challenge the veracity of these propositions and supplant them with more rational ones (David et al., 2010). This sense of cognitive change reduces maladaptive behavioral responses and promotes the downregulation of negative emotion in its mediation of future goal-incongruent events (Clen et al., 2014). It is hypothesized that the facet of treatment representing the crux of the clinical objective is not this communication per se, but the ‘thinking’ task of clinicians that supports it: Namely, clinicians need to actively *recogitate* clients' articulated thoughts—that is, to reconsider their utterances in a way that determines what it is about them that makes them irrational. Clinicians subsequently articulate their reasons to clients to help them discern the same things and reach the same epistemic conclusions.

If recogitation is to be understood beyond this level of commonsense-psychological explanation, its description as a mental task should consider also consider situations in which it might be used in the absence of observable behavior (e.g., social interaction). Recall that a major goal of cognitive interventions is to cultivate adaptive thinking tendencies that promote mental health not only within clinical environments but also outside of them (Crum, 2019). This means that clients are to learn to independently recogitate their thoughts about goal-related events in everyday life. An absence of social engagement in these situations might require that recogitation be carried out without interpersonal and verbal cognitive operations. Therefore, these kinds of operations can potentially be ruled out as necessary processing components. This also means that the critical components supporting recogitation are probably not qualitatively different from those which are predominantly and typically carried out in the absence of observable behavior—when thought is stimulus independent (e.g., covert arithmetic). More specifically, it is plausible that a mental process supporting the intervention strategies that cultivate mental health is a metacognitive procedure of endogenous thought, whereby semantic representations (i.e., content of beliefs) are identified, challenged, and rejected: recogitation. Interestingly, although this procedure is not necessarily verbally mediated, it is linguistically so. The propositional attitudes that recogitation presumably processes and manipulates are available to consciousness and inner speech that is endogenous in nature (Bermúdez, 2005); they are available to awareness in a structural linguaform sense (Churchland & Churchland, 2013). But that does not mean forms of propositional attitudes such as beliefs, appraisals, and intentions are to be explained in purely symbolic terms with respect to how the mind models them—by some language-of-thought (e.g., Fodor, 1975). So, from a task analysis perspective, the involvement of information-processing systems in recogitation is presumably different depending on whether maladaptive thoughts are the object of cognitive change in clinical practice or intrapersonal situations.

It is important to note another aspect of language, namely that clients can utter propositions that articulate their appraisals about goal-incongruent events in ways that are virtually unlimited, which likely has some bearing on the overall cognitive task of recogitation. There appear to be a limited number of types of maladaptive attitude (e.g., demandingness, awfulization, self-depreciation, etc.) that contribute to unhealthy negative emotions and moods (Ellis, 1994). That is, individuals share the same thinking tendencies and routinely commit the same cognitive errors (e.g., anxious individuals catastrophizing different states of affairs). However, the verbal expression of these beliefs and appraisals (explicitly and internally) is open to the same combinations and content as the language people use everyday life (Chomsky, 1957/2020). This means that the information representing the input to recogitation is typically novel to clinicians. In addition, although the clinical procedures of practitioners are routine and limited in the sense that they are applied consistently across clients (Hofmann, 2014), instances of verbal intervention are as free as their objects to vary in articulation, substance, and direction. In other words, replies to clients are not limited to a definitive sequence or set of responses to be selected and implemented in each instance; rather, the clinician's thoughts and articulations are generated with as strong an element of novelty as that of clients' in these interpersonal interactions. Therefore, these features of the information that is to be manipulated and the strategy by which to implement it suggest that recognition is a non-routine problem for the mind.

That is, recogitation is an open-ended, ill-structured reasoning problem (see Shallice & Cipoltii, 2018, for review of this class of problem-solving). So, mental health interventions are a special-case application and orchestration of the neurocognitive functions that are somewhat already understood in cognitive neuroscience as being general to informational domains (i.e., domain-general mechanisms, discussed in the following chapter).

In addition, the goal of interventions to encourage the use of this ‘thinking’ task outside clinical settings means that, in information-processing terms, the object is to shift the initiation of recogitation from an other- to self-initiated procedure, revealing a distinct role of learning. People are so psychotherapeutically trained as to successfully recogitate their thoughts unassisted, and this helps prepare clients to deal with real-world situations in which the universe does not conform to the normativity they have imposed on it. This metacognitive procedure is therefore predicated on certain aspects of knowledge. For example, disputing dysfunctional appraisals would be markedly difficult insofar as individuals were devoid of any procedural knowledge on how to first identify them. In this case of initial identification, the insight of cognitive mediation (i.e., b-c connection) is a conceptual prerequisite; people need a cogent understanding of the basic interrelations between thinking, feeling, and behaving to know to search for the beliefs they might have about goal-incongruent events. Although learning this metacognitive knowledge is an important step in the process of psychotherapeutic change on the part of the client, clinicians are individuals who are experts at recogitation: They do not require the explicit instruction of this information during verbal intervention. Such insights are already learned from their vocational training (Dryden 2006). So, the general task instructions for the mind to recogitate thought and action in certain situations should ideally rely on schemata in long-term memory. More specifically, recogitation is not only metacognitive but also largely prospective as a task, especially in its clinical application. Although the absence of such learning requires psychoeducation in clinical practice, it is conceivable that this learning could consist of a training epoch or priming paradigm in the tradition of experimental psychology.

For example, in a proof-of-principle study, Crum (2016) investigated the effects of priming participants with the dialectical discourse that is commonly used in CBT-based treatments. To emulate in a non-clinical environment the clinical paradigms that empirically examine cognitive change as a function of treatment, two groups of participants completed the General Attitude and Belief Scale (GABS), a 55-item self-report measure of irrational beliefs as defined in REBT theory (David et al., 2010) that has demonstrated excellent construct and discriminate validity and internal consistency (Bernard, 1998; Owings et al., 2013). The scale was also counterbalanced to enable independent pre- and post-experimental manipulation scores. After collecting pre-test scores, the experimental group was instructed to carefully study and think critically about several paragraphs for 5 minutes, with each one relating to a particular type of irrational belief. More specifically, there was an irrational belief proposition within each paragraph, then a sentence or two dedicated to encouraging the b-c connection and challenging the validity and soundness of the dysfunctional appraisal using the same tactics used in clinical practice, and finally a sentence or two offering a new, more functional belief for adoption as a conclusion of this disputation. The control group did not receive this dialectical ‘priming’ and waited. Post-test scores of irrational beliefs were collected immediately afterward. Crum (2016) found that levels of irrational belief significantly decreased in the experimental group compared to the control one. Although this study had numerous limitations (e.g., participants did not explicitly challenge the propositions), its findings bolster the idea that recogitation is empirically tractable from the perspective of traditional experimental psychology and outside clinical environments.

1.4 Conclusions

In sum, normativity is a core feature of the human psychological constitution. The mind consists of basic operations for actively transforming information in favor of goal states. Thinking and acting on such states share a sense of intentionality. This is exemplified in the propositional attitudes people form and adopt about what they believe should be—or ought to have been—the case with respect to the self, others, and world. These normative evaluations about the personal significance of goal-incongruent events are ‘appraisals’, which are a critical component of the emotion-generative procedure; they are conceptual, affective valuations. Sometimes these types of propositional attitudes (beliefs, appraisals) are erroneous, inflexible, and absolutistic because people are innately fallible—another important feature of the mind. Left unchecked, these thoughts tend to engender unhealthy negative emotions and moods. That is, appraisals are *dysfunctional* to the extent that they are ungrounded in reason, logic, empiricism, and pragmatism, and relate to emotional distress and future goal obstruction. Rather than being inherently etiopathogenic, dysfunctional appraisals interact with the pathogenesis of psychopathological symptoms in cognitive-vulnerability models. They are therefore the objects of cognitive restructuring in numerous mental health interventions. Verbal intervention strategies form the core facet of this restructuring. Verbal disputation challenges the epistemic veracity of maladaptive thoughts to help clients form healthier, adaptive beliefs and appraisals.

The facts that reveal these thoughts as irrational constitute reasons which count in favor of revising thoughts under consideration. It is hypothesized that *recogitation* is the mental process that generates this information in support of the verbal intervention strategies used in clinical environments. The exemplar of clinical practice constrained a task analysis of the potential cognitive operations of which recogitation is comprised. Namely, the present task analysis has shown that recogitation is a goal-directed and largely endogenous task, in that it need not depend on external stimuli to be carried out successfully. For example, the informational input to this metacognitive procedure might consist of not only uttered propositions but also propositions in memory that are retrieved from past autobiographical events, and prospective propositions constructed from memory. In the clinical domain, this input is typically an appraisal in relation to emotion generation, but sometimes other types of input are challenged, such as logical inferences, future intentions to act, and descriptive statements (true or false declarative statements). The task of recogitating appraisals is other-initiated insofar is facilitated by an interpersonal or computer-based interaction. Self-initiated recogitation in everyday life (e.g., during a goal-incongruent event) is the overarching clinical objective, but difficulties with this might arise if the appropriate procedural memories are not encoded; therefore, additional task parameters are requisite to instill them in practice (e.g., instructions, training, psychoeducation).

That there are different task situations in which recogitation might be used raises the plausibility of differences in the quantitative and qualitative resource requirements of the task. However, the constant in recogitation is that its implementation is probably not routine, such that each instance in which the task is carried out represents a novel, open-ended problem (for both clinicians and clients). Therefore, the relevant information-processing subsystems are likely general to the domain of information on which they operate, in that these cognitive operations are used in many other types of cognitive task that require the modulation of not only semantic representations but also visuospatial and motor ones (Schneider, Owen, & Duncan, 2000).

Importantly, they share a property of *control* in enacting the semantic manipulations that recogitation aims to achieve. In other words, recogitation might best be characterized as a metacognitive procedure for solving an ill-structured, reasoning problem. That such problems place computational demands on specialized information-processing subsystems (cognitive control resources) provides a promising theoretical direction for further developing a psychological theory of recogitation into a neurocognitive one. The following chapter considers the neural systems and localizations into which this form of cognitive control might fractionate.

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Chapter 2: Principles of Frontal Lobe Function

2.1 The control of cognitive operations

Recall from the preceding chapter that the general characterization of the active mind, such as its directedness towards goals and its function to modulate information processing in the service of these ends (Shallice & Cipoltii, 2018). On some views, all thought is goal-directed in this way and all goal-directed thought is equal to problem-solving and, therefore, all thinking is problem-solving (Newell, 1990). Conceptually, then, active thinking encompasses the research domains investigating reasoning, decision-making, and problem-solving. Although all active or *controlled* thought might indeed be equated with problem-solving, this does not necessarily entail that all thinking is such—that problem-solving is the core function of the cognitive system. Shallice and Cooper (2011) keenly point out that there are instances of goal-directed activity which do not involve problem-solving (e.g., responding with a learned sequence) and instances of thinking which are not goal-directed (e.g., associative cognition). Therefore, because all forms of active thinking share normativity in their emergent intentionality, and because this is also the case at least sometimes for more passive, less-goal directed modes of thought, it is insufficient to describe the inner working of the human mind in general terms of the predominant features of its active states; similarly, on the converse, it is insufficient to do so by virtue of its more associative, *automatic* facets, as behaviorism has erroneously committed itself (see Hergenhahn & Henley, 2014, for a historical review). Rather, a more comprehensive account will explain the governing dynamics underlying interactions within this qualitative dichotomization of thought (Shallice, 1988): how the cognitive system is so organized as to yield appropriate, adaptive responses to experiences of situations for which the more passively mediating aspects of the mind are both ill- and well-equipped.

Theorizing in experimental psychology and cognitive science has traditionally bifurcated the nature of the information-processing mind by positing thought as either controlled or automatic (e.g., Atkinson & Shiffrin, 1968; Shiffrin & Schneider, 1977). For example, a number of different interpretations of dual-interacting systems have been advanced defining them as rule-based and associative (e.g., Sloman, 1996), analytical and heuristic (e.g., Evans, 1984, 1989), explicit and implicit (e.g., Reber, 1993), analytical and interactional (e.g., Levinson, 1995), rational and experiential (e.g., Epstein, 1994), reasoning and intuitive (e.g., Haidt, 2001), and so forth; there are also triarchic accounts (e.g., Chein & Schneider, 2011). The common theme between these accounts is the division of the cognitive system into subsystems that have specific functions, such as a system 1 and a system 2 wherein the processing of the former controls that of the latter and is itself controlled in a largely conscious way (see Evans, 2008; Evans & Frankish, 2009; Kahnemann & Frankish, 2002). The influence of one or the other system in a given dual-processing theory ultimately depends on the particular task the mind is carrying out as well as elements of long-term memory. For example, the degree to which a given task demands cognitive control resources changes as a function of experience, as activity-dependent, plasticity mechanisms strengthen task-relevant pathways (Baudry & Davis, 1997; Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013). However, that certain tasks require less cognitive effort through learning is not equal to the idea that the control mechanisms tapping these resources are so automatized as to no longer serve their *executive function*: Their control role, or supervisory make-up, is inherent to the system they constitute (Shallice, 1988). So, the control of cognitive processes generally refers to the ‘effort’ with which the cognitive system modulates information processing in favor of generating and implementing goal-directed sequences of thought and action (Schneider, Owen, & Duncan, 2000; see Hockey, 1993;

Matthews, Warm, Reinerman, & Langheim, 2010), and it is widely held that this cognitive control is required for completing tasks with which the automatized process of action and thought selection is unable to cope, namely in novel situations wherein prior learning is insufficient; whereas automatic processing supports overlearned, routine tasks (e.g., Norman & Shallice, 1980, 1986; Shallice, 1982, 1988).

However, the above mentioned accounts deriving from the approaches of experimental psychology and artificial intelligence are predicated on an important assumption. Demarcating the human cognitive system into highly specialized and largely independent subsystems for controlled and automatic processing endorses the position that the organization of mind is in some way *modular* (e.g., Posner, 1978; Morton, 1981). More specifically, modularity is a metatheoretical tenet of cognitive neuroscience and loosely refers to the notion of systems being informationally encapsulated, but like any other term in the philosophy of psychology, there are different interpretations of modularity and the sense in which the mind is so. For example, the absence of any modularity underpinning information processing suggests that there are no functionally-specific operations supporting it and that, as a consequence, progressive damage to any part of the human cognitive system results in a ‘graceful degradation’ of the overall performance of the system (Rumelhart & McClelland, 1986). That is, the parts of an information-processing system are *equipotential* in their ability to assume any or all operations driving performance in a ‘mass action’, as famously termed by the animal psychologist, Karl Lashley (see Shallice, & Cooper, 2011, for review). In contrast, modularity in the strongest sense involves systems that are not only computationally modular but also potentially computationally autonomous (Fodor, 1983, 2000). With respect to the former term, *computational modularity*, information-processing psychologists (e.g., Posner, 1987; Tulving, 1983, 1985) generally accept that, as Sternberg (2001) has carefully described and as Shallice and Cooper (2011) have elegantly revised, the characteristics of this aspect of modularity are as follows: (a) two parts of a mental process are modules if and only if they are separately modifiable; (b) the ‘process’ is a specific cognitive operation with an input-output mapping; (c) the output of this operation is a unique representation in either a discrete or continuous dimension and, if it is the recipient of more than one distal system, is symbolic (e.g., Newell, 1990); (d) the functions of subsystems form into complex networks that serve an overall function; (e) these functions can be highly abstract; and (f) they might overlap with those of other subfunctions, such as when a “higher-level process piggy-backs on that of a lower-level one.” A system is weakly computationally modular in so far as it satisfies criteria *a*, *b*, *d*, *e*, and *f*, but strongly so if criterion *c* is also met. Examples of strong modularity often involve systems whose representations are categorically specific to a domain of information, such as low-level sensory and motor operations. For example, the output data of the primary visual cortex (e.g., V1) is exclusively visual, suggesting *domain-specificity*, which is also the case for subsequent systems into which these data are the input (Zeki, 1995/2005): dorsal and ventral pathways dedicated to spatial features such as motion and depth and non-spatial ones such as form and color, respectively (e.g., Milner & Goodale, 2006; Rizolatti & Matelli, 2003; Ungerleider & Mishkin, 1982). However, computational functions of cognitive operations that are executive in nature are conceptually less modular than domain-specific, non-central systems, in that they appear to be more *domain-general* to the information on which representations are operated (see Owen, 2000; Petrides, 2000, for reviews). That is, control subsystems qualitatively differ from basic input-output operations (e.g., sensory-motor ones) by their being organized according to the respective functions they serve in modulating thought and action rather than to the respective domains of information they process.

For example, an executive function for manipulating information in a short-term memory buffer is able to carry out its suboperations on both spatial and non-spatial representations of stimuli.

On some views, modularity also involves the second aforementioned term, *computational autonomy*, in that systems sharing this property do not share cognitive resources between modules. However, computationally autonomous modules are implausible, because a great many empirical examples have since demonstrated the involvement of particular systems in a wide range of computational functions at various levels of scientific explanation (Shallice, & Cooper, 2011). For example, at a macro level, functional neuroimaging and electrophysiological methods have evidenced top-down effects of attentional subsystems on early stages of perceptual ones (e.g., Macaluso & Driver, 2005; Moran & Desimone, 1985, respectively) and, at a more micro level, neurotransmitter systems of noradrenaline, acetylcholine, serotonin, and dopamine, for example, each support implementing a plethora of computational functions (see Yu & Dayan, 2005; Dayan & Huys, 2009). However, there is another sense of modularity which is more plausible, and not only highly so but also crucial to constituting cognitive neuroscience as a ‘hard’ science in so far as the above criteria are true of the organization of mind: *anatomical modularity*. This refers to the idea that cognitive subsystems have unique base-region localizations. More specifically, as Shallice & Cooper (2011) argue, the additional characteristics of modularity that directly relate to the material world are (g) subsystems need to be relatively spatially localized in the brain and (h) can be acquired by learning, and (i) “the anatomical realization of subsystems does not entail that any neuron, hyper-column (or other anatomical unit) is a part of only one system; they could be part of more than one.” This last feature is the anatomical complement to criterion *f* above and contrasts with the antiquated views of phrenology.

That cognitive subsystems are anatomically modular is an important postulation, because a distinct theoretical problem is raised without it and which cannot be resolved without an appeal to the neurosciences. Namely, the critical objection to theories deriving purely from experimental psychology and computer science that posit computationally modular systems for processing information is epitomized in the following question: What, then, controls the control of cognition, and what controls that, and so forth? This refers to what is known as the 'homunculus problem' (Dennett, 1969, 1978) and it is a serious issue because the implication of this enquiry is a regress into subsequent 'black-box' explanations of cognitive control *ad infinitum* (see Monsell & Driver, 2000, for further review). To address this problem, it has been necessary for cognitive neuroscientific methods to constrain cognitive theorizing of the specific executive functions into which cognitive control *fractionates*. Such constraint derives from the theoretical presupposition of contemporary cognitive neuroscience that cognitive models are ultimately unfalsifiable (see Popper, 1956/2002) in so far as they are untestable and unrealizable in the real world: namely, through a material, neural substrate. Cognitive computational modeling attempts to describe the inner workings of so-called 'box-and-arrow models' at a finer-grain level of explanation and this is particularly useful when done in a biologically plausible way (see O'Reilly & Munakata, 2000, for review), but ultimately modalities of observation that complement the behavioral and simulated data typically used in non-neuroscience subfields are requisite. More specifically, investigating the structural and functional constitution of the brain to map information-processing models onto it works towards not only neuroanatomically fractionating the 'homunculus' but also limiting the number and type of plausible executive functions that exist; that is, systems fractionating into subsystems *ad infinitum* at a single, horizontal level of scientific explanation (i.e., that of the level of information processing) is unlikely (Bermúdez, 2005).

2.2 The human brain

That sensing, motioning, and thinking are generated nowhere else than in the brain is an idea that can be traced farther than 2,000 years ago to Pre-Socratic philosophers such as Hippocrates in 400_{BC} (see Cohen et al., 2016, for an anthology). Although ontological and epistemological discussions on the nature and intelligibility of the mind stem from this ancient epoch of philosophy, the influential works of the 17th -19th century empiricists, rationalists (see Ariew & Watkins, 2009 for an anthology), anatomists, experimental physiologists, and neuropsychologists (see Benton, 1991, for review) have impacted the contemporary understanding of the mind and brain the greatest. As discussed in the previous chapter, theoretical dualisms between mind and brain are rejected from the point of view of cognitive neuroscience; and, so, naïve realism is false, but also is idealism: The mind and its emergent property of consciousness are the product of interacting neurobiological systems—systems which constantly mediate the relations between stimulus, organism, and response. Reductionism is endorsed, then, as a theoretical tenet, but not as the exclusive means by which to discover the cognitive functions of brain structures, because questions at this level of explanation often require top-down as well as bottom-up approaches (Shallice & Cooper, 2011). For example, one of the previously theoretically enigmatic and methodologically elusive realms of discovery in the past three centuries has regarded the seat of controlled cognition in the brain. And emerging from the collective efforts and approaches of the particular subfields of cognitive neuroscience mentioned above is the elucidation that it is the frontal lobes (right and left) which makes active thought possible—that holds the subsystems supporting the complex cognitive operations involved in higher-order forms of thought such as reasoning, planning, mentalizing, and so forth (Levin, Eisenberg, & Benton, 1991; Monsell & Driver, 2000; Schneider et al., 2000; Shallice, 1988; Shallice & Cooper, 2011; Stuss & Knight, 2002, 2013).

In the vertebrate, the branches of nerve pairs in the sacral, lumbar, thoracic, and cervical regions of the body collect along the spinal cord, a dense collection of bidirectional nerve fibers comprising of dendrites of neuron cells (grey matter) surrounded by the axions extending from them (white matter) that together are insulated by meninges—connective tissues such as pia mater, arachnoid, and dura mater—and protected by bone: vertebra. This cord of nerve fibers extends down to the coccyx, or tail bone, but begins at the base, or stem, of a vital organ: the brain. Situated within the protective intracranial cavity of the skull, the brain is also encased in meninges and cerebrospinal fluid (CSF). Specifically, the contents of this cavity are approximately 80% brain tissue, 10% blood, and 10% CSF, with brain tissue being comprised of 77-78% H_2O, 10-12% lipids (fatty molecules), 8% protein, 2% soluble organic substances, 1% carbohydrate, and 1% inorganic salts (Carter, Aldridge, Page, & Parker, 2019). Molecularly, most of these contents constitute the cytoplasm and membranes of the billions of brain cells underlying this tissue. There are approximately 86 billion neurons and ten times as many glial cells that support them in the human brain (see Kandel et al., 2013, for review of these cells). The relative volume of the modern human brain is somewhat unique compared to evolutionarily antecede hominids and other closely related primates. Namely, it is the largest (~1,500 cubic centimeters) in volume, with the exception of *homo neanderthalenis* (~1,600), compared to the *homo erectus* (~900) and chimpanzee (~400), for example. Although there is considerable variation across individuals and between sex, the average adult human brain approximately weighs 3.25lb (1.5kg); extends 6.5in (167mm) from its most rostral (anterior) to caudal (posterior) ends (i.e., in the direction of the nasal to inion bones of the skull; see a brain image from the midsagittal plane [Figure 2.1]); extends 5.5in (140mm) from its most lateral (outer) right and left surfaces (see a brain image from the coronal plane [Figure 2.1]); and extends 3.5in (93mm) along the axis running dorsal (superior) to ventral (inferior) (Carter et al., 2019).

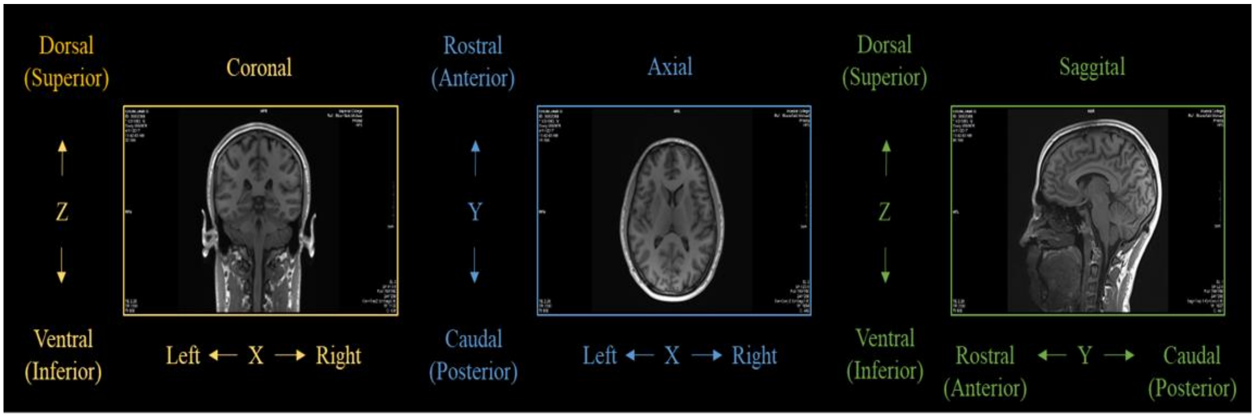

Figure 2.1 A depiction of the three main axes used in the standard coordinate space for structural MRI (images collected from the author's own brain).

However, what is most unique about the human brain is not its species-relative size but rather the nature of its gross morphology. Compared to other vertebrates such as reptiles, birds, fish, amphibians, and so forth, mammals have not only well-developed subcortical brain regions but also a well-developed cerebrum. These types of animals and mammals all share a spinal cord that integrates into a brain stem. The brain stem serves life-preserving functions for regulating breathing, heart rate, sleeping, and eating, and is the collective, mediating structure through which sensory-motor neural signals are sent to and received from the rest of the physical body. It segregates anatomically into the hindbrain (medulla oblongata—to which the spinal cord connects—pons, and cerebellum) and, above this, the midbrain brain, and these structures further subdivide into specific nuclei (see Hariri, 2015, for review). The forebrain (prosencephalon) is situated directly above the midbrain and comprises the diencephalon and telencephalon. The former is a collection of associated structures referred to as the thalamus, hypothalamus, subthalamus, and epithalamus, which also anatomically subdivide into many nuclei that serve a great many information-processing functions essential to sensing the world and responding appropriately to stimuli. For example, some associated nuclei include the putamen and caudate nuclei (dorsal striatum), nucleus accumbens (ventral striatum), globus pallidus and subthalamic nuclei, ventral pallidum, and substantia nigra (Carter et al., 2019). The latter (telencephalon) is the cerebrum. The cerebrum is the largest in mammals, filling up to 75% of total brain volume in man, and is divided into two hemispheres (a left and right one) that are connected through white matter—a dense collection of bidirectional axion fibers—known as the corpus collosum, and the cerebrum consists not only of such white matter but also the outer layers of grey matter as well as other subcortical structures such as the hippocampus and amygdala and their nuclei (Kandel et al., 2013).

The outer cerebral mantle of grey matter of the cerebrum is the cerebral cortex (Saladin, 2012). The cerebral cortex divides into several lobes: the right and left occipital, parietal, temporal, and frontal lobes (Arnold, 1838; Chaussier, 1807). These divisions are largely based on the outer structural features of the cerebral cortex, namely on the patterns of bulges or ‘wrinkles’ (gyri), shallow grooves (sulci), and deeper grooves (fissures) (e.g., Ecker, 1869). Historically, “there seemed to be as little reason to assign names to these bulges and creases as there would be to specify every fold in the intestines,” (Benton, 1991) but over time the observations of anatomists of consistent patterns, such as symmetries and asymmetries, across fresh cadaver brains warranted further identification of these structural features. For example, Ronaldo (1831) identified the precentral and postcentral gyri whose central sulcus now demarcates the frontal lobe as the portion of cerebral cortex anterior to it on the lateral surface (see Damasio, 1991). In addition, gross structural asymmetries were identified between the left and right hemispheres. For example, in the most rostral lobes of the cerebral cortex, the right frontal lobe is wider, and slightly thicker, than and protrudes over the left frontal lobe, and the converse is true of the most caudal ones—the left occipital lobe is wider than and protrudes over the right occipital lobe—a double asymmetry to which many refer as the Yakovlevian torque (see Goldberg, 2001).

Other neuroanatomical aspects also divide the cerebral cortex into the neocortex and allocortex. In particular, the neocortex forms 90% of the cerebral cortex and has a thickness of about 1/16th - 3/16th inches (2-5mm) and, importantly, has a 6-cellular layer characteristic (Filimonoff, 1947). From the outside inward, these are the molecular (I), external granular (II), external pyramidal (II), internal granular (IV), internal pyramidal (V), and multiform layers (VI) (Carter et al., 2019). Cutting through these horizontal layers are vertical columns of neuronal ensembles which are each approximately comprised of 70,000 neurons, and there are roughly 500,000 columns in the cerebral cortex (~35 billion; Hariri, 2015). These features of neuroanatomical organization, together with other aspects of local composition, arrangement, and connections, form unique *cytoarchitectonic* (i.e., ‘cell architecture’) subdivisions of the cerebral cortex. Systematic investigations into cytoarchitectonics—largely through the dissection of monkeys—has led to a standard framework for labeling subregions of the cerebral cortex. Namely, the German neuroanatomist, Korbinian Brodmann (1868-1918), developed the cytoarchitectonic system that is presently used and which now bears his name: Brodmann’s areas, or BA (Brodmann, 1909). There are 52 BAs, but they are not precise from a cross-species perspective; for example, there are considerable differences between macaque monkeys and humans (see Petrides & Pandya, 1994; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012, for reviews).

2.3 Prefrontal structures

Early observations of the consequences of loss of brain tissue through experimental methods and destructive afflictions such as stroke, tumor, and traumatic injury bolstered the postulation that the neuroanatomists' structural divisions of the cerebral cortex might have some bearing on functional specificity. Experimental physiologists conducted studies on the effects of surgical ablations of particular brain regions on domains of cognition. For example, Panizza (1855) linked in both dogs and humans impairment of vision to lesions in occipitoparietal regions. Munk (1878, 1879) accomplished the same in studying dog ablations, as well as discovered relations between subregions of the frontal lobe and motor functions. So, localization evidence has long amassed in favor of modularity for low-level sensory-motor systems. However, experimental ablations to the frontal lobes of monkeys and dogs yielded no clear sensory or motor deficits when the procedures were carried out on subareas rostral to what are now referred to as the primary motor cortex (BA4) and premotor cortex (BA6) (Bianchi, 1895, 1920/1922). Moreover, human case studies of brain damage to the frontal lobes in the 19th (e.g., Jastrowitz, 1888; Harlow, 1848, 1868; Oppenheim, 1890; Welt, 1888) and 20th (see Levin et al., 1991; Shallice, 1988, for reviews) centuries were also consistent with a lack of sensory-motor impairment. However, despite the absence of such deficits, virtually all such cases, together with the frontal ablation studies of the animal physiologists, noted similar consequences to behavior and personality of the integrity of this cerebral tissue in this particular cortical region being comprised, namely that, and often in the presence of other conspecifics, dogs, cats, monkeys, and people exhibited inordinate signs of agitation, fear, apathy, aggression, distractibility, fatigability, uninhibitedness (e.g., utilization and perservation behavior), attentive rigidity, and unsociability—as though their ‘character’ were in fragments. Although these symptoms widely varied across human cases in both categorical and dimensional terms, and despite frequent variation in lesion or tumor site, the condition of subjects was attributed the blanket term of frontal lobe ‘disease’ or ‘syndrome’ (see Eslinger & Damasio, 1985; Milner, 1964; Stuss & Benson, 1986). Further refinement and division of this diagnostic classification was clearly requisite, but the frontal lobes were hereafter no longer accepted as passive or ‘silent’ areas of the cerebral cortex of which theorists could not meaningfully speak (Wittgenstein, 1921).

Such experimental physiological and cognitive neuropsychological findings have led to functional distinctions within the frontal lobe. More specifically, motor, premotor, prefrontal, and limbic sectors have been delineated (Fuster, 1989; Mesulam, 1987; Stuss & Benson, 1986). The prefrontal sector, or prefrontal cortex (PFC), is somewhat characterized along the lateral surface as the portion of cerebral cortex rostral to the precentral sulcus of BA6 (premotor cortex) and, along the medial surface, the portion dorsal, rostral, and ventral to the cingulate sulcus, but this does not provide as objective a border as does the more cytoarchitectonic grounds for this division. Namely, the premotor cortex lacks the internal granular layer (IV) that is predominant in the PFC (Brodmann, 1909). The human PFC is thought to include Brodmann’s areas 8, 9, 10, 11, 12, 44, 45, 46, and 47 (Figure 2.2; see Duncan, 1991, for review).

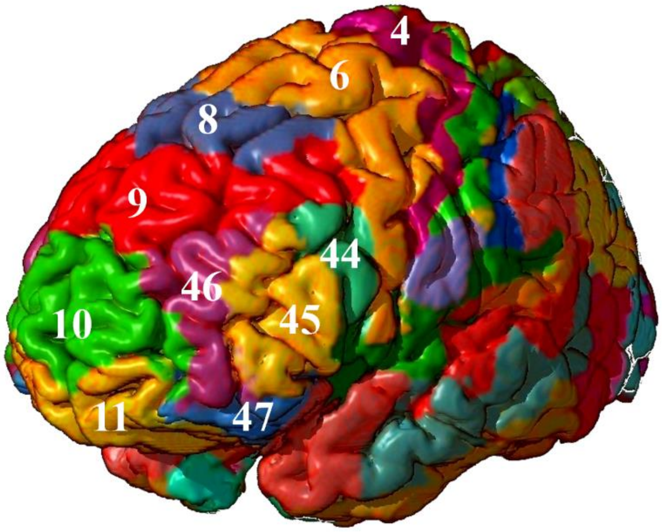

Figure 2.2 3D representation of Brodmann’s areas corresponding to the frontal lobe (image adapted from Public Domain/Commons).

These regions approximately account for 29% of the total cortex in humans, 17% in the chimpanzee, 11.5% in the gibbon and the macaque, 8.5% in the lemur, 7% in the dog, and 3.5% in the cat (Brodmann, 1909; see Goldberg, 2001). Also, about 80% of neurons in the PFC are excitatory glutamatergic pyramidal neurons and ~20% are inhibitory gamma-aminobutyric acid (GABA) interneurons, with about 5-10 times as many glial cells as neurons (Hariri, 2015). Anatomically, the ventral, dorsal, lateral, and rostral areas of the outer surface of the PFC comprise several subregions: the left and right orbitofrontal gyri (BA11, BA10) superior frontal gyri (BA8, BA9), middle frontal gyri (BA46, BA9, BA10), inferior frontal gyri (BA44, BA45, BA47)—also known as pars opercularis, pars triangularis, and pars orbitalis, respectively—and frontal poles (BA10). So, some Brodmann’s areas touch parts of more than one PFC gyrus, such as BA9 and BA10. Lastly, proportions of BA8, BA9, BA10, BA11, and BA12 also reside within the medial surfaces of the PFC. On the basis of cognitive neuroscientific evidence, subregions of the PFC are also commonly referred to in terms which are more functional than structural, including rostral PFC (BA10), dorsolateral PFC (dlPFC; BA46, BA9), and ventrolateral PFC (vlPFC; BA44, BA45, BA47), with dorsomedial PFC (dmPFC) and ventromedial PFC (vmPFC) receiving rather inconsistent terminological use as regards the Brodmann's areas they include. For example, sometimes the former refers to only medial BA8 and BA9, but also sometimes to dorsal-rostral portions of BA32 and BA24 (i.e., subregions of anterior cingulate cortex [ACC]). The latter frequently refers to only BA11 and BA10, but also sometimes to as many areas as these as well as BA12, BA32, and even BA25 (subgenual area); this is often due to conflation of the medial frontal lobes with the medial surfaces of the PFC. So, for current purposes, future mention of vmPFC and dmPFC will refer to Brodmann's areas rostral to ventral anterior cingulate cortex (vACC) and dorsal anterior cingulate cortex (dACC), respectively.

The ipsilateral (within hemisphere) and contralateral (between hemisphere) connections between PFC subregions, to more caudal cortical areas, and to subcortical ones also characterize and, indeed, distinguish the PFC. Specifically, the PFC is the most interconnected area of the cerebral cortex, with projections between "every distinct functional unit of the brain" (Goldberg, 2001; see Nauta, 1972, for review). In addition to connections to more caudal 'association' regions of the cerebral cortex, including the frontal (i.e., BA4, BA6), parietal, temporal, and occipital lobes, as well as the cingulate cortex and insula, the PFC also has deep connections to the hippocampal formation (parahippocampal cortex, entorhinal cortex, perirhinal cortex, subiculum, & dendate gyrus), cerebellum, brain stem, amygdala, and many other subcortical nuclei. For example, there are long, axion-dense pathways to the dorsomedial thalamic nucleus (Levin, 1936; Minkowski, 1923, 1924a, 1924b; Walker, 1935, 1938), which is the apex of information integration occurring within the thalamus and which receives input from the ventral striatum through the ventral pallidum, as well as to the dorsal striatum, which receives input from the ventral striatum through the substantia nigra (see Harari, 2015, for review). Biochemically, the indirect connections with the ventral striatum are important because this node in the ‘corticostriatal circuit’ receives neurotransmitters from the midbrain mesocortical dopaminergic system, particularly from the ventral tegmental area, but the PFC also has direct projections to the midbrain (see Robbins, 2000; Robbins & Rogers, 2000, for review). Although some of the subcortical connections to the PFC are to the dlPFC, many of these are mediated by ventral medial subregions (e.g., BA11, BA12) (Goldberg, 2001). Another subcortical region worth noting is the amygdala, the hub of the ‘corticolimbic circuit’. Of the 13 distinct nuclei that comprise it, the basolateral complex of the amygdala (BLA) has efferent (output) pathways to vmPFC whereas the intercalated cell masses (ICMs) mediating this nucleus and the central nucleus of the amygdala (CeA) receive afferent (input) projections from dmPFC. What is more is that, in addition to lateral PFC, especially dlPFC, having many bidirectional projections connecting to the hippocampal formation—the hub of the ‘coritcohippocampal circuit’ (Hariri, 2015)—the dlPFC and vlPFC also receive dense projections from important posterior regions of the cerebral cortex such as the inferior parietal lobule (Anderson et al., 1985; Barbas & Mesulum, 1985; Cavada & Goldman-Rakic, 1989; Mesulam et al., 1977; Petrides & Pandya, 1984) and ventral temporal regions (Barbas, 1988; Bullier, Schall, & Morel, 1996; Chavis & Pandya, 1976; Distler et al., 1993; Jacobsen & Trojanowski, 1977; Jones & Powell, 1970; Kawamura & Neito, 1984; Kuypers et al., 1965; Seltzer & Pandya, 1989; Shiwa, 1987; Ungerleider et al., 1989; Webster et al., 1994). For exhaustive reviews on the structural nature of the PFC, see Barbas and Pandya, 1989; Goldman-Rakic, 2011; Pandya and Yeterian, 1998; and Petrides and Pandya, 1994.

2.4 Functional specializations

Although a great sort of species has contributed to the study of the PFC, albeit involuntarily, the strongest evidence for what bearing its structural integrity might have on its functional significance to cognitive operations derives from invasive experimental studies on non-human primates, since their PFC anatomy best represents that of humans. Of the 19th and early 20th century neuropsychological findings suggesting that destruction to the PFC yielded wide variation in aspects of personality, attention, memory, and so forth—that is, a ‘frontal lobe syndrome’—early studies on delayed-response tasks (Hunter, 1913), which require subjects to delay a behavioral action for a short period of time by maintaining a ‘set’ or representation of the environment (i.e., stimuli) in a memory ‘buffer’, indicated that the PFC might function across species to mediate perception and action in actively representing learned associations between stimulus and response (e.g., Hebb, 1945; Hebb & Penfield, 1940; Jacobsen, 1931, 1935; Jacobsen & Nissen, 1937; see Benton, 1991, for review). Studies in the late 20th century further supported this hypothesis in non-human primates and monkeys using refined paradigms that included additional task demands such as the need to manipulate (e.g., compare novel with previous stimuli) information in various ways whilst held in this short-term memory buffer during retention intervals (see Levy & Goldman-Rakic, 2000; Petrides, 2000, for reviews).

These lines of research, together with the known inter- and intra-connections of the PFC, raised the question of the way in which the PFC is organized at the level of information processing. For example, inferior parietal lobule and ventral temporal areas have long been implicated in the so-called ‘dorsal stream’ (Rizolatti & Matelli, 2003) and ‘ventral stream’ (Milner & Goodale, 2008; Ungerleider & Mishkin, 1982) for processing the ‘where’ and ‘what’ of stimuli, respectively, which, as mentioned above, begin with the output of the primary visual cortex of the occipital lobes. And because lateral PFC subregions such as dlPFC and vlPFC have extensive connections with these areas, as detailed above, some frontal lobe theorists have posited that these subregions of the PFC are functionally specific to the domain of information they process from these streams (Goldman-Rakic, 1994, 1995; see Goldman-Rakic, 1987; Levy & Goldman-Rakic, 2000, for reviews). Namely, middle (BA46, BA9) and inferior (BA44, BA45, BA47) frontal gyri process visuospatial and non-spatial information, respectively. Despite whether this is in fact the case, the important contribution of these findings to frontal lobe theorizing was to link particular frontal structures to different aspects of *active* information processing, mounting strong evidence in favor of modularity and against notions of 'mass action'.

Although these findings in non-human primates seemed to trend towards domain-specific mechanisms localized within dlPFC and vlPFC regarding visuospatial and non-spatial information processing, respectively, theoretical interpretations of other non-human primate studies as well as human neuroimaging ones have advanced that PFC subregions such as dlPFC and vlPFC are functionally organized according to their computational operations rather than by the information domains of the objects of such processes (Owen, 1997; Owen et al., 1996a, 1996b, 1998, 1999; Petrides 1989, 1991, 1994, 1995; Petrides et al., 1993). More specifically, on delayed-response tasks, the human vlPFC has been implicated in the active maintenance of representations of stimuli across virtually every domain of information, and dlPFC has been implicated in the manipulation and monitoring (i.e., continuous or periododic checking) of information held in this short-term memory buffer (see D'Esposito, Postle, & Rypma, 2000; Owen, 2000, for reviews). Together, the findings of invasive non-human primate and human neuroimaging studies that have employed both types of experimental design are by and large in line with a domain-general functional organization of PFC in man, as well as contribute to the idea of an anatomically fractionated ‘working’ memory system (e.g., Baddeley, 1986, 2007; Baddeley & Hitch, 1974) localized in the lateral surfaces of the PFC.

However, a consistent association of cognitive operations such as maintenance and manipulation with vlPFC and dlPFC, respectively, does not confirm these operations as the chief functions of lateral PFC. These areas are not only polymodal in a multi-domain sense but also as regards the operations they serve. Namely, there are many other operations involved in delayed-response tasks, including those which are exclusive to humans such as in verbal backward digit span tasks, and other tasks of a more executive nature which activate these aspects of lateral PFC, such as encoding, attentional shifting among items held in retention (Garavan, 1998; McElree, 1998), inhibition of prepotent responses (Diamond, 1990), mediation of proactive interference (Jonides et al., 1998), monitoring, retrieval, response preparation (D’Esposito et al., 1995), coordination of multiple subtasks (D’Esposito et al., 2000), and motor execution. Drawing upon the chronometric approach of traditional experimental psychology, it is possible to decompose such tasks into their subcomponents in experimental designs using neuroscientific methods (Posner, 1978). However, achieving ‘pure insertion’ in the subtraction method of blocked experimental designs in these paradigms is virtually impossible, because even the ostensibly simplest of tasks will recruit a multitude of cognitive operations that might not be of particular interest but which are critical to task performance; see Shallice and Cooper (2011) for a detailed review of the pros and cons of macro and micro aspects of experimental designs in cognitive neuroscience. So, it has also been important to adopt event-related designs in which different facets of a given trial, such as epochs of encoding, maintenance, retrieval, and action, can be assessed and compared across others. For example, if the independent variable is whether or not the manipulation of information in active maintenance is required, then nonconsecutive trials of a delayed-response task containing epochs of maintenance can be compared against those of maintenance + manipulation, with a statistical contrast of maintenance + manipulation > maintenance, obviating some of the temporal shortcomings of blocked designs. Such event-related designs have reliably associated multiple suboperations of working memory with both vlPFC and dlPFC, but with the latter area being preferentially active during encoding, manipulation, and retrieval (i.e., scanning) and when the retention load increased (see D'Esposito et al., 2000, for review); interestingly, vlPFC tends to be preferential in resolving conflict at retrieval.

Therefore, these subregions are important to not only the maintenance and manipulation (e.g., dynamic updating) of information, as operationally defined within a working memory system, as well as to other demands of tasks designed to tap this system, but research also suggests these areas are so for a multitude of cognitive operations which are not exclusive to such a system and that other areas are involved in supporting those which are. For example, there are operations constituting a form of 'manipulation' that demand cognitive resources of PFC subregions other than left dlPFC. That is, although the manipulation of buffered information is reliably localized to this area on working memory tasks requiring a sustained and strategic 'retrieval mode' (Tulving, 1983), such PFC subregions as left vlPFC have been also found to enact manipulation-like operations on both verbal (e.g., Papagno et al., 2009; Rapp et al., 2004) and nonverbal (Burgess & Shallice, 1996a; Reverberi et al., 2005) tasks that do not fall strictly within classical paradigms of working memory and, instead, require the 'abstraction' of new meanings (e.g., relations, rules) from concrete or known ones; this has been interpretated as reflecting a suboperation for constructing hierarchical structures (see Shallice & Cooper, 2013). Moreover, although maintaining representations over short periods of time relies markedly on the PFC, it is not a unique ability for which any of the particular subregions comprising it is functionally specialized. For example, other regions of the brain have been concomitantly associated with this sense of active maintenance: The active retention of information mediating encoding and retrieval appears to be also a property of certain parietal areas (e.g., Ravizza, Delgado, Chein, Becker, & Fiez, 2004). So, manipulating diverse domains of goal-related information is largely a shared feature of the PFC rather than the global function of a particular subregion. In fact, Duncan and Owen (2000) found that many types of cognitive control tasks, such as of auditory discrimination, visual divided attention, self-paced response production, task switching, spatial problem-solving, and semantic processing of words, involving manipulations of task demands of response conflict, task novelty, perceptual difficulty, memory load, and retention interval recruited bilateral vlPFC, dlPFC, dACC, and, to a lesser extent, orbitofrontal PFC (BA11) (see Duncan, 2010). That tasks developed to engage cognitive operations of a more controlled or executive nature typically recruit these areas is consistent with long held theoretical postulations that the PFC collectively works to modulate thought and action, especially in non-routine situations: that together its subregions operate in the “programming, regulation, and verification of activity” (Luria, 1966; Luria & Tsvetkova, 1964), such as in tasks requiring the temporal organization of action (see Fuster, 2000).

However, if it is both the case that PFC subregions are frequently recruited together on executive function tasks and each subregion more than likely supports a number of subfunctions of different multi-region networks (e.g., episodic memory, language, motor coordination, attention, etc.; see Fernandez-Duque & Posner, 2001; Fan et al., 2002, 2005, in the case of attention), then what qualitative differences are there in the PFC regarding functional specialization? In so far as the PFC is fundamentally modular, which experimental neurophysiology and cognitive neuropsychology have long indicated, these suboperations—so implicated in a given PFC subregion—are explicable in terms of a broader, isolable system for which the local area is functionally specialized and, therefore, amenable to experimentation aiming to demonstrate differential localization of function. Some such evidence has converged from neuroimaging and neuropsychology methods to suggest this is the case. For example, the role of left vlPFC, particularly BA44 and BA45 (Broca's areas), in speech production as well as aspects of comprehension is on rather solid ground given the amassed cognitive neuropsychological and neuroimaging evidence on healthy adults and forms of aphasia and dementia (see Shallice & Cooper, 2011, for review). Interestingly, it is perhaps not surprising from a neuroanatomical perspective that the core psycholinguistic facets of syntax, meaning, and sound (Jackendoff, 2002) depend heavily on multi-region interactions along the rostro-caudal axis of the left cerebral hemisphere between inferior frontal gyrus and posterior areas of superior temporal gyrus, because of the bidirectional indirect (arcuate fasciculus) and direct (uncinate fasciculus) ipsilateral fiber tracts connecting these areas (Catani & Jones, 2005). The former is mediational because it first passes through subregions of the inferior parietal lobule (i.e., Geschwind's territory): namely, supramarginal gyrus (BA40) and angular gyrus (BA39). This territory is associated with multi-sensory integration of information such as sight, sound, and body sensation and thicker in humans than in other primates and is one of the last areas of the cerebral cortex to mature (Carter et al., 2019).

As regards language production, left vlPFC appears to be critical to computational functions for mapping lexical representations and their phonological realizations. For instance, evidence has been consistent with an isolable 'rule system' (Pinker & Prince, 1988; Pinker & Ullman, 2002), whose base-region localization is in left vlPFC, that is dissociable from operations unique to a long-term memory ‘mental lexicon’, whose base-region localization is in posterior superior temporal gyrus (e.g., Tyler, Marslen-Wilson, & Stamatakis, 2005; Tyler, Stamatakis, Post, Randall, & Marslen-Wilson, 2005). Because left vlPFC is also important to aspects of language comprehension, such as to syntactic operations and semantic ambiguity (e.g., Ben-Shachar, Palti, & Grodzinsky, 2004), Hagoort (2005) has advanced that left vlPFC, including left BA47 and ventral areas of BA6, supports an overall linguistic mechanism of ‘unification’ that actuates combinatorial suboperations on syntactic, semantic, and phonological information (see Vosse & Kempen, 2000). Critically, this process of unification inevitably requires *selection* between potential and competing syntactic, semantic, and phonological structures, an operation which also appears necessary in other domains of research, such as on verbal and nonverbal semantic judgment and retrieval tasks, and which has been particularly localized to BA44 and BA45 (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Robinson, Blair, & Cipolotti, 1998; Robinson, Shallice, Bozzali, & Cipolotti, 2010; Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; see Jonides & Nee, 2006). So, that vlPFC is specialized for the domain-general selection of active task-set representations is plausible (Shallice & Cooper, 2011).

Cognitive neuroscientific studies on executive function assessing aspects of attention, memory, response inhibition, motor planning, and so forth frequently implicate the dlPFC (BA46/9). This subregion has long been thought to be indispensable to the systems the PFC supports (e.g., Petrides, 1991, 1994) and to hold even a special position within the hierarchy of cognitive control (Badre, 2008; see Badre & Desrochers, 2019, for review); it is worth noting that an organization of control based on computational domains along the rostro-caudal axis of the PFC is plausible provided the apparent qualitative differences between these domains (e.g., internal logic) are also fully explained (see Shallice & Cooper, 2011). Such a special position derives not from the common observation of preferential engagement and coactivation with other PFC subregions when task demands for controlled processing are marked (i.e., high load), but rather from its tendency to exhibit a substantial degree of modulation over processing in other brain regions, including those within the frontal lobes. This interpretation is consistent with neuroanatomical findings suggesting that dlPFC has an important role as a ‘node’ in the corticostriatal circuit for movement and motivation, as well as in other circuits (see Hariri, 2015). For example, regarding the direction of information flow within said circuit, areas of the vmPFC receive and integrate subcortical signals relating to basic drives and motivations (e.g., hunger) and extrinsic stimuli (e.g., food) in a ‘bottom-up’ manner and, as a consequence of selection converging from other regions in layers I-III, dlPFC returns signals directly and indirectly via efferent projections in layers V and VI in a ‘top-down’ manner to subcortical and cortical areas to orchestrate, as it were, the action and thought that ultimately satisfy or inhibit these motivations and drives (e.g., grab and eat recognized food). Another example is the modulation of the corticohippocampal circuit in situations in which retrieval is not spontaneously cued, wherein the dlPFC actively affects processing in the hippocampal formation to facilitate access and reintegration of specific declarative traces in long-term memory, bringing them into active maintenance (i.e., short-term buffers). In other words, the neuroanatomical realization of the information-processing function of dlPFC is the biasing of posterior and subcortical brain activation in favor of task-relevant pathways (see Miller & Cohen, 2001, for review). Although this modulatory feature is pronounced in dlPFC, given its structural connections, it is not entirely unique to it: This biasing is, on the whole, a collective function of the PFC. So, in information processing terms, what else might accompany, or temporally precede, this biasing and perhaps better characterize that for which dlPFC is largely functionally specialized?

One interpretation is that because dlPFC has been frequently recruited in a multitude of neuroimaging and neuropsychological tasks involving volition and aspects of response generation, modality, rate, and selection, this lateral area—particularly in the left hemisphere—might predominantly function according to a subsystem for the ‘response sculpting’ of problem spaces (Newell, 1990), in that “the dlPFC is most likely involved in defining a set of responses suitable for [a given] task and biasing these for selection when external inputs achieve such selection to only a very limited degree” (Frith, 2000). Before self-generated responses can be carried out, regardless of the form a behavioral response might take (e.g., moving a joystick with a hand, mouthing meaningless syllables; Frith, Friston, Liddle, & Frackowiak, 1991; Spence, Hirsch, Brooks, & Grasby, 1998), it is necessary to construct or generate candidate ones—potentially based on entirely arbitrary stimulus-response associations—whose selection then facilitates the biasing of activation signals in favor of the posterior brain regions in which the appropriate responses are represented (e.g., selection of each word in the temporal lobe, of each finger in parietal lobe; Friston et al., 1991). This sense of generation might explain not only self-generated response selection but also situations or problems in which there is no overt behavior, but for which self-initiated hypothetical solutions need to be specified (e.g., mental arithmetic, planning sequences of distant-future actions, etc.). So, more broadly, the left dlPFC might be critical to generating *strategies* for non-routine tasks, together with their corollary set of potential productions (e.g., the ‘programming function’ of Duncan’s (2010) multiple demand units).

However, an ability equally important to such a procedure and to continuously ‘sculpting’ responses throughout the course of such tasks is one which actively *monitors* outcomes to ensure that aspects of a given procedure do not conflict with active goal states. According to Petrides (1994), active monitoring involves an “expectation of what must or will occur, and verification of what has occurred against the expectation.” Research using multiple cognitive neuroscientific methods has found that such a subsystem is supported predominantly in right dlPFC (e.g., Fleck, Daselaar, Dobbins, & Cabeza, 2006; Reverberi et al., 2005; Sharp, Scott, & Wise, 2004; Stuss et al., 2005; Vallesi et al., 2007). This subsystem is largely characterized by operations for detecting and checking for errors. Errors, broadly understood, constitute any incongruence between two or more state of affairs, and the nature of such affairs can range from concrete mismatches between perceived behavior and active goals, to abstract mismatches regarding temporal intervals, subjective valuations, or inductive inferences (e.g., Burgess & Shallice, 1996b; Rizzo et al., 1995). If sustained or periodic checking leads to the detection of an error—whose source, for instance, is one’s actions rather than an extrinsic variable—such that responses are too slow, then other subsystems are subsequently upregulated to adapt the current strategy to reduce future errors (e.g., increase preparation during shorter inter-trial intervals). According to Shallice & Cooper, 2011, active monitoring is particularly necessary during situations in which there is marked uncertainty, a provisional solution or response has been actuated, or the rejection of alternatives is requisite; failures of this system, such as in the case of a lesion to right dlPFC, lead to unintended errors in performance due to alternative responses not being appropriately rejected (e.g., ‘capture errors’; Reason, 1979, 1984).

2.5 Functional specialization within rostral PFC (BA10)

Although generating and selecting strategies, and monitoring their outcomes, are integral to adapting behavior to novel situations, these procedures and those implemented under them do little good towards this end insofar as they are ineffectively applied. Some early observations in cognitive neuropsychology have revealed that some people with PFC damage tend to fail at performing actions that execute non-routine strategies despite showing preserved abilities on measures of intelligence, retrospective memory, perception, movement, and language (e.g., Ackerly & Benton, 1947; Bricker, 1936; Penfield & Evans, 1935). Later observations further strengthened the link between PFC damage and impairments in applying strategies appropriately (i.e., 'strategy application disorder') (e.g., Duncan, 1986; Eslinger & Damasio, 1985; Goldstein, Bernard, Fenwick, Burgess, & McNeil, 1993; Levine et al., 1998; Shallice & Burgess, 1991a). The behavioral failures in these studies typically involved actions that, though often task-related, hindered goal acquisition by being carried out at incorrect moments, on incorrect objects, and at incorrect places, as well as in an incorrect order. But these behaviors go beyond the mere lapses in conscious awareness or 'action slips' (Norman, 1988; Reason, 1984, 1990) with which most people are likely acquainted (e.g., accidently pouring milk into a bowl before cereal)—beyond the nature of tasks involving a prespecified serial sequence of action. Rather, these failures arose when individuals were behaving in a different type of situation: an open-ended one. Open-ended tasks seldom involve only one or two actions, but rather a multitude of discrete subtasks requiring not only tentative scheduling with respect to their serial sequence (Cooper, & Shallice, 2006) but also dynamic, self-initiated interleaving, such as after updates to their respective priority towards the overall goal. This meta-organization of behavior is referred to as multitasking (see Burgess, 2000a, for review), but open-ended and, particularly, 'ill-structured' tasks involving multitasking have the additional characteristic of either unspecified goals and starting positions or, more commonly, unspecified "consequences of selecting one [decision] from the finite set of alternatives available at any stage of the problem … (Shallice & Cipolotti, 2018). Importantly, multitasking implies that intentions must be actively delayed until temporally preceding ones are executed, but also that some must sometimes be executed in ways that interrupt ongoing actions, and these interruptions are largely at one’s discretion. For example, having breakfast is a subtask amongst others under the overall goal to get ready for work in the morning, but it also contains its own subtasks. For instance, breakfast might involve two main subtasks: making an omelet and French-pressed coffee. Each of these subtasks contains subtasks which are too obvious to further describe, but, in short, if these two things are being made semi-simultaneously to save time, and if one desires neither coffee that is too strong nor an omelet that is cooked over, then sometimes interrupting the placing of ingredients inside the omelet to press down the coffee is necessary. The coffee needs to be pressed once the amount of time for steeping is up (e.g., ~4 minutes), to which attention towards the omelet must then be returned. So, in this example, the above mentioned findings suggest that individuals with PFC damage would press the coffee too early, too late, or not at all. More specifically, the neuropsychological evidence, including studies using tasks developed specifically to index these features of multitasking (e.g., Multiple Errands Task; Shallice & Burgess, 1991a; Six-Element Test; Burgess et al., 1996) pointed towards the possibility of a computational disruption to the maintenance and retrieval, as opposed to the formation and execution, of delayed intentions to act within the scope of an overarching goal (e.g., Burgess, Veitch, Costello, & Shallice, 2000; Shallice & Burgess, 1991a; see Burgess, 2000b; Shallice & Burgess, 1991b, for reviews). Interestingly, these observations of multitasking impairment all involved a particular PFC subregion, namely rostral PFC (BA10), raising important questions about the nature of intentions and functional specialization.

Rostral PFC, particularly the cortical region constituting BA10, which is sometimes also referred to as anterior PFC and frontopolar cortex, is larger in humans than in any other animal, including the great apes, and is the largest single architectonic region of the PFC, approximately covering 25-30 cubic centimeters and comprising of ~500 million neurons (Holloway, 2002; Ongur et al., 2003; Semendeferi, Armstrong, Schleicher, Zilles, & VanHoesen, 2001). It is also the last region of the brain to achieve myelination and reach maturation (Bonin, 1950; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999, 2004), with supramarginal gyrus (BA40) and angular gyrus (BA39) of the inferior parietal lobule coming in second (Carter et al., 2019). In fact, the grey matter density and cortical myelination markedly increase between the ages of 5 and 11 years and continue to increase throughout development and well into adulthood (e.g., ~30 years). One interesting neuronal feature is the relatively lower cell density in the supragranular layers, which potentially creates greater space for connections with other subregions; indeed, rostral PFC is better connected with PFC subregions than any other subregion of the PFC (Semendeferi et al., 2001). Some have proposed that rostral PFC divides further into three cytoarchitectonically-distinct subregions: rostrolateral PFC (rlPFC), rostromedial PFC (rmPFC), and caudal rmPFC (e.g., Moayedi, Salomons, Dunlop, Downar, & Davis, 2015; Orr, Smolker, & Banich, 2015). Functional connectivity of rlPFC is shared with dlPFC, ACC, anterior insula, and lateral parietal cortex whereas rmPFC co-activates with vmPFC, temporal poles, temporal sulcus, and posterior cingulate (Gilbert, Gonen-Yaacovi, Benoit, Volle, & Burgess, 2010). These differences in cytoarchitecture, structural connectivity, and functional co-activation raise the possibility of distinct functional organizations within BA10.

Considering these features of BA10, together with the evidence from cognitive neuropsychology, the observations indicating dysfunction in the ability to treat future events or acts as non-routine suggests that multitasking performance was affected due to the type of cognitive operations on which it likely depends, namely those supporting prospective memory (PM; see McDaniel & Einstein, 2007a, for review), and that some areas of BA10—rather than the entire subregion—might be uniquely critical to supporting them. PM is an important facet of the broader human ability involved in episodically simulating and planning future scenarios and behavior (i.e., prospection; see Seligman et al., 2016; see Schacter & Addis, 2007; Schacter, Addis, & Buckner, 2008; Schacter et al., 2012, for reviews on episodic simulation). As regards the particular prospective rudiments of memory, intentions to act in some specific way at certain moments in time (time-based intentions), or in the event of some hypothetical contingency (event-based intentions), constitute mnemonic representations of states of affairs that have yet to occur: that is, “memories of the future” (Ingvar, 1985). The ability to encode, retrieve, and act on these representations has a number of similarities and differences with those involving retrospective memory (Burgess & Shallice, 1997), with the chief distinguishing feature of PM being its temporal dimension, but another difference is that, in everyday life, PM is largely self-cued as well as the most common type of memory failure (Reason, 1990). Delayed intentions vary by their contextual nature (e.g., time, event, habitual, activity-based; Ellis, Kvavilashvili, & Milne, 1999) as well as the means by which they are retrieved after a retention interval. Regarding the former within the context of the above example, an intention to press the coffee when it ‘feels’ as though the requisite amount of time has passed is an example of a time-based intention, and an intention to press the coffee once one hears a preset alarm ringing is an example of an event-based intention. Although these types of intention differ in important ways (Kvavilashvili & Ellis, 1996; Meacham & Leiman, 1982), they are most similar in the sense that all intentions are more or less time-based (Block & Zakay, 2006), but even the most time-based intentions tend to involve event-based cues (Graf & Grondin, 2006)—albeit perhaps unintentionally. Fortunately, in contrast to everyday life, time-based PM can be isolated under laboratory settings by removing any external elements that might elicit event-based processing (McDaniel & Einstein, 2007a). Regarding the means by which delayed intentions are retrieved, that retrieval can be achieved through either spontaneous (i.e., automatic) or controlled (i.e., executive) operations is largely postulated (McDaniel & Einstein, 2007b). More specifically, when there are sufficiently salient environmental cues with which intentional representations can interact, retrieval occurs almost effortlessly, spontaneously, which is an idea that, in the retrospective domain, can be traced back to psychologists such as Ebbinghaus (1885/1964) and Freud (1938). That this interaction is mainly reflexive and associative in nature (McDaniel, Robinson-Riegler, & Einstein, 1998; Moscovitch, 1994) has received much empirical support (e.g., Breneiser & McDaniel, 2006; Einstein & McDaniel, 1990; Einstein et al., 2005; Hicks, Marsh, & Russell, 2000; Kvavilashvili & Mandler, 2004; Marsh, Hicks, Cook, Hansen, & Pallos, 2003; McDaniel, Guynn, Einstein, & Brenseiser, 2004; Reese & Cherry, 2002).

However, sometimes there are no salient environmental features to cue retrieval and the objects of ongoing actions contain little to no information about PM targets (see Maylor, Darby, & Logie, 2002). In these situations, it becomes necessary for the cognitive system to upregulate attentional resources to strategically monitor for the appropriate conditions under which to actuate an intention. On some views, this attentional monitoring is continuous (Smith, 2003; Smith & Bayen, 2004, 2006) and, on others', periodic (Harris, 1984; Harris & Wilkins, 1982; Miller, Galanter, & Pribram, 1960). The principal difference between these accounts appears to be whether the retrieval context is event- (continuous) or time-based (periodic). One reason is that, when task demands of ongoing behaviors are marked and retention intervals are longer than about 60 seconds, executive resources for monitoring quickly deplete; executive functions operate on finite cognitive resources (Shallice & Cooper, 2011). So, it becomes more efficient for the cognitive system to engage in periodic checking rather than continuous searching procedures in particular situations. Indeed, strategic monitoring tends to increase most just before intention retrieval cues are predicted to occur (Ceci & Bronfenbrenner, 1985; Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Kvavilashvili & Fisher, 2007; Harris & Wilkins, 1982). That such prediction operations are running in the 'background' from the outset of intention encoding suggests 'preparatory attentional and memory processes' which are probably continuous, but which might not tax cognitive control resources to a great degree (Smith, 2003). Thus, strategic monitoring likely involves both periodic checking and sustained attention, with their relative role in intention retrieval depending on the demands of a PM paradigm. For reviews on intention retrieval and the key parameters constituting a PM paradigm, see Burgess, Gonen-Yaacovi, & Volle, 2011; Ellis et al., 1999; Einstein & McDaniel, 1990; Graf & Uttl, 2001; Kliegel, McDaniel, & Einstein, 2000).

In light of the aforementioned neuropsychological evidence amassing in favor of a link between PFC damage, particularly to BA10, and impairments in the PM processing underlying multitasking behavior, neuroimaging research sought to investigate more rigorously the stage of PM processing at which disruption was occurring and the PFC subregions to which it can potentially be localized. For example, one seminal study was that of Burgess, Quayle, & Frith (2001) who used the neuroimaging technique of positron emission tomography (PET) to assess the neural underpinnings of intention maintenance and realization (i.e., retrieval and execution). In this study, the key contrast involved trials in which there was no intention realization, in that encoded intentions were maintained and retrieval cues were expected, but none occurred. Within the frontal lobes, this was associated with increased regional cerebral blood flow (rCBF) to lateral rostral PFC (BA10), bilaterally, and right dlPFC (BA46). Intention realization did not elicit this pattern of activation; in fact, rCBF in right dlPFC decreased (see also Burgess, Scott, & Frith, 2001). These findings were consistent with those in the cognitive neuropsychological research pointing towards rostral PFC as a subregion whose deterioration leads to a compromised ability to maintain future intentions (i.e., to sustain ‘intentional markers’). Later neuropsychological and neuroimaging studies have suggested some hemispheric differences regarding retrieval context, such that time-based PM tends to localize to right rostral PFC and event-based PM: the left (e.g., Morillon, Kell, & Giraud, 2009; Okuda et al., 2007; Picton, Struss, Shallice, Alexander, & Gillingham, 2006; Volle, Gonen-Yaacovi, Costello, Gilbert, & Burgess, 2011). This is in line with other research findings that people with damage to right PFC demonstrate poor performance on time estimation tasks (e.g., Coslett, Shenton, Dyer, & Wiener, 2009; Koch, Oliveri, Carlesimo, & Caltagirone, 2002; Harrington, Haaland, & Knight, 1998; Wiener & Coslett, 2008); that is, time-related processing seems to be generally favored by right PFC. For further review on the links between rostral PFC and PM, see Burgess and Wu (2013) and Burgess and colleagues (2012).

Although these links are well supported by neuropsychological and neuroimaging methods, such evidence does not decisively show PM as the function(s) for which rostral PFC is functionally specialized. Indeed, many other cognitive neuroscientific studies have implicated this region in many other cognitive domains—from paradigms of simple conditioning (e.g., Blaxton et al., 1999), to those of complex problem-solving (e.g., Christoff et al., 2001). But the evidence does indicate a potential subsystem that is capable of providing the functional support requisite of all these implicated cognitive operations. A subsequent study of Burgess and colleagues (2003) found evidence for a dissociation along the medial-lateral axis of rostral PFC, in that the PM conditions elicited relatively greater lateral activation than the ongoing-only ones, replicating the findings of their previous study, but, importantly, the ongoing conditions showed relatively greater medial activation. The emerging interpretation from these and other findings (e.g., Koechlin, Basso, Pietrini, Panzer, & Grafman. 1999; Okuda et al., 1998) was that BA10 supports a specialized subsystem for regulating attending between representations of the environment and those independent of it (Burgess, Dumontheil, & Gilbert, 2007a). More specifically, Burgess and colleagues have advanced the ‘rostral attentional gateway hypothesis’ which postulates that specific areas of BA10 support different modes of attending, namely stimulus-oriented thought (SOT) and stimulus-independent thought (SIT) (McGuire et al., 1996): rmPFC sustains SOT operations and rlPFC sustains SIT operations (Burgess et al., 2007b, 2007c; Burgess, Gilbert, Okuda, & Simons, 2006). Interestingly, research in this vein found that rlPFC not only biases activation in favor of SIT, regardless of the form it takes (e.g., from high-demand thinking tasks to low-demand ones such as ‘mind-wandering’) but also is responsible for transient switches between SIT and SOT (Gilbert, Frith, & Burgess, 2005; Gilbert, Simons, Frith, & Burgess, 2006; Gilbert, Spengler, Simons, Frith, & Burgess, 2006; Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; Simons, Owen, Fletcher, & Burgess, 2005; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006). Importantly, the use of the conjunction design (Price & Friston, 1997) provided significant explanatory power towards this attentional gateway system being domain-general. Other studies have also further specified the spatial area of rmPFC which biases activation in favor of SOT by evidencing differences in functional specialization along its rostral-caudal axis (Benoit, Gilbert, Volle, & Burgess, 2010; Gilbert & Burgess, 2008; Gilbert et al., 2006; Gilbert et al., 2007). Specifically, anterior rmPFC supports SOT, but posterior areas support aspects of a system that likely receives marked SIT biasing (Figure 2.3), namely ‘mentalizing’, which refers to the ability to think about mental states, particularly propositional attitudes, of others and the self (see U. Frith & C. Frith, 2003, 2006, for reviews). Thus, there is strong cognitive neuroscientific evidence in support of differential functions along the medial-lateral and rostromedial-caudalmedial axes of rostral PFC.

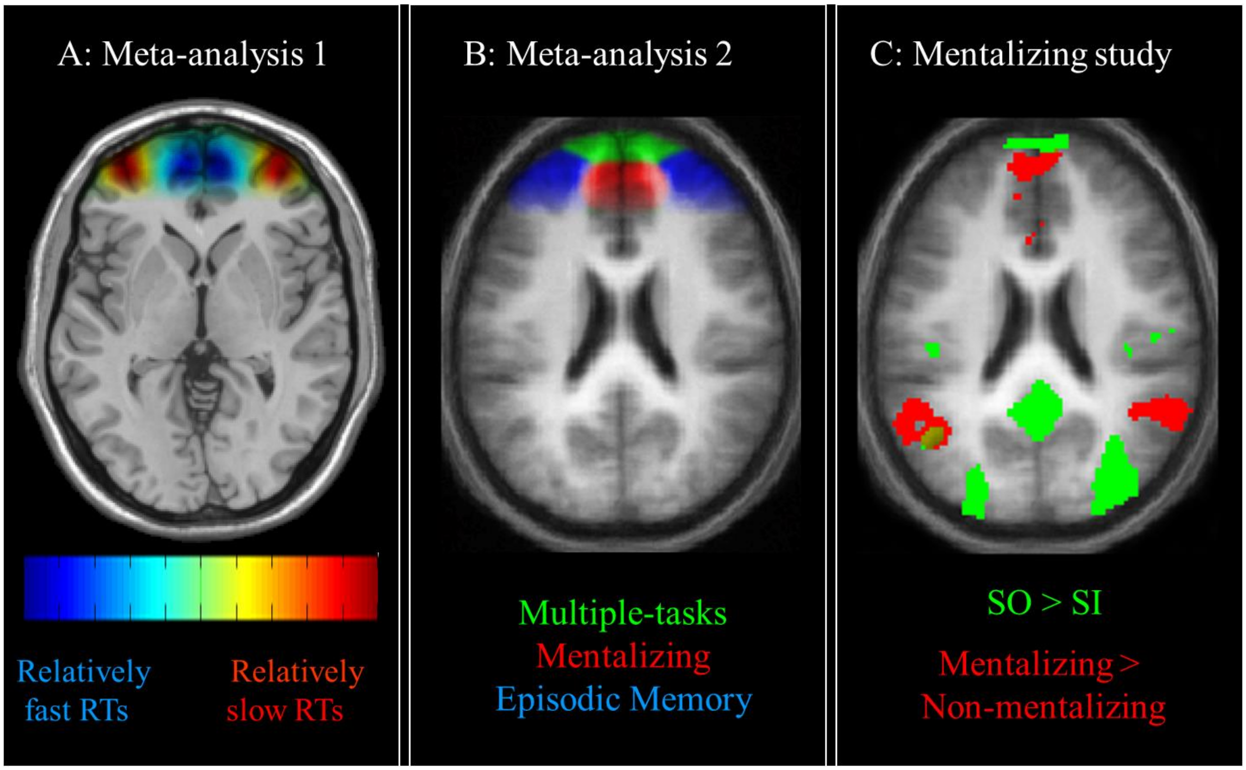

Figure 2.3 (*a*) Smoothed RT data from a meta-analysis of 104 functional neuroimaging studies reporting activation peaks in rostral PFC (Gilbert et al., 2006b). On average, contrasts producing activation peaks in regions colored blue involved faster RTs in the experimental task than the control task against which it was compared. By contrast, those contrasts where the RTs in the experimental task condition were slower than the control condition tended to produce activation peaks in the regions marked in red. This pattern occurred regardless of the type of paradigm under use (e.g., episodic memory, mentalizing, etc.). (*b*) Results of the second meta-analysis of these 104 studies, which investigated the association between different types of task and the location of activation peaks within rostral PFC (Gilbert et al., 2006c). Note that the studies involving multiple-task coordination tended to yield activation peaks rostral to those involving mentalizing. (*c*) Results of an fMRI study that crossed the factors of attentional focus (SO versus SI) with mentalizing (mentalizing versus non-mentalizing judgments; Gilbert et al., 2007b). The regions of activation in rostral PFC produced by the SO versus SI contrasts were rostral to those produced by the mentalizing versus non-mentalizing contrast. In both (*b*) and (*c*), the results are plotted on an axial slice ($z = 24$) of the participants’ mean normalized scan. Adapted from “Function and localization within rostral prefrontal cortex (area 10),” by Burgess et al., 2007, *Mental processes in the human brain*, p. 217, with permission from authors and Oxford University Press.

2.6 The Supervisory System

Therefore, the evidence for ipsilateral and contralateral differences in PFC functional specialization concords with the principal assumptions and predications of what is presently the most eminent theory of executive function in cognitive neuroscience: the Supervisory System model of cognitive control (Norman & Shallice, 1980, 1986; Shallice, 1988, 2004; Shallice & Burgess, 1991b, 1993, 1996, 2002; Shallice & Cooper, 2011). According to this model, the functional specializations discussed above are isolable, weakly modular subsystems of a broader system localized in the PFC. The general function of this system is to deal with situations for which more posterior brain regions involved in the automatized process of action and thought selection (i.e., contention scheduling; see Cooper & Shallice, 2000) are ill-equipped. Such situations are best characterized as novel problems: Task demands are not adequately learned, environmental stimuli do not meet activation thresholds in contention scheduling, or contention scheduling fails to satisfy active goal states. So, this broader system holds a modulatory or ‘supervisory’ role over contention scheduling and, indeed, the rest of the brain in such situations (Figure 2.4).

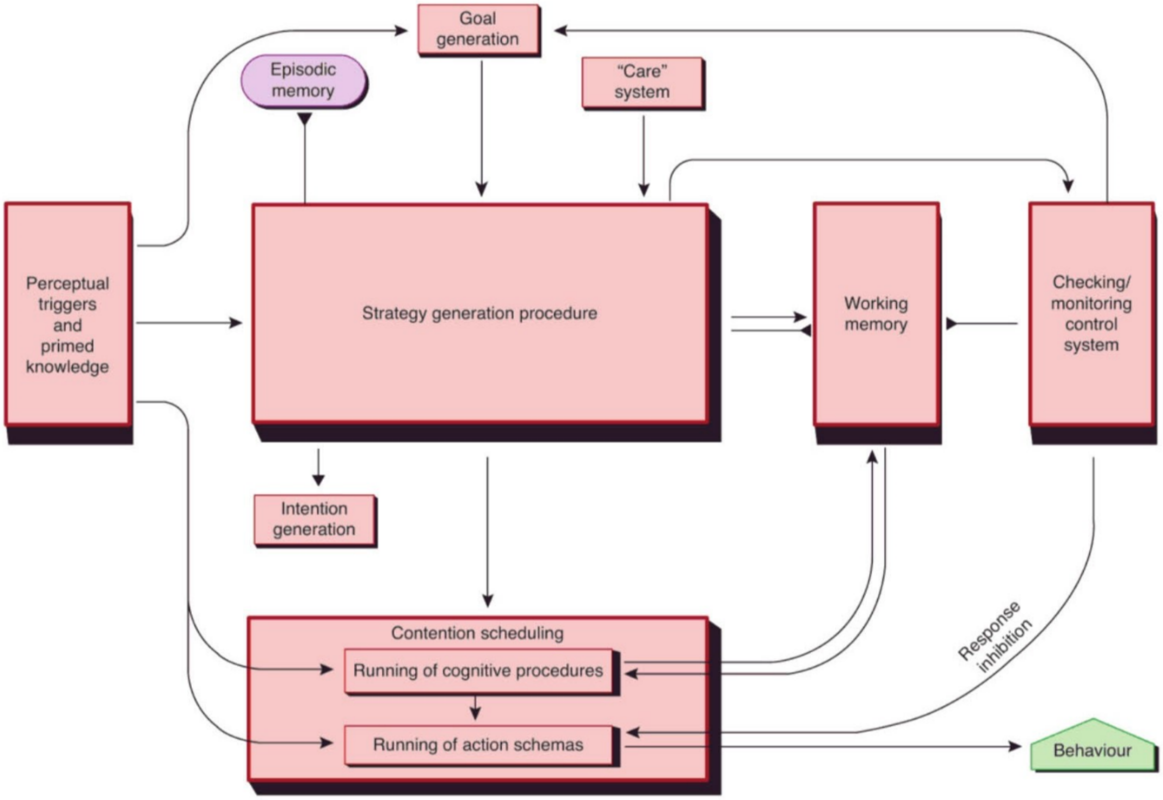

Figure 2.4 The Supervisory System (Mark III) and contention scheduling. Adapted from "*On the Organisation of Mind*," by Shallice and Cooper, 2011, p. 499, with permission from Oxford University Press.

There are three procedures by which the Supervisory System adapts action and thought to respond to novelty (Figure 2.5). Specifically, within its 'strategy generation procedure', it can generate and implement strategies prospectively, in that prespecified strategies (i.e., delayed intentions) are realized; episodically, in that they are retrieved and adapted based on previous strategies; and analytically, in that they are generated and selected or rejected based on the neurocognitive mechanisms of model-based problem-solving. This third method is the most taxing on control resources and probably the most common in everyday life considering the frequency with which environmental events and outcomes of antecedent actions create an impasse to, or change in the real-rime utility of, steps in a plan, requiring re-planning.

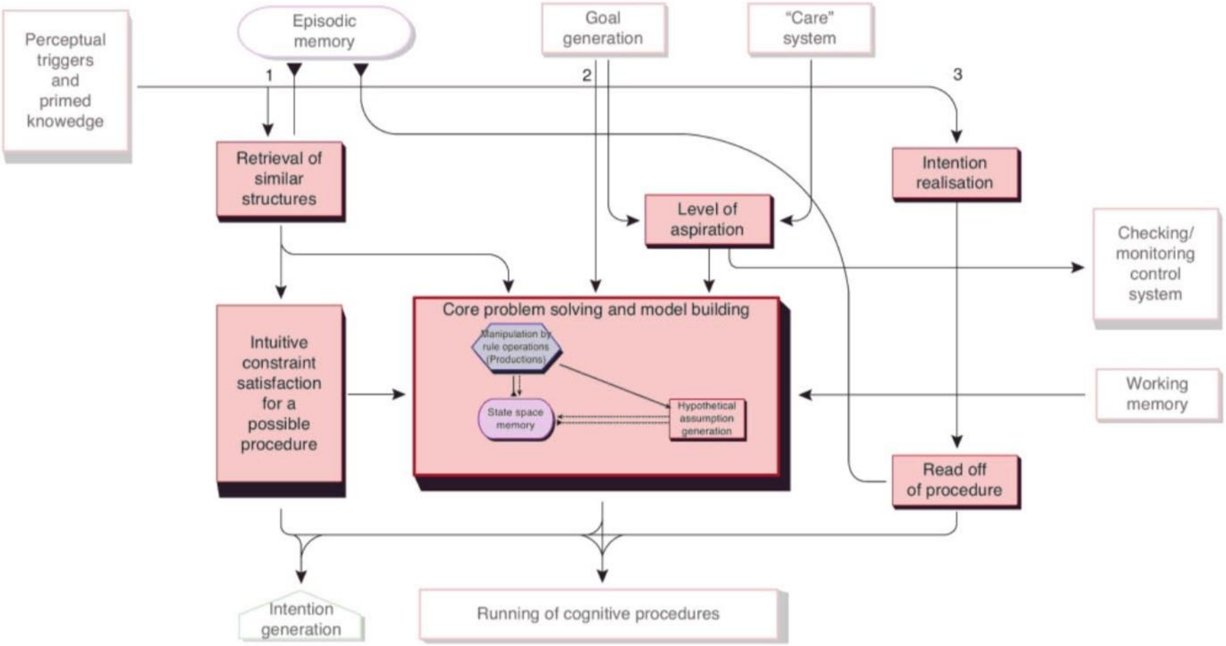

Figure 2.5 "The strategy generation procedure of the Supervisory System model. Three routes are proposed: through retrieval and adaption of a previous strategy; through model-based problem-solving; or through realization of a previously generated intention." Adapted from "*On the Organisation of Mind*," by Shallice and Cooper, 2011, p. 500, with permission from Oxford University Press.

Early evidence for this theory derives from neuropsychological paradigms linking PFC lesions to behavior that would be expected of contention scheduling running in the absence of supervisory modulation, such as utilization (e.g., Boccardi, Della Sala, Motto, & Spinnler, 2002; Brazzelli & Spinnler, 1998; Shallice, Burgess, Schon, & Baxter, 1989; see Lhermitte, 1983) and perservation behavior (see Sandson & Albert, 1984, for review). The former refers to behavior which is carried out uninhibited despite being unintentional, whereby some object in the environment triggers an action in the absence of a goal to act on the object: for example, incidentally opening and closing cupboards simply because they were there (see Eslinger, 2002). The latter refers being “stuck-in-set” during tasks for which there are strong stimulus-response contingencies, which are analogous to the ‘condition-action pairs’ of symbolic production systems in artificial intelligence (e.g., Newell & Simon, 1972), whereby ongoing actions are not inhibited in a way that allows for switching to other actions and thoughts based on changes in context and task demands (Milner, 1964; Sanders & Albert, 1984): for example, continuing to shake someone’s hand or having difficulty releasing it. Within the supervisory framework, contention scheduling refers particularly to the resolution of conflict between competing actions or thoughts and, more specifically, between the cognitive resources on which they depend—so operations requiring the same resources are not selected (Shallice & Burgess, 1991b). The actions and thoughts constituting the objects of strategies refer closely to Bartlett’s (1932) original sense of a *schema*, an efficient description of a state of affairs, but most closely to Piaget’s (1936), in that it “also is held to produce an output that provides the immediate control of the mechanisms required in one cognitive or action operation” (Shallice, 1988). That is, they are procedural memory structures akin to a ‘program’ at the level of information processing (Schmidt, 1975). Schemata are hierarchical in the sense that, for example, a ‘source’ schema represents an action sequence (e.g., making coffee, driving a car) and its component or ‘child’ schema control suboperations of particular actions (e.g., to open a coffee can, to accelerate, break, and turn). Complex behavior involving many source schemata that are moderately spaced in time (e.g., driving to a café for coffee and then returning home) have been conceptualized as relying on ‘memory organization packets’ (Schank, 1982), which are essentially ‘scripts’ that tie—as it were—higher-level schema together. There are typically many potential schemata—some appropriate, others inappropriate—that can be carried out at each given stage of an action sequence; the same applies to lower-level component schema. For example, when making coffee, the stage of opening a screwable lid of a coffee can might have two reasonable possibilities: twisting the lid clockwise or counter-clockwise. The former action is highly automatic (i.e., learned) for most people who make this coffee regularly and, therefore, there would be little need for the supervisory system, but in a foreign country wherein such objects are conversely turned, the prepotent schema will need to be so biased (i.e., inhibited) after detecting its ineffectiveness as to facilitate the generation, selection, and execution of less well-learned actions that might achieve the present goal.

Such solutions are seldom as obvious in everyday life as this exemplar and, consequently, the relative efforts of the supervisory subsystems of the PFC often need to be marked to achieve satisfactory solutions. But what is the nature of the cognitive ‘effort’ that upregulates supervisory subsystems? Evolutionarily, it would make little sense for a Supervisory System to operate invariably across novel situations and between individuals within them: Sometimes the nature of particular novel situations calls for the dedication of an inordinate degree of concentrated effort, yet those which do not sometimes receive it nonetheless because of the idiosyncratic importance ascribed to it on the part of individuals. So, the notion of exerting a motivated effort to sustain focus on a less than well-learned task accounts in part for this variability. At the level of commonsense psychological explanation, differences in the extent to which people are committed to a task are typically clear, but less so are the potential neurocognitive mechanisms driving them. Studying brain-behavior relationships has been central to building a more detailed understanding at the cognitive neuroscience level of explanation. Neuropsychological investigations in this area have pointed towards the medial rather than lateral surfaces of the frontal lobes. For example, studies using simple response time (RT) paradigms (e.g., 5-choice serial reaction time task) have linked a slowing of RTs to damage to superior medial areas (e.g., Alexander, Stuss, Shallice, Picton, & Gillingham, 2005, 2007; Stuss, Binns, Murphy, & Alexander, 2002; Stuss et al., 2005; Picton, Stuss, Alexander, Shallice, Binns, & Gillingham, 2007; Shallice, Stuss, Picton, Alexander, & Gillingham, 2008; Shallice, Stuss, Alexander, Picton, & Derkzen, 2008). This suggests that areas such as the ACC might provide a mediating role in supervisory operations, particularly by generally facilitating them (Posner & Di Girolamo, 1998). For example, in Stroop paradigms, pre-stimulus activation has been typically associated with dlPFC whereas post-stimulus intervals have largely recruited ACC and, importantly, increases in dlPFC activation over trials have been predicted from the preceding changes in ACC activation (Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000). In other words, ACC sustains activation to the lateral surfaces of the frontal lobes whilst they carry out their supervisory functions. Therefore, superior medial frontal regions seem to hold a slow, global function of *energization* that initiates rather than implements supervisory operations; at a more commonsense level of explanation, it is critical to supporting concentrated efforts (Shallice & Cipolotti, 2018).

One isolable information-processing subsystem of particular relevance to energization and the Supervisory System is the above discussed rostral attentional gateway. Conceptualized within a supervisory framework, this system is a domain-general subsystem of the Supervisory System that is anatomically localized along the medial-lateral axis of BA10 (Figure 2.6; Burgess et al., 2007). Its general function is to dynamically regulate activation gain in favor of stimulus-oriented and -independent attending to support the modulation that other supervisory subsystems exert over contention scheduling. So, rostral PFC serves a mediating role that is similar to the superior medial areas linked to energization. That is, it does not directly carry out the control operations that create, select, monitor, and reject cognitive strategies, but facilitates and sustains activation gain in favor of the SIT and SOT aspects of supervisory operations. This gives the rostral attentional gateway an aspect of computational precision that energization lacks—that contrasts with the slow, global function of sustaining the arousal, as it were, of the Supervisory System. For example, in the area of problem-solving, the responsibility of rlPFC is to direct and sustain activation gain towards pathways in other areas of the PFC which implement abstract thought operations.

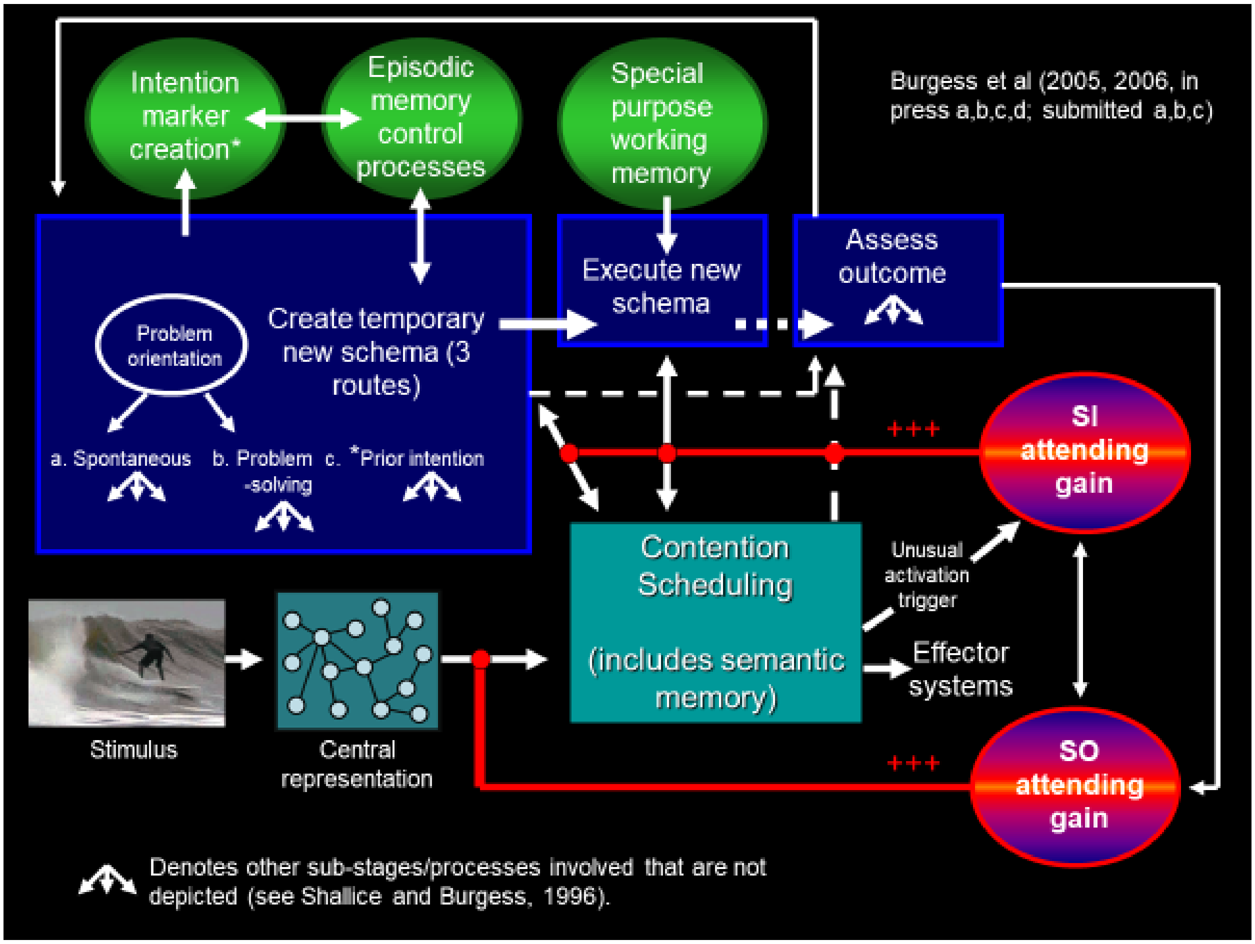

Figure 2.6. The Rostral PFC Attentional Gateway Hypothesis expressed within the framework of the Supervisory System model. Temporally distinct processing stages effected by the supervisory attentional system are shown in dark blue, with a sample of the specialized control resources these stages draw upon shown in green. Selection of an established behavioral routine (‘schema’) is effected at the ‘contention scheduling’ level. Processing stages between sensory input and the formation of a central representation or schema are not shown. The influence of the rostral PFC ‘attentional gateway’ is represented by red ellipses. Adapted from “Function and localization within rostral prefrontal cortex (area 10),” by Burgess et al., 2007, *Mental processes in the human brain*, p. 217, with permission from authors and Oxford University Press.

Another example is PM, in that rlPFC appears to be critical to maintaining the ‘retrieval mode’ to which Tulving (1983) alluded. Although sometimes the nature of a task places demands specifically and solely on SIT, such as those supporting creating and solving random arithmetic problems in one’s mind, everyday-life situations (e.g., multitasking) more often call for dynamic gating within rostral PFC. Attention needs to be allocated at particular moments to executing actions and monitoring for exogenous outcomes that would determine whether an active strategy is still useful towards facilitating some goal state. At the same time, multiple future intentions require maintenance, as does a tentative procedure for revising them as a consequence of detecting such feedback, and frequently actions need to be interrupted to execute some of these intentions and then resumed. Interestingly, because BA10 is probably the most extensively connected regions of the cerebral cortex (Semendeferi et al., 2001), and because the computational power of such an anatomically large subregion probably requires marked metabolic support from other regions, it is possible that its supervisory gateway subsystem is especially sensitive to changes in energization. Indeed, its lateral aspects that control switching between SOT and SIT also share functional connectivity with superior medial areas such as ACC (Gilbert et al., 2010). This could mean that low-level neurobiological effects—excluding long-term potentiation—influencing improvements to executive task performance might, at the level of information processing, be due to their effects on the upregulation of energization to the rostral supervisory gateway; subsequent chapters will further discuss this possibility in the context of these effects being the resultants of physical activity.

Thus is the general function of the Supervisory System: to modulate contention scheduling towards the generation and selection of schemata that run the cognitive operations appropriate for satisfying goal states arising from situations wherein there is either marked novelty, considerable consequences of failure, or salient stimuli that elicit inappropriate stimulus-response contingencies, which typically involves defining a problem stage, generating options, weighing them, forming intentions, monitoring outcomes, and responding to feedback (e.g., De Groot, 1965; see Shallice & Cooper, 2011, for further review). Energization arising from superior medial regions provides general and long-term support for the initiation of the laterally-localized subsystems into which the Supervisory System fractionates, and the attentional gateway of BA10 regulates the modes of thought involved in their implementation; for example, because novel situations often call for the creation of a temporary schema, this subsystem needs to sustain the operations involved in carrying out the strategy generation procedure.

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PART II

A PROPOSED SYSTEM AND EMPIRICAL METHOD

Chapter 3: A Model of Recogitation and the Ecological Challenges to its Investigation

3.1 Introduction

Characterizing recogitation using observations from clinical practice and principles of clinical theory is useful in producing some predictions at the level of information processing, such that recogitation is a cognitive task that falls within the domain of active thought: It represents an ill-structured, linguistically mediated problem that requires controlled reasoning in the interest of psychological well-being (Chapter 1). However, as with any type of cognitive system, scientific falsification (Popper, 1952) requires that it is ultimately realizable through a material substrate, so a neurocognitive theory of recogitation ought also to be constrained by the broader nature and organization of the human brain (Chapter 2). It is therefore hypothesized that the cognitive operations supporting recogitation are the executive functions of the prefrontal cortex (PFC). This is perhaps not a surprising or bold prediction given that its clinical application is to deliberately and consciously identify, refute, and supplant thoughts (self or others) promoting emotion dysregulation and maladaptive behavior. That is, a considerable executive effort is probably needed to carry out this metacognitive procedure, especially if it involves interpersonal dialectical discourse. So, the more pressing question is this: How might the brain facilitate specific applications of cognitive control to support the strategic goal of recogitation given what is known about the PFC and its role in reasoning?

3.2 The cognitive neuroscience of reasoning

Although the broader human ability to understand and respond to reasons has long been appreciated in philosophy, cognitive science, and experimental psychology (see Adler & Rips, 2008, for an anthology), it has been the neuroscientific research amassing from neuropsychological and neuroimaging methods that has provided the scientific constraint in theorizing about the information-processing systems into which reasoning ultimately fractionates in the brain. A predominant view in cognitive neuroscience is that reasoning is a higher-order emergent construct whose component processes, or neurocomputational operations, are largely executive in nature. For example, Shallice and Cooper (2011) state the following:

> An alternative way to unify thinking is to consider various forms as involving the generation of some kind of internal representation (a 'mental model', in the sense of Gentner & Stevens, 1983) of a situation and the manipulation of that representation according to task-dependent rules—a process that may or may not be goal-directed. What this and the 'thinking as problem-solving' approach have in common is the requirement for some form of temporary storage system in which a potentially abstract, counterfactual or hypothetical task representation can be maintained and manipulated. Both approaches also require processes for proposing and selecting modifications to the representation (hypothesis generation and selection), as well as some kind of monitoring and evaluative mechanisms, and presumably mechanisms for drawing on previous experience.

So, from this cognitive neuroscience perspective, although reasoning, problem-solving, and decision-making are sometimes conceptualized and studied as independent domains, their basic elements are largely realized through some of same executive functions that make any goal-directed form of thought possible in the brain.

There are several modes of reasoning that cognitive neuroscience has investigated, namely analogical, deductive, inductive, causal, correlational, counterfactual, relational, and abductive reasoning (see Krawczyk, 2018, for review). Many aspects of these types of reasoning are predicated on each other, with relational reasoning perhaps being the most rudimentary. Relational reasoning involves inducing or abstracting rules or relations from stimuli (e.g., literal, analogical) and integrating this relational information (i.e., relational integration) in a way that serves the task. For example, all informal and formal arguments in logic involve some relational integration (e.g., inferring a conclusion from premises), typically by way of syllogism. That is, whether the task is to infer something particular from generalities (deduction) or something general from particulars (induction), relationships between multiple premises and between these premises and their conclusion(s) need to be inferred and compared, including whether the stimuli are linguistic propositions, abstract symbols, or concrete images.

One example from the neuropsychological literature is the task of producing a rule for some relation. For instance, Burgess and Shallice (1996) developed the Brixton Spatial Rule Attainment Task that shows participants a series of cards. There are rows of white circles on these cards, but one circle is blue. The position of this blue circle changes as participants are shown new cards, and their task is to abstract what rule these changes might be following. This particular study used patients with damage to different areas their frontal lobes, as well as a control group. They found that the subgroup with damage to the left lateral PFC performed worse than any other group. Reverberi and colleagues (2005) later investigated the idea that the essential cognitive operation underpinning relational reasoning, such as in the case of rule induction, is the generation of hypotheses about stimuli (i.e., about stimulus-dependent representations). Rather than asking patients to discern a rule or two as in the aforementioned study, participants were required to generate as many different rules about the Brixton task as possible, finding that those with left lateralized PFC lesions produced the fewest rules (see also Wolford, Miller, & Gazzaniga, 2000). These findings are consistent with the idea that *hypothesis generation* (e.g., of a potential relation, rule, etc.) is critical to even the most basic forms of reasoning and, more broadly, is a largely left lateralized executive function (BA46). Hypothesis generation is a single suboperation of the core problem-solving and model building facet of the strategy generation procedure of the Supervisory System (Chapter 2) and is probably not the only executive function that is essential to human reasoning.

For example, many reasoning situations call for people to self-generate information about the semantic product of several relations. For example, Christoff and colleagues (2001) used a form of the Progressive Matrices task (Penrose & Raven, 1936) to investigate reasoning situations in which the solution (i.e., conclusion) needed to be self-generated. However, the middle frontal gyrus that was significantly recruited in this condition was on the right hemisphere rather than the left. One explanation is that although certain stimulus-independent thought (SIT) manipulations were carried out, the to-be-manipulated information was not self-generated: Participants selected a solution from several options. Shallice and Cooper (2011) argue that what was perhaps most computationally demanding in this paradigm was some verification process, which is consistent with the previously discussed findings on the role of right BA46 in monitoring and checking. So, the process of hypothesis generation is probably closely linked to a subsequent one involving verification: *hypothesis testing*. Indeed, others have implicated this subregion of the right PFC in the rejection of invalid analogies in verbal analogical reasoning paradigms as well as in the detection and resolution of belief-based reasoning conflicts (Goel & Dolan, 2003a, 2003b). It is worth noting that Goel argues that the right PFC, particularly right pars orbitalis (BA47), is particularly involved in reasoning problems that are ill-structured.

Unsurprisingly, rostrolateral PFC (BA10) is also commonly recruited in reasoning studies (Wendelken, Nakhabenko, Donohue, Carter, & Bunge, 2008), including the above-mentioned ones. Attentional support for the endogenous operations (e.g., abstracting, comparing, rejecting relations/inferences) that form a major part of people's ability to reason is presumably behind this association. For example, with respect to generating relational hypotheses about stimuli, Kroger and colleagues (2002) found greater activation in BA10 when the number of inferences (i.e., hypotheses) that need to be generated was increased. Involvement of this area should be expected given that these hypotheses constitute self-generated information—information whose generation in other regions needs endogenous biasing. These finding are therefore consistent with the 'rostral attentional gateway hypothesis' (Burgess, Dumontheil, & Gilbert, 2007). Another aspect of this role of BA10 in reasoning is that the objects of problems are not always stimulus-dependent representations (e.g., propositions written on a screen). For example, when a financial adviser is thinking about plans for developing a diversified investment portfolio whilst driving to work—rather than researching potential index funds on a computer—attention is periodically biased towards SIT to carry out this thinking task. The task is self-initiated and the relevant information derives not from the external world, but from self-generation. So, greater involvement of BA10 would be expected in these situations.

Importantly, although reasoning problems are largely PFC-based, executive functions are not the only cognitive components supporting these mental tasks. Reasoning tends to implicate functions that draw on features of the semantic network (e.g., concrete and abstract information retrieved from declarative memory) within more posterior regions of the brain (Krawczyk, 2018). For example, comparing and compounding semantic associations to reach a new one (i.e., insight) has been associated with right anterior superior temporal gyrus (STG) (Bowden & Jung-Beeman, 2003; Jung-Beeman et al., 2004). Interestingly, the bringing together of more distance semantic content (relational integration) in creative analogical reasoning problems places greater demands on lateral BA10 biasing (e.g., Green et al., 2006); Green and colleagues (2017) showed this again using transcranial direct-current stimulation [tDCS]).

So, the information on which the executive functions relevant to human reasoning operate are not always dependent on immediate perception. These functions (e.g., hypothesis generation and testing) seem to be integral to several modes of reasoning, notably problems that are ill-structured and linguistically mediated. But reasoning is not carried out in the frontal lobes entirely. The integrity of semantic systems located in more posterior areas of the brain, such as the temporal lobes, is as potentially important to performance as the more rostrally localized ones. That there is an anterior-posterior dynamic of functional activity during reasoning problems, and active thought more broadly, has some bearing on what can be expected of a brain supporting a recogitation task.

3.3 An information-processing model of recogitation

According to Ochsner and Gross (2014), the role of appraisal in emotion can be described in terms of the functional architecture of valuation, which consists of a three-stage processing cycle: a perception-valuation-action (PVA) cycle. Specifically, the perception stage involves processing sensory stimuli, namely the thalamus and primary, secondary sensory cortices encode sensory input and, subsequently, send the information to systems responsible for computing value (Kravitz, Saleem, Baker, & Mishkin, 2011). The valuation stage involves the processing of multiple valuations that vary in complexity (Sherer, 2001): core, contextual, and conceptual valuations. Core valuations represent basic affective responses that are automatically activated by stimuli, which are predominantly processed by subcortical and brain-stem systems such as the amygdala and ventral striatum (Delago, Jou, LeDoux, & Phelps, 2009; Holland & Gallagher, 2004; Wager et al., 2008). Contextual valuations process S-R mappings in light of motivational, historical, and social contextual information. For example, contextual valuations determine the degree to which the value of a stimulus changes as a function of a certain context and, therefore, whether in that context the stimulus ought to be pursued or avoided. There are several brain regions important for processing contextual valuations, namely the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) (Lin, Horner, Bisby, & Burgess; Ongur, Ferry, & Price, 2003; Price, 1999), as well as the temporoparietal junction (TPJ) (Saxe, 2006; Young, Camproden, Hauser, Pascual-Leone, & Saxe, 2010) and anterior insula (Craig, 2003; Harrisonn, Gray Gianaros, & Critchley, 2010; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Zaki, Davis, & Ochsner, 2012).

Conceptual valuations are available to consciousness and linguistic expression (Ochsner, Ray et al., 2009). The rostromedial prefrontal cortex (rmPFC) and dorsomedial prefrontal cortex (dmPFC) have been implicated in the task of describing the semantic meanings of a stimulus to which one is selectively attending (Cato et al., 2004; Kalisch, Wiech, Critchley, & Dolan, 2006; Lindquist & Barret, 2008; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Mitchell, 2009; Olsson & Ochsner, 2008; Zysset, Huber, Ferstl, & von Cramon, 2002). The ventrolateral prefrontal cortex (vlPFC) has also been implicated in conceptual valuation, in that it has been found to be important for selecting and inhibiting value representations—regardless of valence (Aron, Robbins, & Poldrack, 2004; Badre & Wagnew, 2007; Barrett, 2006; Gallaghter & Frith, 2003; Lieberman et al., 2007; Lindquist & Barrett, 2008; Mitchell, 2009; Olsson & Ochsner, 2008; Thompson-Schill, Bedny, & Goldberg, 2005). Finally, the action stage involves responses according to the preceding valuations. Specifically, these adjustments are either mental or physical in that the former encompasses cognitive processes from vision-based actuations to manipulations in working memory, and the latter comprises behavioral and physiological actuations such as facial gestures and sympathetic nervous system activation (Ochsner & Gross, 2014).

The neurocognitive evidence for this functional architecture bolsters the explanatory power of the emotion generative procedure discussed in Chapter 1 (Figure 1.1). Importantly, the brain areas implicated in emotion generation, particularly conceptual valuations (i.e., appraisals), raise the question of whether these are the neuroanatomical objects of change in mental health interventions. This seems to be the case in the medial PFC (Yoshimura et al., 2014), but what are the neurocognitive systems engendering this change? It is postulated that the information-processing systems in the brain underpinning people's ability to reason are still at work when moving from descriptive propositions to affective ones about the self, others, and world. Take, for example, the philosophy of logic: A deductive argument is formally valid to the extent that its conclusion necessarily follows from its premises, regardless of their truth. An argument is sound if its premises are also true. Informal arguments (i.e., inductive ones) whose conclusions follow from its premises—albeit unnecessarily—are considered cogent rather than valid. So, both types of logic involve not only producing conclusions from premises but also verifying whether an argument structure is valid or cogent, as well as if its premises are sound. As discussed above, producing and verifying inferences likely depend on hypothesis generation in the left lateral PFC (BA46) and monitoring and checking procedures in right lateral PFC (BA46), respectively, as well as on marked SIT biasing on the part of rostral PFC (BA10). These executive functions are at work in virtually any reasoning problem and their domain-general nature means that they can act on not only linguistic propositions that describe the features of reasoning problems but also those that might reflect normative ones.

For example, dysfunctional appraisals, as the objects of recogitation in clinical practice, can be framed in a similar way to logical arguments, namely as a conclusion in an argument that is typically valid, yet unsound: (P1) “People who make little money are losers”; (P2) “my new job pays very little”; and (C), therefore, I am a loser, which I must not be.” Formally, the inference is valid, but P1 is false. This logical structure representing maladaptive schema (P1), goal-incongruent events (P2), and appraisals (C) is something that clinicians attempt to extract from the verbal communication they have with clients. This provides them with a better understanding of how unhealthy emotional responses were elicited and, importantly, the input for recogitation. That is, once the appraisal of interest is detected (self- or other-initiated), this information is presumably maintained in a short-term buffer whilst other operations carry out manipulations. These two steps are represented as the first two elements of the cognitive model of recogitation below (Figure 3.1). When interpersonal interactions are absent (e.g., outside clinical settings) and individuals need to detect their thoughts during an emotional experience, this information will need to be brought into activate maintenance through other means.

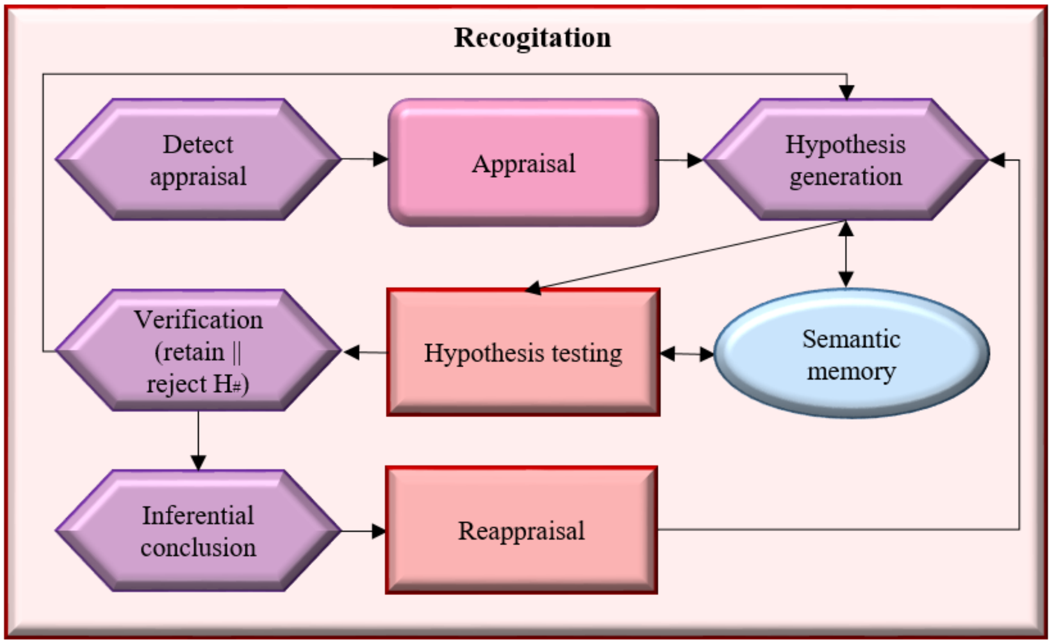

Figure 3.1 An information-processing model of recogitation, with box- and -arrow diagram key based on the COGENT formalism (Figure 1.2).

Once these personal semantics about a goal-incongruent event are explicitly identified and maintained, clinicians carry out verbal intervention strategies, such as those in cognitive-behavioral therapy (CBT)-based forms of psychotherapy (Hofmann, 2014), that target dysfunctional thoughts. As argued in Chapter 1, this verbal behavior should have cognitive underpinnings and antecedents: The ‘thinking’ subtask of clinicians, and someday their clients, is to ‘again-jointly-turn over’ the logical, empirical, and practical merits of a propositional attitude(s) in active maintenance. The executive functions relevant to this recogitation of thought might therefore be those involved in generating hypotheses (i.e., reasons) about these merits and their semantic content—about why a particular inference is erroneous and harmful to continue believing. This is the third element in Figure 3.1 and is potentially a central cognitive operation of recogitation. So, a clinician might self-generate a hypothesis about P1 in the example above, such as “This belief is irrational because the premise involves a universal ascription about one’s personhood, and no one aspect of an individual’s life (e.g., salary) defines who one is (H1).” That is, P1 is tenuous because any positive aspect about oneself provides the evidence that falsifies the universal claim (e.g., one black swan refutes the premise that all swans are white). It is worth noting that hypothesis generation is not unique to reasoning in the clinical domain, because many other reasoning problems in other professions likely rely on it, such as mechanics, physicians, computer technicians, lawyers, and so forth. This clinical example of hypothesis generation raises an important insight that Ellis (1994) has frequently described as the psychological trap of self-esteem. For example, if a higher paying job was acquired in the future, how would one then *become* more worthwhile; how is one’s value subject to vacillation by external events if it is an inherent property? Inherent properties are analytically immutable. In addition, why *must* one always be worthwhile? Addressing this demandingness as well as the tendency to use universal ascriptions obviates falling into the psychological trap of esteeming. That is, this clinical example appropriately refutes both the irrational schema (P1) and dysfunctional appraisal (C).

However, it is not enough to simply generate reasons for why certain propositional attitudes might be irrational, because hypotheses will likely vary by how well they satisfy semantic criteria for that which constitutes a thought as maladaptive. Other executive functions are needed to determine the appropriateness of a hypothesis and whether it should be retained or rejected as a belief. More specifically, each hypothesis that is generated plausibly requires active testing/checking to gauge how well it refutes the content of an appraisal. That is, if a hypothesis is detected as erroneous in some way, then it is rejected and a new one needs to be produced and selected before moving forward with verbal elaboration (e.g., interpersonal communication with a client). One possibility is that a retained hypothesis signals an inference that the appraisal under recogitation should be rejected, epistemologically, and that the goal-incongruent event(s) that initially elicited negative affect should be reappraised. These processes represent steps 4-7 in the recogitation model (Figure 3.1). New beliefs that are the result of reappraisal (e.g., "Making less money than I have in the past is undesirable, but I am no less worthwhile if I do, and there is no reason why I must make more.") are subject to the same fallibility as the old ones and the hypotheses generated about them, which should call for additional monitoring of the reappraisal, too. In other words, creating new meanings for goal-related stimuli needs to be checked against semantic criteria that constitutes a reappraisal as a functional, healthier alternative to the appraisal being supplanted (final step in Figure 3.1). Lastly, new propositional attitudes are encoded throughout the semantic network in posterior brain regions for long-term storage—until the next goal-incongruent event. This cognitive restructuring as a function of recogitation might then influence future interactions with goal-incongruent events; the new beliefs affect the emotion generation procedure in future instances, yielding decreases in parameters such as intensity and duration.

So, if recogitation is a metacognitive, reasoning task that uses executive functions such as hypothesis generation and testing to modify the semantic content of conscious thoughts, then the neural correlates of these cognitive operations should be the same as those implicated in executive function research and, importantly, they should be present during naturalistic interpersonal interactions in clinical settings. This means that significant changes in left and right BA46 might be expected prior to verbal articulation. The recruitment of left vlPFC might also be expected given the linguistic and retrieval demands of covert self-talk as well as that of selecting hypotheses and inhibiting rejected ones. Moreover, the ill-structured and novel features of recogitating might require support from right vlPFC, particularly BA47, in a similar way to other reasoning problems. In addition, activity in certain nodes of the semantic network (e.g., supramarginal and angular gyri in the inferior parietal lobule) might represent aspects of the propositional attitudes under recogitation and their subsequent semantic change. However, the need to bias the mind in favor of these SIT operations will likely have marked resource demands and, therefore, marked recruitment of BA10 might be expected, which could potentially overshadow observations of less critical subsystems.

This list of candidate subregions for a recogitation network is not exhaustive, with other areas likely working together to support the overall task, such as medial PFC and anterior cingulate areas. The number of cortical regions that potentially support this information-processing model will vary depending on the task parameters at the outset of task initiation. For example, if interpersonal communication is involved, as it is in the clinical domain, then the nodes of that social network would also be at work during intervention strategies that rely on recogitating dysfunctional beliefs. Another example is the fact that the objects of recogitation can vary. The stimulus-independent thoughts that are recogitated can be descriptive or normative, and these propositions can be retrospective, prospective, or *in situ* (during an experience).

Take, for example, the research area of prospection, episodic simulation represents a SIT-based mental task that has been known to elicit affective valuations (Demblon & D'Argembeau, 2016; Szpunar, Jing, Benoit, & Schacter, 2015). More specifically, this system allows people to simulate what experiencing future states of affairs might be like. According to the 'constructive episodic simulation hypothesis', "episodic memory supports future simulation by allowing people to flexibly retrieve and recombine elements of past experiences into novel representations of events that might occur in the future" (Schacter, Benoit, & Szpunar, 2017). Neuroanatomically, subregions of the hippocampi are largely involved in mediating this constructive process (see Schacter & Addis, 2007, for review), particularly the right hippocampus, as well as the vmPFC and the functional connectivity it shares with these regions (Campbell, Madore, Benoit, Thakral, Schacter, 2017). The vmPFC supports not only the generation of an episodic simulation but also the integration of its details with affective valuations to produce a more general, hedonic evaluation of stimuli (Benoit, Szpunar, Schacter, 2014). So, valuations (appraisals) in the modal model of emotion (Ocshner & Gross, 2014) can be prospective in nature. It is perhaps therefore unsurprising that a hallmark symptom of emotion dysregulation in anxiety disorders is the propensity to simulate potential events that are catastrophic (prospective catastrophizing). So, the different contexts and situations involving the task of recogitation potentially affect the quantity and quality of systems that are recruited in the brain (e.g., social interaction). Moreover, although the executive functions into which recogitation fractionates are domain-general mechanisms, the types of propositional attitudes they modify have distinct informational domains which might tap different cognitive resources depending on the systems that formed them.

In sum, this neurocognitive model of recogitation is based on theoretical syntheses of clinical psychology and cognitive neuroscience. Its general function is to use the executive and semantic systems supporting human reasoning to modify propositional attitudes. Its application to clinical practice lies in the targeting and updating of aspects of the human belief system that are deleterious to mental health (Figure 3.1). The hypothesized neuroanatomical correlates of this cognitive procedure are testable, but there are several theoretical and methodological challenges to studying recogitation as a subject of clinical cognitive neuroscience.

3.4 The problem of ecological validity

At the information-processing level of theorizing, is it not critical that the resource demands tasks place on the cognitive system reflect those consumed in nature—in the commonsense psychological descriptions of human adaption which have after all always been the first source of inference to latent constructs? The methods of experimental psychology, cognitive neuropsychology, and neuroimaging bridge the explanatory gaps between cognitive theorizing and knowledge of brain function (Shallice & Cooper, 2011), but sometimes experiments involve behaviors that are not closely linked to the situations in which they are purportedly carried out. One reason is that theoretical constructs of neurocognitive mechanisms typically drive the development and selection of macro- and micro-aspects of experimental design, and of the methods employed to index dependent variables in a paradigm, but seldom do the observable, real-world functions of these mechanisms direct these decisions in cognitive neuroscience. Traditional experimental psychology has long been criticized for using paradigms that fail to reflect the natural situations upon which certain forms of cognition are called (e.g., memory; Neisser, 1981). The extent to which tasks represent functions at the level of the person and generalize in their predictability of responding in everyday-life situations is the degree to which they are valid, *ecologically*. Neisser's critique is now commonly included in introductory textbooks of cognitive psychology, but cognitive neuroscientific research tends to ignore this admonishment. However, the subfield of cognitive neuropsychology provides some good exceptions (Shallice, 1988). For example, a multitude of neuropsychological tests for assessing acquired and developmental deficits have been developed as formalized versions of real-world activities (see Burgess, Alderman, Evans, Emslie, & Wilson, 1998), and it has been demonstrated that tasks which have taken a more function-led approach in their development are equally psychometrically sound and more predictive of the ways in which people (un)successfully interact with their environments to attain goals (see Burgess et al., 2006, for review).

However, functional neuroimaging appears to have taken ecological validity less seriously. One reason is that neuroimaging is the newest methodology in the arsenal of the cognitive neuroscientist and, consequently, most studies have elected pre-existing, construct-led tasks from traditional experimental psychology to validate brain-behavior relationships with these techniques. But this has implicitly, as Kingstone, Smilek, and Ristic (2003) have cogently stated, "… eliminate[d] any need or obligation by the scientist to confirm that the factors being manipulated and measured in the lab actually express themselves in the real world." Low ecological validity risks the possibility of neuroimaging designs failing to capture all the component processes supporting the phenomenon of interest, potentially hindering an understanding of their organization in the brain. In other words, if there is only the smallest vestige of a translation of a task into features of the environmental or social world with which people interact, there is a neglection of the link which ought to be secure between observed changes in functional activation and that which is purportedly engaged during these interactions.

This neglection—that the real-world functions of constructs do not thoroughly inform task development and analysis—is a serious issue for explanation in cognitive neuroscience in terms of being able to infer the cognitive operations which realize behavior in real life, but it is not deliberate on the part of cognitive neuroscientists: Factors inherent to laboratory environments and certain methods restrict ecological validity. For example, that testing environments of neuroimaging laboratories (e.g., functional magnetic resonance imaging [fMRI]) are foreign to participants highlights a rudimentary limitation in the ability to contrive neuroimaging tasks that address this issue. Namely, laying on one's back in a rather noisy machine is not something to which anyone is accustomed, and participants cannot physically carry out a multitude of actions. As Shamay-Tsoory & Mendelsohn (2019) have recently characterized the issue, these are person- and situation-dependent factors that restrict the ability of participants to behave and move naturally as agents in environments resembling real-life contexts. These factors introduce limitations to the enterprises investigating particular domains of research such as episodic and spatial memory and social cognition. For example, to what extent can the uniquely human subsystems enabling spatial navigation be understood insofar as neuroimaging research fails to elicit the situations in which the brain fully integrates the multifaceted information concomitant to navigation, such as idiothetic information (see Park, Dudchenko, & Donaldson, 2018; see also Spiers & Maguire, 2007)? Importantly, a construct-driven approach to a program of investigation does not necessarily engender erroneous inferences to the localization of isolable subsystems, but it does lack the theoretical constraint that a more function-led approach places on inference, and this lack of ecological validity raises an issue when the postulated operations are of any applied, clinical relevance (e.g., Burgess et al., 2006). Namely, if the task developed or selected to recruit the subsystem(s) of interest contains few features derived from observable functions (i.e., low representativeness), there is almost certainly also a loss in sensitivity to the clinically relevant real-world phenomena to which it aims to predict and generalize (predictive validity).

That neuroimaging tasks and environments are not ecologically representative does not suggest that they all ought to be. For example, a measure with high ecological validity in the clinical domain is the continuous motor tracing task, which measures the loss in specificity of coding in Parkinson's disease (i.e., fine motor actions) observed during writing and tracing. However, some tasks developed to investigate low-level, automatic processes do not need to closely reflect some complex, real-world behavior to recruit the base-region localizations of the subsystems of interest. For instance, flashing checkerboard and finger-tapping tasks are sufficient in stimulation to elicit basic sensory and motor systems in the occipital and parietal lobes, respectively. But many important neuroscientific questions postulate information-processing systems that are intricate and dynamic and not so straightforwardly captured by computer-mediated stimulus designs. To place the appropriate computational demands on these higher-order cognitive functions, more ecologically valid stimulus designs are required—ones that contain the real-world events which typically elicit the behavior of interest. For example, a theory about the unique neural bases of human-to-human interaction (e.g., Di Paolo & De Jaegher, 2012) is best tested using an experimental design capable of including real conspecifics, as compared to images and videos of other people (e.g., Noah et al., 2020). So, although some paradigms do not call for higher levels of ecological validity, some predictions (e.g., clinical ones) are perhaps best studied using environments and tasks that have been developed to recreate the natural behaviors that function to help people to adapt to novel situations.

Cognitive neuroscientific research has discovered much in the clinical areas investigating relationships between the pathogenesis of psychopathological symptoms and abnormalities in the brain, such as hyper- and hypo-activation in regions supporting aspects of affective, semantic, and executive processing, as well as underconnectivity in the functional connections between such regions (see Hariri, 2015, for review). Other research has focused on more structural, developmental, and genetic relations with functional aspects of the brain and psychopathological symptoms. Another vein of research is that which investigates interventions for psychopathological symptoms (e.g., CBT-based forms of psychotherapy, pharmacological treatments). Investigating the treatment of such symptoms generally begins with the selection of one or more different methods to quantify cognitive, emotional, behavioral, and neurophysiological outcomes of treatment (Barlow, Durand, Lalumiere, & Hofmann, 2021). More successful treatments are those which lead to decreases in psychopathological symptoms and increases in positive emotion, rational beliefs, and adaptive behavior, as well as physiological changes in the brain, such as a less reactive amygdala in the case of anxiety. These outcome measures that assess changes over time as a function of treatment are best understood in this vein of research, because experimental designs have easily allowed for such periodic collections of data. For instance, patients' participation often involves leaving the clinical setting to attend a scheduled appointment at a neuroimaging laboratory to have their brains examined, with data being collected at different times: before, between, and after treatment. Thus, a common framework used to examine the effects of interventions on mental health is to collect data *periodically* at multiple instances rather than *continuously* within clinical settings (Crum, 2021).

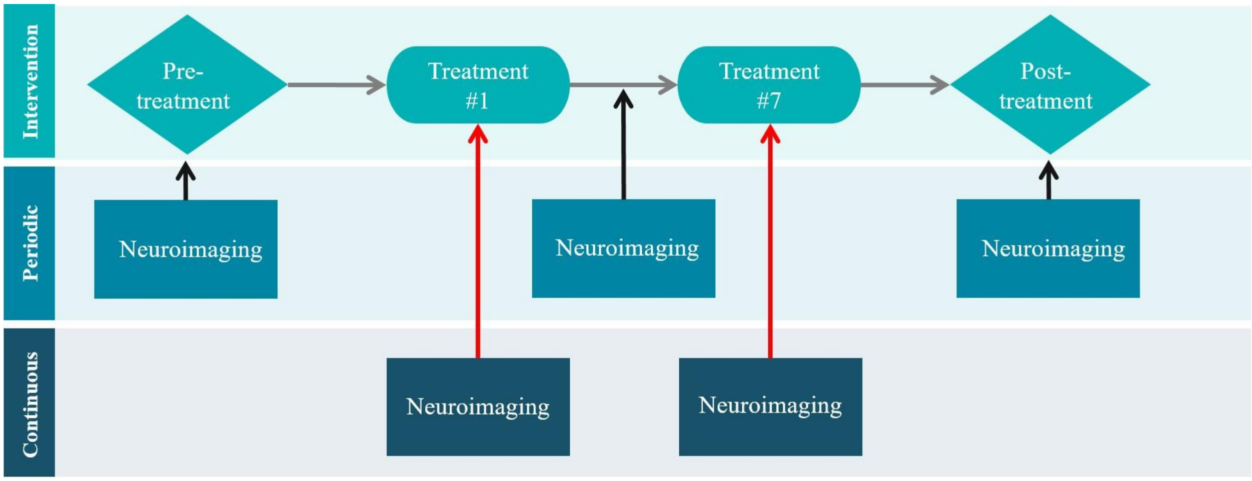

Figure 3.2 Data collection in psychotherapy. Neuroimaging and psychological methods typically collect physiological, behavioral, cognitive, and affective data *periodically*, such as pre-treatment, between treatment sessions, and post-treatment, to examine the effects of an intervention on the dependent variables of interest over time, leaving an explanatory gap regarding the potential neurocognitive mechanisms by which these effects are actuated and cultivated within treatment sessions. Adopting a more *in situ* approach that collects data within particular treatment sessions should address this issue. So, a hybrid approach of the former and latter stands the best chances of capturing the changes facilitating mental health.

This repeated design is ubiquitous and powerful in the clinical domain for its ability to assess the effects of a given intervention over time, but there is an explanatory gap regarding the ability to capture the implementations of the subsystems posited as being involved in such change. That is, research on the treatment of psychiatric conditions aims to link changes in regional metabolic activity and synaptic neurotransmission with changes in cognitive and emotive outcome measures that indicate decreases in dysfunctional thought operations and emotional reactivity, which is important to better understand the ways in which these changes in the brain relate to improved well-being, but the functional architectures engendering these changes throughout the course of treatment remain unclear. For example, psychotherapy for depression facilitates increased activity in left rostral anterior cingulate cortex compared to before treatment (e.g., Sankar et al., 2018), suggesting that this subregion might have undergone adaptive changes that play a role in the task of downregulating negative emotion, but what isolable subsystems in the brain—that were presumably engaged during treatment, and elicited on the part of the clinician—worked together to engender these functional changes? So, the approach of testing psychopathological populations on emotion regulation strategies to investigate brain regions that are hyperactive or hypoactive, or weak in functional connectivity with other regions (see Harari, 2015), and examining the ways in which these trends change as a function of time (i.e., treatment), is limited in its ability to infer from these observed changes the networks trained during treatment. Thus, little is understood at the levels of information processing and the brain about the transient cognitive and functional changes that take place within the clinical intervention sessions that underly improvements to mental health.

Because neuroimaging is not conducted whilst clients engage in psychotherapy-based treatments in a way that is designed to examine mechanisms of change, cognitive neuroscientists interested in studying such mechanisms have instead largely focused on one of the most important factors of psychotherapy: emotion regulation (Gross, 2014). The general approach has been to develop experimental tasks that require clinical and non-clinical populations to engage in various regulation strategies to downregulate negative emotion, with cognitive change at the center of this research (Figure 3.3). Reappraisal involves attributing a new meaning, a new appraisal or affective valuation (Lazarus, 2001; Scherer, Schorr, & Johnstone, 2010), to a goal-incongruent situation. Several fMRI studies have investigated the neural correlates of reappraisal tasks (e.g., Braunstein, Gross, Ochsner, 2017; Kohn et al., 2014; Messina, Bianco, Sambin, & Viviani, 2015; Ochsner & Gross, 2005; Ochsner & Gross, 2008; Ochsner, Silvers, & Buhle, 2012), finding that the greatest cognitive demands are placed on subregions in the executive and semantic systems—along the anterior-posterior axis, respectively.

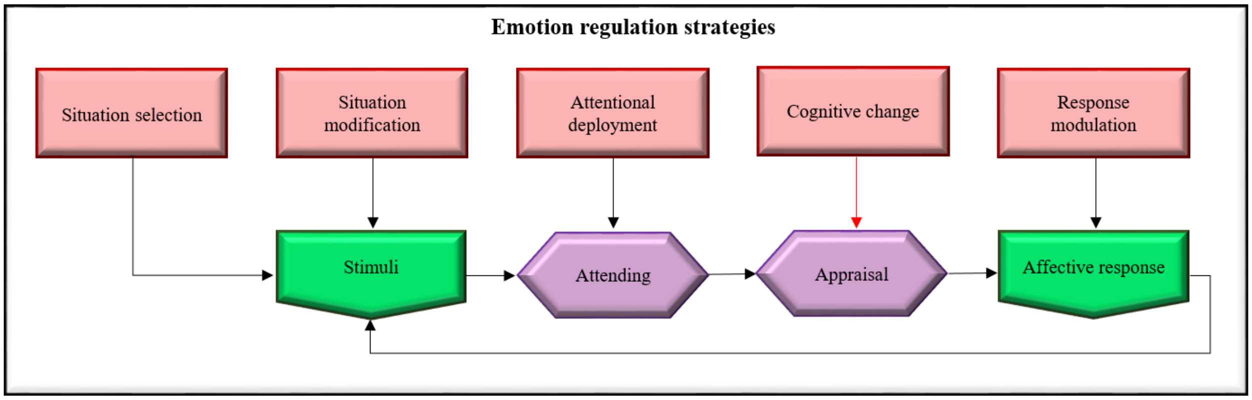

Figure 3.3 The process model of emotion regulation (see Gross, 2014).

The veins of research investigating cognitive change from a general framework of human functioning and from the context of emotion dysregulation have found that reappraisal relates negatively with negative emotions and psychopathological symptoms, respectively, and is an adaptive strategy for attenuating them (see Johnstone & Walter, 2014; Ochsner & Gross, 2014, for reviews).

Although reappraisal paradigms have used tasks designed to elicit the downregulation of negative emotion, they poorly reflect the cognitive strategies used in clinical practice. For example, the operational definition of reappraisal has varied across neuroimaging studies, with some paradigms using reappraisal as a reinterpretation tactic whereas others have used it as a distancing tactic: Reappraisal as conceptualized as reinterpretation involves imagining negative stimuli in a neutral or positive light, finding the silver lining, as it were, and distancing as reappraisal requires participants to adopt the perspective of a detached observer. These different tactics are apt to differ in their cognitive resource demands of the subsystems that support them, which would be evidenced by variation of activity across brain regions, and, indeed, this has been found (see Ochsner et al., 2012). This is informative from a task analysis perspective, and not necessarily an issue if the aim is to investigate different strategies by which to regulate emotion, but this cognitive neuroscientific approach to investigating reappraisal does not contribute much to an understanding of the neurocognitive mechanisms underlying effective treatments such as CBT-based forms psychotherapy. This is because reappraisal is not equal to recogitation: Reappraisal is the revaluation of goal-incongruent events—it is potentially the rational belief about an activating event that supplants the dysfunctional one in the clinical domain. However, recogitation is a reasoning procedure that operates more generally on propositional attitudes: It is not just the generation of a different, more ‘positive’ appraisal of a goal-incongruent event; in its clinical application, it predominantly operates on (re)appraisals directly rather than on representations of goal-incongruent events.

What is more is that reappraisal research fails to capture the fact that the process of cognitive change is necessarily linguistically mediated in clinical practice; more specifically, it has not been representative of the dialectical nature of verbal intervention: the *disputation process* (e.g., Beal, Kopec, & DiGiuseppe, 1996; Beck, 1976; Ellis, 1962, 1994; David, Lynn, & Ellis, 2010). Requiring participants to view stimuli of creepy spiders, crying strangers, and burning buildings in a more positive light to assess, for example, the modulatory role of prefrontal subregions in downregulating limbic ones is a markedly different thing than having them actively identify and dispute their irrational beliefs (i.e., maladaptive appraisals and schemas) and to form more semantically adaptive propositional attitudes about them. Furthermore, such emotion regulation paradigms bring about cognitive change in a sense that is *online*, in that there is a goal-incongruent stimulus (e.g., a predator) that is perceived, eliciting an automatic appraisal (e.g., it is dangerous) and affective response (e.g., fear). This appraisal needs to be reappraised in light of the affective response (e.g., the animal is not dangerous to humans). However, cognitive change in clinical settings is often carried out in an *offline* sense: Appraisals about goal-incongruent events are assessed, but these events are not actively occurring. But sometimes other-initiated retrieval of goal-incongruent events (via clinicians) elicits an appraisal and, therefore, an emotional response; this is why clinical environments are equipped with boxes of tissues.

3.5 Recogitation as an emotion regulation strategy

Recogitation is used in the same way in these cases of ‘hot’ verbal intervention, beginning with appraisal detection. To better illustrate the application of recogitation to emotion regulation and its distinction from reappraisal, a broader, illustrative model has been developed below (Figure 3.4). Beginning with goal generation and strategy selection, a goal to self-regulate and the selection of a regulation strategy by which to achieve acute and chronic changes in emotion and mood can be formed not only after an undesirable emotional response is elicited but also before it as a prospective, future intention to self-regulate in a certain way in the event of emotional distress; note the bidirectional arrows with the emotion-generative procedure. A goal to regulate emotion *in situ* as well as in the future can be self- or -other initiated, in that the cognitive task to modulate emotion can be facilitated by a clinician during an intervention as well as self-generated outside clinical settings; indeed, neurotypical people regulate their emotions in everyday life without ever seeing the inside of a clinic. Presumably, self-initiated emotion regulation involves a motivational element underpinning the willingness to make the effort, which likely reduces to orbitofrontal and limbic systems.

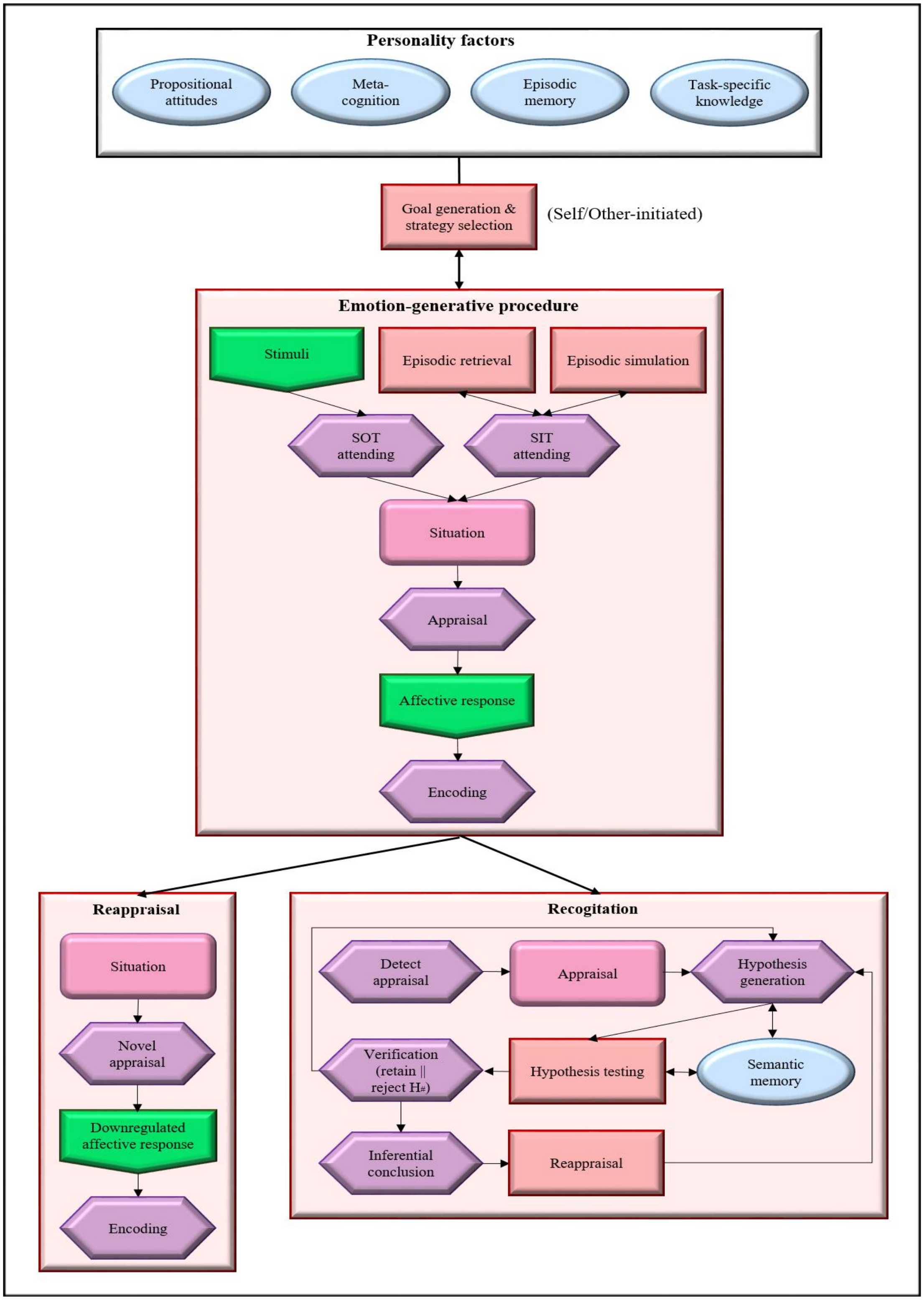

Figure 3.4 An information-processing model of recogitation in the context of emotion regulation.

Regardless of whether an unhealthy, negative emotional response has occurred before or after the activation of a goal to regulate emotion using a particular strategy, the emotion-generative procedure has been adapted from the model of Ochsner and Gross (2014) to include not only stimuli that are goal-incongruent but also episodic representations and simulations that are goal-incongruent, because people can experience a range of emotions simply from recalling experienced events and from constructing scenarios that are goal-incongruent, especially in the case of anxiety. Experiencing a goal-incongruent event in real-time orients attention towards it whereas remembering and simulating such an event orients attention towards endogenous thought (i.e., SIT). So, a short-term memory buffer maintaining goal-incongruent representations is realized through immediate experience, retrieval, or prospection. The remaining sequence of emotion generation is in line with the modal model, in that these representations then receive an affective valuation (i.e., appraisal), either novel or recapitulated in the case of episodic retrieval, eliciting a negative or positive emotional response. Finally, the association between the goal-incongruent representations and the appraisal is encoded, such as via hippocampal binding (see O'Reilly & Munakata, 2000) and stored throughout the semantic network.

If reappraisal is the selected cognitive strategy for downregulating emotion, then the object of the brain is to manipulate the association between a goal-incongruent event (e.g., a salient stimulus in a trial) and the automatic appraisal it elicited. This is done by generating a new appraisal, which can be carried out in different ways. Generating a different meaning of a stimulus influences the intensity, duration, and quality of an affective response. This new and more adaptive appraisal creates an association with the goal-related situation under active maintenance and, then, this association is encoded throughout the semantic network to 'override' that of the automatic appraisal (see Gross, 2014, for further discussion of reappraisal).

Alternatively, recogitation can be selected and enacted *online* in the presence of an emotional response, as discussed above. The remaining component of the model relates to different aspects of long-term memory that overarch the cognitive task to regulate emotion: ‘Personality factors’. These factors plausibly account for individual differences. For example, that the emotion-generative procedure produces responses that can be unhealthy (anxiety) or healthy (concern), and that regulation strategies can be selected that are maladaptive (suppression) or adaptive (recogitation), constitutes qualitative variability; moreover, there are also quantitative features to be explained such as intensity, duration, and frequency. According to the predominant theoretical framework in psychotherapy, one long-term memory factor comprises the propositional attitudes in people’s personal semantics about the self, others, and world (David et al., 2010). These are the beliefs people bring into any situation that is relevant to one’s goal(s); some are measured and accurate descriptions of events whereas others are absolutistic, calamitous, and unsound ascriptions of truth. Next, metacognition is a factor because cognitive change strategies involve the conscious articulation of thought and insight into the principle of cognitive mediation. Episodic memory is included as the next factor because of its ostensible role in retrospective and prospective operations in emotion regulation. Lastly, a factor that might explain variation in terms of goal-generation, regulation strategy selection, and downregulation success is task-specific knowledge. For example, what might differentiate experienced clinicians from amateur ones and inexperienced clients is the task-specific and procedural knowledge of recogitation. Such differentiation might be reflected by the extent to which this information is learned, specifically in terms of the resource demands placed on not only the PFC but also posterior regions such as inferior parietal lobule, with the latter perhaps representing access to the semantic criteria (e.g., verification that an appraisal is erroneous and warrants rejection).

3.6 Implications for research

So, the limitations of current experimental designs and tasks in clinical cognitive neuroscience suggest a general problem of ecological validity. The ecological issue is that the experimental designs in these paradigms do not reflect the tasks in clinical situations, nor does the testing environment reflect the interpersonal interactions (e.g., verbal intervention) that are integral to them. These paradigms are sufficient for investigating the neural bases of emotion regulation but are limited in the ways they represent and generalize to the clinical domain, hindering an understanding of the neural correlates of cognitive restructuring and their role in cultivating mental health. This is in part because the typical testing environments (e.g., fMRI laboratories) physically limit the extent to which emotion regulation paradigms represent clinical situations. This problem elucidates how an understanding of the neurocognitive mechanisms of change is necessarily limited, but it also suggests a solution: Collect data continuously during treatment to study these mechanisms more directly. This approach might be combined with the periodic-measure design that is frequently used in clinical cognitive neuroscience to link each arrow in Figure 3.2.

However, bringing neuroimaging methods into clinical settings to investigate the information-processing dynamics governing cognitive restructuring would be premature and impractical as a first approach. Instead, the nature of clinical settings and, importantly, the interpersonal interactions within them ought to be better represented at the level of experimental design and task development in clinical neuroscience. This means that a multi-person neuroscience approach is needed (see Redcay & Schilbach, 2019). Research could then work to fractionate the subsystems generally supporting verbal intervention in psychotherapy. More specifically, experimental designs would need to be developed specifically for the type of treatment of interest and its subtasks would need to be structured to reflect the various stages of interaction typically occurring between clinicians and clients. This could markedly improve the ecological validity of a line of research interested in linking mechanisms of change at a neurobiological level of scientific explanation with that of cognitive theorizing. Many of the advantages of electing to use more ecological designs have recently been discussed at length by Shamay-Tsoory and Mendelsohn (2019). One possibility is to begin with fractionating interventions into agent-specific epochs of speaking, listening, and 'thinking': Namely, an epoch for periods during which a client utters dysfunctional appraisals about goal-incongruent events; one for the clinician who is listening to this at the same time; one for the period during which the clinician is not listening, but thinking of what it is about these propositions that render them irrational; one for the vocalization of the clinician's reasoning; and one for the period during which the client listens to this disputation. Such a design could straightforwardly account for these epochs in a semi-naturalistic setting. Neuroscientific predictions about the spatial localizations of these various subtasks of verbal intervention can then be put forward for investigation.

In sum, neuroimaging and neuropsychological methods have contributed much towards an understanding of the information-processing systems of the human brain in the last few decades, but to what extent do cognitive neuroscientific findings represent and generalize to the inter- and intra-brain dynamics engaged in adapting to naturalistic situations? If it is not marked, and experimental designs lack *ecological validity*, then this stands to potentially impact the practical applications of a paradigm. In no other domain is this more important to acknowledge than in human clinical neuroimaging research, wherein reduced ecological validity could mean a loss in clinical utility. Clinical neuroimaging has largely been limited to examining the neurophysiological outcomes of treatments for psychiatric conditions rather than the neurocognitive mechanisms by which these outcomes are brought about as a function of clinical strategies, and the cognitive neuroscientific research aiming to investigate these mechanisms in non-clinical and clinical populations has been ecologically challenged by the extent to which tasks represent and generalize to intervention strategies. One way to improve the generalizability and representativeness of findings is to adopt a more “real-world” approach to the development and selection of experimental designs and neuroimaging techniques to investigate the clinically relevant phenomena of interest. But what are the appropriate methods and procedures for carrying out an experimental design tailored to fractionate clinically relevant phenomena? The present work advances that recent technological and methodological improvements to neuroimaging techniques, such as functional near-infrared spectroscopy (fNIRS) and fNIRS-based hyperscanning, provide novel opportunities to investigate mechanisms of change in more naturalistic and interactive settings, representing a unique prospect for improving our understanding of the intra- and inter-brain systems supporting the cultivation of mental health. These are methods to which the present work now turns.

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Chapter 4: Functional Near-Infrared Spectroscopy (fNIRS) as a Neuroimaging Method

4.1 Principles of optical neuroimaging

Electromagnetic radiation (i.e., light) interacts with biological tissue in several ways, including light absorption, scattering, fluorescence, and Doppler shift (Villringer & Dirnagl, 1997), and different optical methods take advantage of the principles of these interactions to assess brain tissue. Some of these techniques are near-infrared spectroscopy (NIRS) (Chance, Zhuang, UnAh, Alter, & Lipton, 1993; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993), in vivo fluorimetry (Chance, Cohen, Jobsis, & Schoener, 1962; Grinvald, Anglister, Freeman, Hildesheim, & Manker, 1984; Kauer, 1988), and laser Doppler flowmetry (Dalkara, Iruka, Huang, Panahian, & Moskowitz, 1995; Lindauer, Villringer, & Dirnagl, 1993). The principles of light absorption and scattering are crucial to understand for valid and reliable NIRS measurements. Light absorption refers to the occurrence of molecules in a given medium absorbing photons and, when this occurs, it means that the intensity of the detected light will no longer equal that of the transmitted light. Accounting for this source of attenuation is more complex when that medium is the biological tissue of a person or other animal because compounds in tissue not only absorb light but also scatter and reflect it (i.e., the deflection of photons from their path). So, measurements of the attenuation of light intensity, or optical density (OD), in the brains of humans or otherwise are accurate only if these properties are considered.

There are a number of tissue chromophores to which light attenuation can be attributed, namely H_2O, lipids, melanin, myglobin, oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (HbR), and cytochrome oxidase (CytOx) (Dobson, Grrard, & Pratt, 2001; Marieb & Hoehn, 2019), but due to their unique absorption spectra in the context of the electromagnetic spectrum of near-infrared light (650-1000nm), HbO_2, HbR, and CytOX represent the most significant sources of absorption in NIRS measurements of brain tissue (Figure 4.1; Flock, Wilson, & Patterson, 1987).

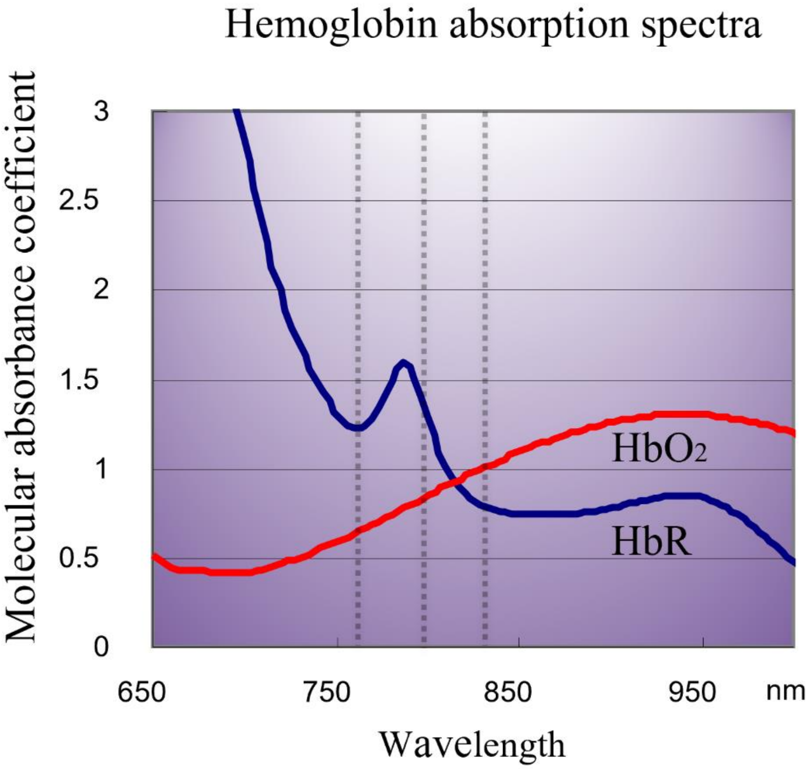


Figure 4.1 Absorption spectra of HbO_2 (red) and HbR (blue) in near-infrared light. Sampling can be acquired from different wavelengths, such as 780, 805, and 830 nm (grey dashed lines).

However, these endogenous absorbers represent insignificant sources of scattering; rather, scattering is largely the result of mismatched refractive indices (i.e., heterogeneity) (Jacques, 1989; Villringer, 1997a). The modified Beer-Lambert law (see Delpy et al., 1988; Kocsis, Herman, & Eke, 2006) can account for both light absorption and scattering in biological tissue: $A = \mathrm{Log}(I_o/I) = \varepsilon_\lambda \cdot c \cdot d \cdot B + G$, where A is light attenuation, I_o is the incident light intensity, I is the detected light intensity, ε is the absorption coefficient of the chromophore, c is the concentration of the chromophore, d is the distance between the points where light enters and leaves the tissue (cm), B is the differential pathlength factor (DPF) for the effect of scattering on pathlength, and G is the attenuation factor for scattering due to tissue heterogeneity. However, if G does not change during measurement, and the tissue is regarded as largely optically homogenous, then it can be held as a constant, making it possible to accurately convert spectroscopic measurements of OD to *changes* in concentrations of HbO_2 and HbR ($\Delta A = \Delta c \cdot \varepsilon \cdot d \cdot B$), including total hemoglobin (Hbt; Hbt = HbO_2 + HbR). In addition, d corresponds more precisely in this case to the separation between the light sources and detectors of NIRS optodes, which is typically 2-4 cm. Pairs of sources and detectors form multiple NIRS ‘channels’ (Figure 4.2).

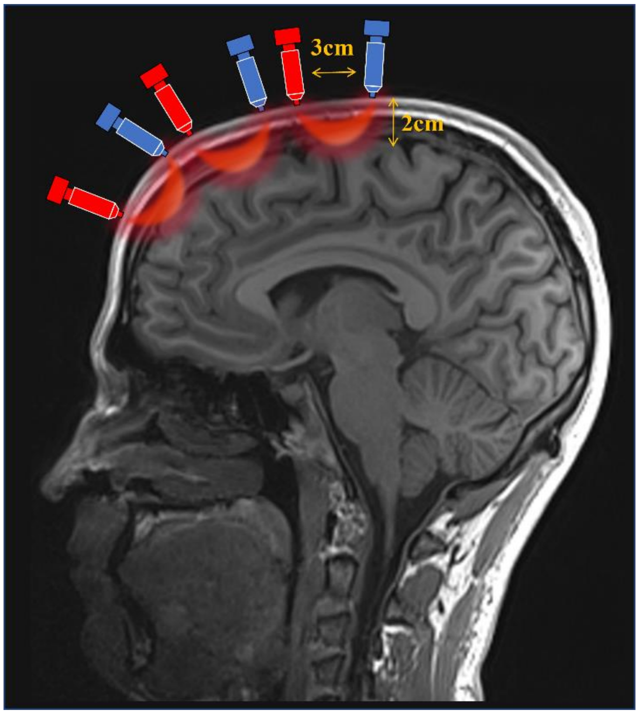


Figure 4.2 Schematic of near-infrared light sources (red) and detectors (blue) forming multiple channels (3) over the skull (author’s structural MRI scan).

So, NIRS is not invasive relative to other optical methods, such as those requiring ultraviolet or visible light on exposed brain tissue or contrast agents. The increased wavelength of near-infrared light achieves a greater penetration depth (~ 3 cm) and, therefore, NIRS does not require invasive techniques to reach the cerebral cortex (Custo, Wells, Barnett, Hillman, & Boas, 2006; Okada & Delpy, 2003a, 2003b; Okada et al., 1997); however, this penetration depth is not so great that deeper subcortical brain regions can be investigated. Jöbsis (1977) first demonstrated real-time, non-invasive monitoring of hemoglobin concentrations in a cat brain at Duke University, and Cope and Delpy (1988) later showed this capability in sick newborn infants at University College London. A number of studies soon followed, demonstrating also that NIRS was reliably safe for in vivo measurements of human brain tissue (see Ferrari & Quaresima, 2012, for review). This cultivated an interest in taking measurements of brain *activity*. So, single- and then multi-channel systems were developed to achieve optical topography of the channels placed over specific cortical locations: hence, functional NIRS, or fNIRS.

fNIRS systems can employ different techniques of illumination (Gervain, 2015). The first is continuous-wave (CW) fNIRS, whereby near-infrared light at two or three different wavelengths is constantly emitted from sources into the scalp and the light the detectors collect index changes in concentrations of ΔHbO_2 and ΔHbR; this represents the most frequently adopted approach in cognitive neuroscience (Figure 4.3). The second technique is frequency-resolved fNIRS, whereby light attenuation is measured as well as phase delay. More specifically, light intensity is manipulated at particular frequencies and the phase-shift that is measured enables scattering and path length to be quantified, which consequently enables absolute values of HbO_2, HbR to be determined (Chance, Maris, Sorge, & Zhang, 1990). A third approach is time-resolved fNIRS, whereby light is pulsated—rather continuously emitted—through the scalp, and the time that the photons are in flight is used to quantify path length to measure absolute concentration changes (Delpy et al., 1988). Another technique is fast optical imaging, whereby an event-related optical signal indexes not the metabolic underpinnings of brain activity, but the electrophysiological effects of firing neurons (Gratton & Fabiani, 1998, 2003; Gratton et al., 1997; Tse et al., 2007).

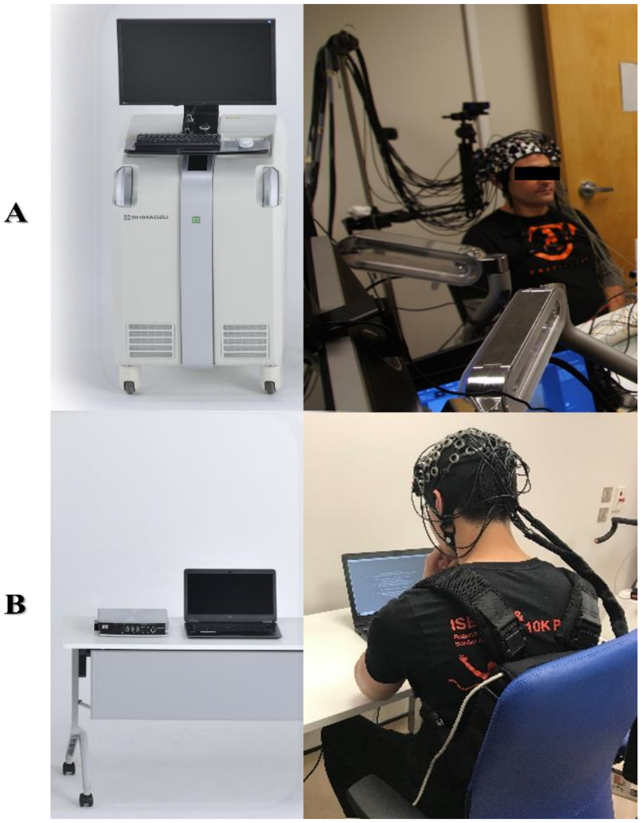


Figure 4.3 Example of two continuous-wave, multi-channel fNIRS devices (Shimadzu Corp). (A) The LABNIRS, a stationary system that allows for over one hundred channels and whole-head coverage; (B) The LightNIRS, a smaller yet portable system that can be used wirelessly on freely-moving participants.

4.2 Neurovascular coupling

However, as with other neuroimaging techniques such as functional magnetic resonance imaging (fMRI), fNIRS is predicated on the principle of neurovascular coupling. This principle refers to the relationship between neuronal firing mechanisms and metabolic mechanisms such as cerebral blood flow. Although aspects of neurovascular coupling are still unknown, it is relatively well understood and has long been instrumental to prediction and explanation in a number of fields (e.g., Figley & Stroman, 2011; Frahm, Merbolt, Hanicke, Kleinschmidt, Boecker, 1994; Lai et al., 1993; Vanzetta & Grinvald, 2008). Neurobiologically, potassium (K^+) ions are postulated as a central mediator of neurovascular coupling, in that neuronal firing releases K^+ into extracellular space and the increase in K^+ concentration elicits local vascular dilation (Kuschinsky, 1997); however, the role of neurobiological mechanisms on the regulation of cerebral blood flow is much more complex than this and resides outside the scope of the present work (see Jueptner & Weiller, 1995; Kleinschmidt & Frahm, 1997; Villeinger & Dirnagl, 1995, for more information on this topic). In short, the typical finding of studies investigating the relationship between hemoglobin oxygenation and neuronal firing is that functional stimulation of a given brain region engenders an increase in the concentration of HbO_2 and a concomitant decrease in HbR (Figure 4.5; see Villringer, 1997b).

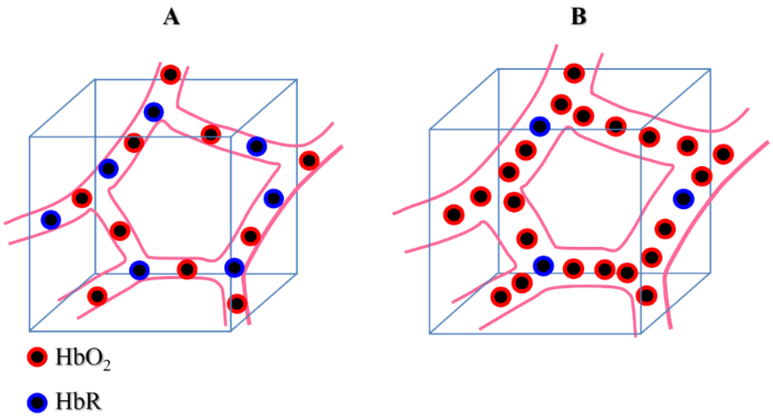


Figure 4.5 (A) Local flow of hemoglobin without functional activation; (B) Local functional activation elicits a relative increase in HbO_2 and decrease in HbR.

This relationship has particularly been evidenced and cross-validated with PET and fMRI (e.g., Kleinschmidt et al., 1996; Obrig et al., 1994; Villringer et al., 1997). What characterizes this hemodynamic response function (HRF) to neuronal stimulation for HbO_2 and HbR signals acquired using fNIRS and the blood-oxygen-level-dependent (BOLD; Ogawa et al., 1990; Ogawa et al., 1992; Ogawa et al., 1993) signal of fMRI is an initial dip in the signal, then a rise until it peaks, after which there is a post-stimulus undershoot and, then, a return to baseline by 12-20 seconds after the functional onset (see Poldrack, Mumford, & Nichols, 2011, for review). The HRFs for both HbO_2 and HbR tend to be largely anti-correlated, in that HbR appears as a reflection of HbO_2 under its signal, but often there are asymmetries depending on the brain region and task in question (Wolf et al., 2002).

4.3 Sources of noise

Importantly, task-evoked brain activity is not the sole source from which changes in ΔHbO_2 and ΔHbR signals are derived: Systemic, extracerebral, and non-evoked brain activity also represent sources of influence on observations. Each of these categories of noise can detract from the integrity of fNIRS signals and neglecting to account for them can lead to statistical false positives and negatives (see Huppert, 2016; Scholkmann et al., 2014; Tachtsidis & Scholkmann, 2016, for reviews). There are a number of confounding variables that are systemic in nature (i.e., basic physiological processes), namely heart rate, blood pressure, breathing rate, CO_2 concentrations, and autonomic nervous system activity. Some of this systemic activity changes as a function of the task in which participants are engaged; whereas some is not task-evoked (e.g., Minati et al., 2009; Minati, Kress, Visani, Medford, & Critchley, 2011; Scholkmann, Gerber, Wolf, M., & Wolf, U., 2013a; Scholkmann, Klein, Gerber, Wolf, M., & Wolf, U., 2014; Scholkmann, Wolf, M., & Wolf, U., 2013b; Serrador et al., 2000; Tachtsidis, Leung, Devoto, Delpy, & Elwell, 2008; Tachtsidis et al., 2008; Tachtsidis et al., 2009; Tisdall et al., 2009). These physiological processes are also interrelated. The upregulation of one can exacerbate the status of another: For example, heart rate and systemic vascular resistance affect mean arterial blood pressure, and autonomic nervous system activity affects cardiac output, systemic vascular resistance, and blood flow (Tachtsidis & Scholkmann, 2016). In addition, physiological sources of noise (both evoked and non-evoked) arise from both extracerebral and cerebral tissue (Figure 4.6).

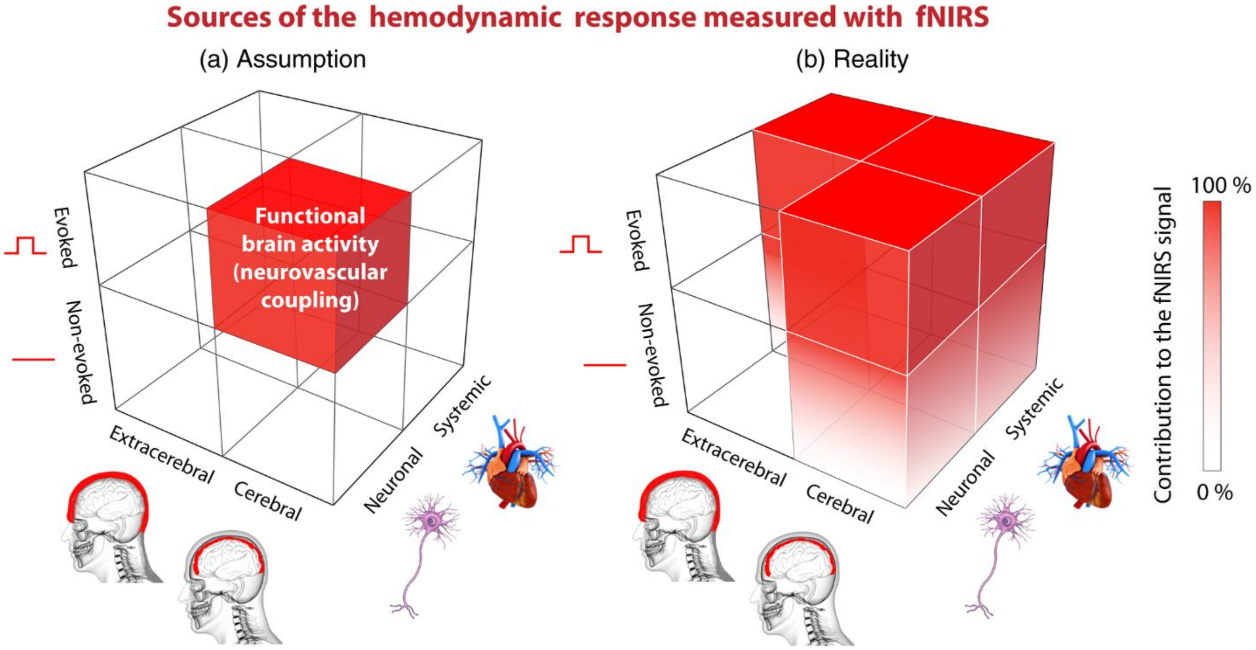


Figure 4.6 Sources of signal change. fNIRS signals comprise six components, and five are potentially confounds. The contribution of the components to the fNIRS signal is visualized by color-coding (red: 100%, white: 0%). The non-evoked/cerebral/neuronal and non-evoked/cerebral/systemic components can contribute to the fNIRS signal to a significant degree. Adapted from “False positives and false negatives in functional near-infrared spectroscopy: issues, challenges, and the way forward,” by Tachtsidis and Scholkmann, 2016, *Neurophotonics*, p. 2.

The aim is typically to have observed signals reflecting only cerebral, task-evoked, non-systemic activity, but acquiring some noise is inevitable since what is being captured in a given experiment is a part of the overarching picture of what is required of the body—including the brain—to carry out a given task. So, when the demands of information-processing resources of particular brain regions are of interest, the best means by which to achieve valid measurements of the hemodynamic changes representing these demands are to carefully consider fNIRS instrumentation, multimodal monitoring, analysis approaches, and experimental design (Tachtsidis & Scholkmann, 2016). fNIRS instrumentation refers to the choice of an illumination technique, as discussed above, but it also includes the option to use addition channels whose separation are extremely short (2.15mm - 8.4mm) to remove noise (i.e., short-channel separation) (Selb, Ogden, Dubb, Fang, & Boas, 2014; Yücel et al., 2015). And multimodal monitoring refers to simultaneously recording system changes such as mean arterial blood pressure, heart rate, respiration rate, and skin conductance, as well as motion changes such as gait and acceleration. Accounting for these data improves the ability of analysis approaches to improve signal quality, such as to use these dependent variables as regressors and independent components.

4.4 Signal analysis

There are a great many pre-processing techniques to remove noise from fNIRS signals, and their use as tools to improve signal quality have consistently varied across research groups, but recent research has demonstrated that some approaches are generally more effective than others (e.g., Brigadoi et al., 2014; Pinti, Scholkmann, Hamilton, Burgess, & Tachtsidis, 2019), leading to the emergence of basic standards for the analysis of fNIRS data (Yücel et al., 2021). In line with these standards, the pre-processing of fNIRS neuroimaging data typically begins with a global conversion of observed light intensities into measures of OD, which is frequently carried out automatically by the algorithms that come standard with proprietary fNIRS instrumentation, but one also typically has the option of downloading the raw voltages and manually converting them to OD using analysis software such as MATLAB (Mathworks, Natick, MA). Similarly, the OD data can be converted at this point to ΔHbO_2 and ΔHbR and then pre-processed, or pre-processing can be carried out on the OD data and the conversion to ΔHbO_2 and ΔHbR can be the final step subsequent to pre-processing; most studies conform to the former sequence, but this decision bears no statistical difference on the integrity of the data (Pinti et al., 2019). If the calculation of ΔHbO_2 and ΔHbR is elected as the final step of pre-processing, then the next step is to convert the OD data from the time-domain into the frequency domain using the Fast Fourier Transform (FFT) to identify noise components and the stimulus frequency band (see, Cohen, 2017, for review on FFT). Next, motion artifacts such as from head movement—or from movement related to real-world tasks such as walking—are removed, for which there are a multitude of techniques. For example, motion-artifact correction can be performed using principal-component analysis (PCA) (Pfeifer, Scholkmann, & Labruyère, 2018; Zhang, X., Noah, & Hirsch, 2016; Zhang, Y., Brooks, Franceschini, & Boas, 2005), targeted PCA (Yücel, Selb, Cooper, & Boas, 2014), spline interpolation (e.g., the motion artifact reduction algorithm; Scholkmann, Spichtig, Muehlemann, & Wolf, M., 2010), wavelet filtering (Molavi & Durmont, 2012), Kalman filtering (Izzetoglu, Chitrapu, Bunce, & Onaral, 2010), and correlation-based signal improvement (CBSI) (Cui & Bray, & Reiss, 2010), as well as with short-channel separations (Robertson, Douglas, & Meintjes, 2010) and accelerometers (Virtanen, Noponen, Kotilahti, & Ilmoniemi, 2011). Wavelet and PCA spatial filtering have been shown to be some of the most effective and robust approaches (see Brigadoi et al., 2014).

Next, the corrected OD data should be filtered to remove any of the above discussed physiological confounds. Pinti and colleagues (2019) recently investigated diverse signal filtering methods with both synthetic and real data and found that band-pass filtering as a filter characteristic and finite-impulse response (FIR) as a filter type are optimal, because the former can cut-off both low-frequency and high-frequency trends and the latter is stable and does not lead to phase distortions or shifts across the frequency band. A low frequency cut-off of 0.01 Hz removes slow trends, such vascular endothelial regulations (Yücel et al., 2016), and a high frequency cut-off (e.g., .09 Hz) excludes higher frequency oscillations (e.g., breathing rate and heart rate: ~0.25 and ~1.3, respectively). FIR filters are more stable than infinite-impulse response filters at higher orders, such as 1,000. Finally, the fNIRS neuroimaging data are converted into concentration changes of ΔHbO_2 and ΔHbR using the above discussed modified Beer-Lambert law (Figure 4.7). At this point, if any channel for each participant shows inordinate fluctuations in amplitude upon examination, then it should be excluded from further analysis to preclude the influence it might have on subsequent statistical tests. Importantly, there is also the question of which signal to interpret. Yücel and colleagues (2021) suggest that both the HbO_2 and HbR signals should always be carried forward from this point and assessed at the first- and second-levels of analysis, but interpreting the results of these analyses should be empirically grounded if that interpretation is restricted to one signal. Indeed, there are some grounds for interpreting the HbR results as most reliable. For example, HbR signals are less affected by systemic confounds (Dravida, Noah, Zhang, & Hirsch, 2017). For example, the influence of physiological sources of noise from extracerebral tissue tends to be stronger on HbO_2 than HBR signals (Kirilina et al., 2012). This is especially notable when the tasks of a paradigm elicit changes in CO_2 that are over and above baseline. For instance, tasks requiring changes in respiration, such as speech production and physical activity, alter the HbO_2 signal to a greater degree than HbR (Scholkmann et al., 2013a, 2013b; Scholkmann et al., 2014).

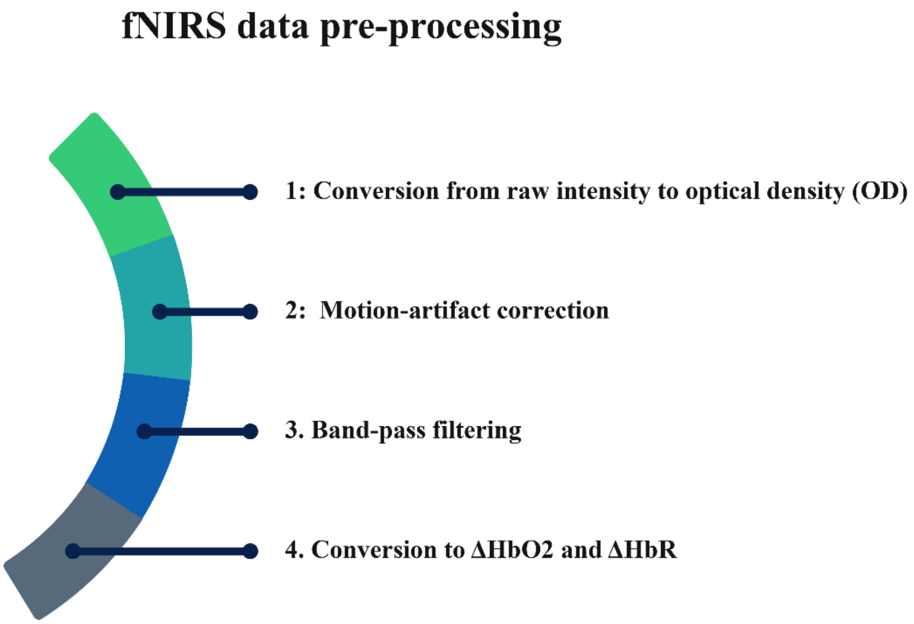


Figure 4.7 Basic pre-processing steps of fNIRS data. Converting observed raw voltages to optical density signals is always the first step (1). Conversion from OD to ΔHbO_2 and ΔHbR (4) can precede motion-artifact correction (2) or follow band-pass filtering (3).

Once fNIRS data have been pre-processed, the cleaned signals can be prepared for statistical inference. This involves extracting a stimulus design of onsets and durations from behavioral data, with which to convolve the fNIRS signals, and using the General Linear Model (GLM) to estimate design matrices at the single-subject level (Figure 4.8). Because there is a high likelihood of serial autocorrelation between the signals from neurovascular coupling and systemic activity (Barker, Rosso, Sparto, & Huppert, 2016), down-sampling the sampling rate (e.g., to 1-5 Hz) and precoloring should be carried out. Down-sampling is typically achieved with interpolation (spline with an anti-aliasing filter) and precoloring commonly involves a form of temporal smoothing in which a low-pass filter is applied to the estimated fNIRS signals (see Cohen, 2017, for a review of interpolation and convolution).

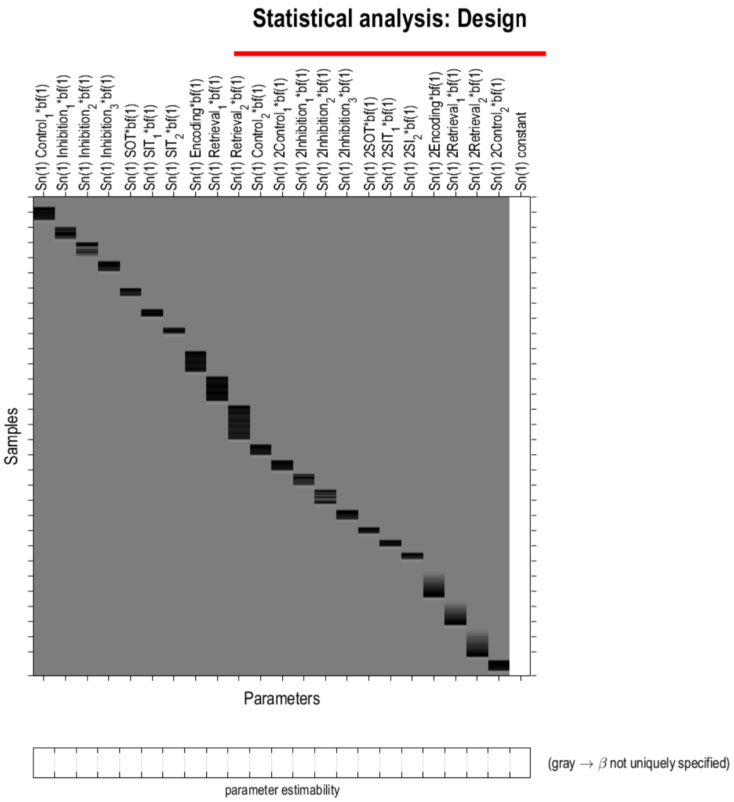
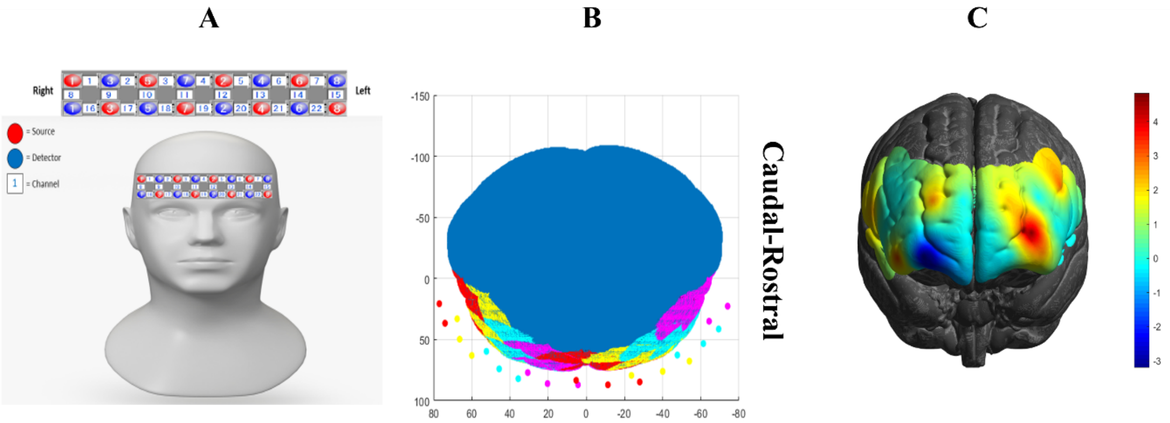


Figure 4.8 Example of a single-subject design matrix of fNIRS data (HbR) from an experiment consisting of 22 blocked tasks.

This is also the time to include any physiological regressors such as heart rate and breathing rate in the design matrix to remove their individual effects, which requires synchronizing and down-sampling their time-series with that of the fNIRS. After the experimental parameters from the single-subject design matrices of a sample are estimated, the data can be considered at a hierarchical, group-level (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). At this level, a random-effects approach is preferable to a fixed-effects analysis because the results of a group are more meaningful if they generalize to a population (i.e., by accounting for between-subject variance; see Poldrack et al., 2011). Covariates can also be included at this stage (e.g., age). Then, statistical contrasts (e.g., independent-samples and paired-sample *t*-tests and Analysis of Variance [ANOVA]) of the conditions of interest can be conducted (see Tak & Ye, 2014, for review of inferential statistics using fNIRS data). The multiple comparisons problem in fNIRS data analysis, and neuroimaging more broadly, is typically addressed using the false-discovery rate (FDR; Benjamini & Hochberg, 1995). This controls for the expected proportion of rejected null hypotheses (i.e., false positives) over multiple whole-brain comparisons; however, it is worth noting that FDR might not be necessary when comparisons are not whole-brain contrasts, such as when there is an *a priori* channel configuration that targets only subregions of interest (ROIs) and a conservative threshold is used (e.g., $p < 0.01$), since this would constitute its own small-volume correction (Poldrack et al., 2011).

Lastly, the resultant activation values can be mapped onto spatially registered brain templates using optical tomographic mapping. Preceding statistical inference, and as part of the protocols for placing an fNIRS device on a participant, the locations of the optodes, which are commonly placed according to the International 10/20 system, are acquired in 3D space with a digitizer (Singh, Okamoto, Dan, M., Jurcak, & Dan, I., 2005) and registered to a standardized brain space (Figure 4.9), namely MNI (Montreal Neurological Institute) space; or, high-resolution 3D MRI scans can be used to improve spatial resolution (Hirth et al., 1997).



Channel Configuration **MNI Coordinates** **Rendered Activation**

Figure 4.9 Channel configuration of sources (red) and detectors (blue) comprising 22 channels (A); registration of the MNI channel locations to a 3D brain mesh (B); rendered brain activation (C).

The pre- and post-processing of fNIRS data can be achieved using the software that is included with fNIRS instrumentation, but several other software provide greater freedom over the customizability of the analysis pipeline: Homer2 & Homer3 (https://homer-fnirs.org), fNIRS Statistical Parametric Mapping (SPM; https://www.fil.ion.ucl.ac.uk/spm/software), NIRSstorm (https://neuroimage.usc.edu/brainstorm), and the NIRS Brain AnalyzIR Toolbox (https://bitbucket.org/huppertt/nirs-toolbox/wiki/Home)—all of which are toolboxes that are run in MATLAB (https://www.mathworks.com). Perhaps the most optimal and customizable analysis pipeline is one that takes the best functions from several software. Lastly, it is worth mentioning that before any data are acquired, there are important quality control measures that ought to be undertaken to protect the integrity of the data, such as ensuring proper optode-scalp coupling (e.g., parting hair), reducing external light contamination, and measuring for cap placement (see Orihuela-Espina, Leff, James, Darzi, & Yang, 2010).

4.5 Validation of fNIRS

The ability of fNIRS to index the intracerebral, hemodynamic sources of task-evoked brain activation has long been validated with multi-modal methods. Some of the earliest fNIRS studies in humans used simple sensory, motor, and calculation tasks such as visual stimulation and finger tapping (e.g., Hoshi & Tamura, 1993a; Hoshi & Tamura, 1993b; Kato, Kamei, Takashima, and Ozaki, 1993; Obrig et al., 1994; Okada, Tokumitsu, Hoshi, & Tamura, 1993; see Ferrari & Quaresima, 2012, for a historical review). The direction of fNIRS research from the early 1990's onward was largely towards neurodevelopmental investigations of infant populations (see Gervain et al., 2011; Lloyd-Fox, Blasi, & Elwell, 2010, for reviews); for instance, one of the first studies in this domain used a visual checkerboard reversal paradigm with 20 infants (Meek, Firbank, Elwell, Atkinson, Braddick, & Wyatt, 1998). From a validation perspective, it was important to demonstrate that observed response patterns from fNIRS reflected those from other neuroimaging techniques. For example, correlations of total hemoglobin (HbT) and cerebral blood flow (CBF) were evidenced in combined fNIRS-PET studies (Hoshi et al., 1994; Villringer et al., 1997).

Cross-validating not only measures of hemodynamic changes but also the spatial localizations of these changes was also critical. A number of combined fNIRS-fMRI studies have shown that these methodologies are highly comparable in this respect (e.g., Cui, Bray, Bryant, Glover, & Reiss, 2011; Heinzel et al., 2013; Noah et al., 2015; Okamoto et al., 2004; Sato et al., 2013). For example, Noah and colleagues (2015) developed a protocol for conducting multi-modal experiments with fNIRS and fMRI to ensure signal comparability, testing it using a complex yet naturalistic motor task (i.e., a dancing game); this procedure also specifies particular software and hardware modifications. fNIRS has also been validated with concurrent EEG measurements (see Chiarelli, Zappasodi, Pompeo, & Merla, 2017, for review) as well as MEG (e.g., Huppert, Barker, Schmidt, Walls, & Ghuman, 2017). Therefore, fNIRS is a valid neuroimaging method with temporal and spatial resolutions that represent an adequate compromise between that of fMRI and EEG, respectively, in that it has greater temporal resolution than fMRI, but not EEG, and greater spatial resolution than EEG, but not fMRI (Pinti et al., 2018a). However, the appropriateness of fNIRS as a technique to adopt in a given study should depend on the scientific question at hand: Neuroimaging techniques are complimentary to each other, and often used together, but they differ in important ways and, therefore, their unique strengths are something of which researchers ought to take full advantage when considering how best to test their neuroscientific predictions—a topic to which the present work will now turn.

4.6 Applications of fNIRS

The marked expansion of neuroimaging research and instrumentation over the past thirty years has been remarkable, and exceedingly so when considering the body of neuroscientific knowledge that has amassed from it. As Poldrack and colleagues (2011) noted in the case of fMRI, it was possible in the mid-1990s to read all the literature on fMRI in a week; today, it is impossible to do this with the number of papers published last week alone. This rapid development has also been reflected in the last decade of fNIRS research, and there is little sign of deceleration. For example, there have been contributions from the research areas of vision, motor activity, somatosensory, memory, attention, language, emotion, executive functions, social cognition, neurodevelopment, neurological disorders, exercise science, moral cognition, brain-computer interfaces, neuroeconomics, neurorehabilitation, aging, psychiatry, and more (see Crum, 2020; Cutini, Moro, & Bisconti, 2012; Ehlis, Schneider, Dresler, & Fallgatter, 2014; Hennrich, Herff, Heger, & Schultz, 2015; Herold, Wiegel, Scholkmann, & Müller, 2018; S. Ho, Zhang, & R. Ho, 2016; Masataka, Perlovsky, & Hiraki, 2015; Naseer, Noman, & Keum-Shik, 2015; Pinti et al., 2018a; Soltanlou, Sitnikova, Nuerk, & Dresler, 2018; Strait & Scheutz, 2014; Yeung & Chan, 2020). Much of this research has replicated or extended existing paradigms in cognitive neuroscience that have previously been explored with other neuroimaging techniques. However, there have been steady advances to fNIRS devices and analysis methods that potentially offer unique contributions to the cognitive neuroscientific enterprise of mapping information-processing models of the mind onto the structural and functional properties of the brain.

For example, fNIRS systems have seen a considerable and rapid rise in technological advancements to their wearability and portability (see Pinti et al., 2018b, for an exhaustive review of studies using this class of device). These systems enable participants to freely perform tasks without constraints on the body and researchers to investigate situations that are difficult to contrive in laboratory settings (e.g., interpersonal interactions), providing an unprecedented opportunity to study complex cognition more naturalistically (e.g., Pinti et al., 2015; Seidel-Marzi, Hähner, Ragert, & Cariu, 2021; Stuart, Belluscio, Quinn, & Mancini, 2019; but see Vitorio, Stuart, Rochester, Alcock, & Pantall, 2017). This means that the neuroscientific questions for which fNIRS is particularly well-suited are those relating to the specialization of function of subregions in the outer cortex, but also those predicting the involvement of such areas in tasks requiring unrestricted movement or human-to-human interaction. So, the real-world applications of fNIRS overcome limitations common to other neuroimaging techniques (see Pinti et al., 2018a, for review), enabling researchers to traverse novel frontiers in experimental design and brain science and, therefore, it seems the calls for greater ecological validity in research (Burgess et al., 2006; Neisser, 1976) are starting to be answered at least in part by the methods now available to researchers.

4.7 Multi-person neuroscience

While the application of fNIRS to real-world situations calls for portable systems and innovation in task development, experimental designs involving multiple interacting people might take advantage of 'hyperscanning', a technique by which fNIRS measures hemodynamic changes and interpersonal brain synchronization between two or more individuals whilst engaging in tasks in naturalistic or laboratory settings (see Crivelli & Balconi, 2017; Redcay & Schilbach, 2019; Scholkmann, Holper, U. Wolf, & M. Wolf, 2013, for reviews). Other neuroimaging methods such as fMRI and electroencephalography (EEG) have employed hyperscanning as a technique in a number of studies, but researchers have rapidly been moving towards fNIRS as the neuroimaging method of choice because of the flexibility afforded to experimental design and improved spatial resolution over EEG. For example, recent research has shown that fNIRS-based hyperscanning is able to robustly assess everyday interpersonal interactions between people in ecologically valid environments (e.g., Cui, Bryant, & Reiss, 2012; Dommer, Jäger, Scholkmann, Wolf, & Holper, 2012; Duan et al., 2013; Funane et al., 2011; Hirsch, Noah, Zhang, Dravida, & Ono, 2018; Holper, Scholkmann, & Wolf, 2012; Jiang et al., 2012; N. Liu et al., 2016; Y. Liu et al, 2017; Noah et al., 2020; Piva, Zhang, Noah, Chang, & Hirsch, 2017; Nozawa, Sasaki, Sakaki, Yokoyama, & Kawashima, 2016; Tang et al., 2016).

What is largely meant by 'ecologically valid' settings is that, from the outset of a testing session, two or more participants are present in the same room and sitting at a table together rather than being separated—viewing each other remotely through a video screen—and laying in positions which do not reflect the orientations commonly assumed during the real-world tasks of interest (Figure 4.10).

[redacted] [redacted]

Figure 4.10 A prototypical fNIRS-based hyperscanning setup.

In a fNIRS-based hyperscanning paradigm, the acquisition channels are typically divided between participants from a single instrument. This reduces the amount of head coverage that is achievable across the sample, but this is not an issue insofar as *a priori* ROIs are posited; if they are not, then using two synchronized instruments will increase head coverage. Once the optodes are placed into the caps of a pair of participants (i.e., a dyad), tasks requiring interpersonal interactions can be completed. Such paradigms constitute what Redcay and Schilbach (2019) have termed the 'simultaneous dual-brain approach', which refers to experimental designs that allow for the dynamic exchange of information between people in real time (Hasson, Ghazanfar, Galantucci, Garrod, & Keysers, 2012); this differs from other multi-person approaches in that these exchanges are live and genuine between human beings rather than being sequentially recorded actions. In terms of data analysis, differences in inter-brain synchronization, or cross-brain coupling, are largely tested using the statistical tool of wavelet coherence analysis: an index of the “cross-correlation of [multiple] time series as a function of frequency and time” (Scholkmann et al., 2013). Significant changes in cross-brain coupling (i.e., ΔHbO_2 or ΔHbR) is often interpreted at a higher level of psychological explanation as changes in some form of social engagement (e.g., Di Paolo & De Jaegher, 2012). But what is social engagement, exactly?

Recall from Chapter 1 that a definitive feature of the organization of mind is that it consists of basic operations for processing information (Kant, 1787/2007); rather than passively recording and storing information, in most cases these functions actively transform and process information in favor of goal states (Shallice & Cooper, 2011). From the perspective of the philosophy of psychology (see Bermúdez, 2005, for review), the nature of goal states is largely captured by the notion of *intentionality* (Brentano, 1874/1973), a property inherent to the everyday propositional attitudes that human beings adopt about the world, self, and others (Churchland & Churchland, 2013). The objects of people’s propositional attitudes are shared during a multitude of interactive tasks. On some views, this ‘collective intention’ is an emergent property of the inter-strategic plans of conspecifics (Searle, 1990), forming the essence of dynamic social cooperation. However, social interactions sometimes extend beyond this sense of intentionality; that is, some interactions are devoid of this sense of coordination (e.g., deception; Pinti et al., 2021). Therefore, the rudiments of social engagement are likely the mechanisms uniquely dedicated to interactive situations in general—of which the cooperation-competition dichotomy is only an exemplar. More specifically, these mechanisms might consist of isolable subsystems whose functions are to infer the intentions of others in interactive situations (e.g., mentalizing; Baron-Cohen, 1995), or they might involve purely ‘enactive’ processes whose properties are so emergent as to be irreducible to single-brain cognitive operations (e.g., the ‘interactive brain hypothesis’; Di Paolo & De Jaegher, 2012).

While the theoretical debate over which of these approaches to conceptualizing the rudiments of social engagement should hold primacy in social neuroscience continues, there remains the question on the part of the researcher as to how to interpret findings of both the presence of cross-brain coherence between dyads who completed interactive tasks with each other and an absence of such coherence within the dyads who completed these same tasks, but did not interact with each other (i.e., when dyads are statistically scrambled). Moreover, what does it mean if there is an absence of a non-interactive condition in an experimental design and the observed difference(s) in cross-brain coherence is between two interactive conditions? The former seems to lend support for the existence of so-called ‘interactive processes’, in that there is something uniquely elicited in social interactions, and the latter seems to suggest that the social interactions of interest differ either quantitatively in interactivity (i.e., social engagement) and/or qualitatively by some factor(s) relating to the nature of the interactions (e.g., normativity). But this evidence is weak, because such measures alone lack the explanatory power requisite to evidence the governing, modulatory dynamics of mechanisms uniquely dedicated to interpersonal interactions (Hamilton, 2021). This is because coherence results are correlational (Scholkmann et al., 2013), which limits the types of inferences that can be drawn from findings of interpersonal synchronization. Indeed, evidence for interpersonal synchronization can be completely incidental in some situations. For example, dynamic coupling can manifest when there is no deliberate intention to interact interpersonally, whereby there is an incidental coordination of behavior and when behavior is not constrained by any explicit instruction for cooperation (i.e., unintentional and spontaneous interpersonal synchronization; Repp & Su, 2013). So, although the analysis tools that are frequently used for fNIRS-based hyperscanning have made important contributions towards multi-person neuroscience, new integrated analysis methods will be critical to further improve our understanding of the information-processing dynamics of social interaction. For example, Granger causality and dynamic multivariate decoding methods stand to augment current coherence approaches (e.g., Pan, Cheng, Zhang, Li, & Hu, 2017; Schippers, Roebroeck, Renken, Nanetti, & Keysers, 2010; Vergotte et al., 2017).

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PART III

EMPIRICAL INVESTIGATIONS

Chapter 5: Neuroimaging Interpersonal Interactions in Mental Health Interventions

5.1 Introduction

A common framework of neuroimaging methods investigating the treatment of psychopathological disorders is to collect neuroimaging data periodically at particular stages of treatment rather than continuously, *in situ* (Crum, 2021a). Although this framework is excellent for examining the effects of clinical interventions on behavioral, affective, and physiological responding (Ehlis et al., 2018), it creates an important explanatory gap regarding the nature of the neural systems by which these changes are brought about during the clinical interpersonal interactions that are central to a multitude of treatments (Figure 5.1). In other words, neuroimaging techniques are currently being used to study etiopathogenic mechanisms and cortical dysregulation as well as the effects and efficacy of (non-)psychopharmacological treatments on changes in neural activity and behavior, such as functional near-infrared spectroscopy (fNIRS) (Ehlis et al., 2018; Ehlis, Schneider, Dresler, & Fallgatter, 2014; C. Ho, Zhang, & R. Ho, 2016; Irani, Platek, Bunce, Ruocco, & Chute, 2007). However, observing only the effects of interventions, such as decreases in maladaptive behavior, emotion dysregulation, and functional dysconnectivity limits our understanding of the neurocognitive mechanisms by which adaptive changes in mental health are cultivated during treatment (Crum, 2021b). The neural systems relevant to both clients and clinicians during interpersonal interactions that foster healthier thinking, feeling, and behaving remain unclear.

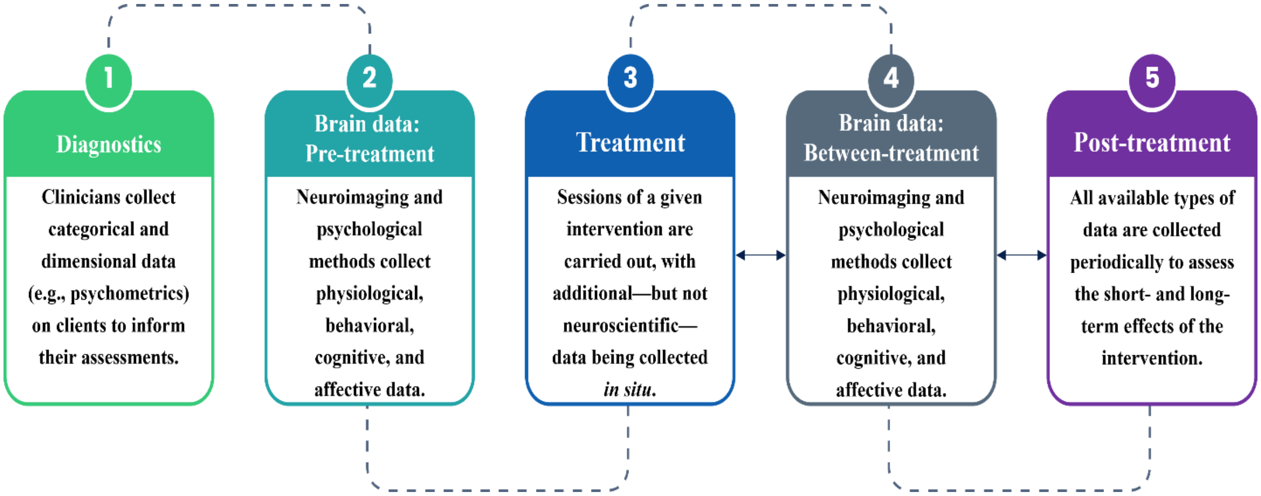

Figure 5.1. Data collection in the clinical neuroscience of mental health interventions. After an initial evaluation period (1), paradigms investigating the periodic effects of treatment (3) on the brain typically collect data from clinical populations before treatment commences (2), between particular stages of treatment (4), such as at 6 weeks, and at short- and long-term stages subsequent to treatment (5), such as after 14 weeks. Note that no neuroscientific data are collected during the interpersonal interactions driving the treatment sessions, leaving an explanatory gap regarding the nature of the information-processing systems in the brains of both clinicians and clients that contribute to the observed effects of interventions (e.g., cognitive change, emotion regulation, functional connectivity, etc.).

Data are not typically collected *in situ* because of the inherent limitations to most neuroimaging methods that constrain the types of experimental designs that can be employed in intervention-type settings (see Crum, 2021a, 2021b). So, to investigate the neurocognitive mechanisms of interest during treatment, the method that should ideally be adopted is one that allows for ‘real-world’ paradigms and the collection of data relating to interpersonal information-processing dynamics. Namely, second-person neuroscience approaches to investigating interpersonal interactions might represent a path towards addressing this explanatory gap. Recent cognitive neuroscientific research has acknowledged the need for a multi-person and, indeed, multi-modal framework by using the neuroimaging technique of hyperscanning to explore the inter-subject systems underpinning human-to-human interaction (e.g., Cui, Bray, Bryant, Glover,

& Reiss, 2011; Dommer, Scholkmann, Wolf, Holper, 2012; Duan et al., 2013; Funane, Kiguchi, Atsumori, Sato, Kubota, & Koizumi, 2011; Hirsch, Noah, Zhang, Dravida, & Ono, 2018; Hirsch, Zhang, Noag, & Ono, 2017; Holper, Scholkmann, & Wolf, 2012; Jiang et al., 2015; Jiang et al., 2012; Liu et al., 2017; Liu et al., 2016; Noah et al., 2020; Piva, Zhang, Noah, Chang, Hirsch, 2017; Nozawa, Sasaki, Sakaki, Yokoyama, & Kawashima; Tang et al., 2016). As discussed in the previous chapter (Chapter 4), hyperscanning measures hemodynamic changes and interpersonal brain synchronization between two or more individuals whilst engaging in interactive tasks in naturalistic or laboratory settings (see Crivelli & Balconi, 2017; Czeszumski et al., 2020; Redcay & Schilbach, 2019, for reviews). Neuroimaging methods such as functional magnetic resonance imaging and electroencephalography have used this technique in several studies, with a growing number of publications using fNIRS-based hyperscanning (Pinti et al., 2018a). For example, portable, wireless neuroimaging systems are methodological complements to experimental designs that are more naturalistic or ‘ecological’ (Pinti et al., 2018b). But what type of ecological experimental design is then appropriate for investigating clinically representative settings and situations, yet retains the degree of scientific control required in contemporary cognitive neuroscience? It is probably one that approaches the conundrum of clinical interpersonal interactions by attempting to *fractionate* their core modality: verbal communication. Interestingly, that the dialog between clinicians and clients is typically dialectical in nature represents the most clinically significant use of language in verbal interventions (Beck, 1976; Ellis, 1962, 1994). For example, clients express thoughts as statements or propositions about goal-incongruent events, reflecting specific dysfunctional cognitive schemas and appraisals (David, Lynn, & Ellis, 2010; Scherer, Schorr, & Johnstone, 2010), and, in turn, clinicians use various adaptive strategies to challenge the veracity and utility of these thoughts (Clark, 2014; Crum, 2019).

Importantly, what is perhaps most demanding of clinicians is their task that immediately precedes this verbal intervention: to critically think about and *recogitate* clients' beliefs (Crum, 2021a, 2021b). A standard position that might be adopted from our knowledge of cognitive neuroscience so far might be that the brain systems taxed by such a process likely depend in part on executive subsystems based in the prefrontal cortex (PFC) that are dedicated to solving ill-structured, linguistically mediated reasoning problems (see Shallice & Cipolotti 2018, for review). And, in this case, these subsystems likely modulate a more posterior, semantic network in which maladaptive schema and appraisal processes are represented and stored (Binder, Desai, Graves, & Conant, 2009). If this is the case, then the literature in this area of cognitive control (Cipolotti et al., 2016; Goel & Grafman, 2000; Goel, Stollstorff, Nakic, Knutson, Grafman, 2009; Goel et al., 2007; Goel, Vartanian, 2005; Robinson et al., 2015; Volle et al., 2012; Shallice & Cooper, 2011; Knight & Stuss, 2013) and emotion regulation (Buhle et al., 2014; Diekhof, Geier, Falkai, Gruber, 2011; Kohn et al., 2014; Messina, Bianco, Sambin, & Viviani, 2015) suggest that rostral PFC (area 10) and middle frontal gyrus (area 46) might play a marked role in this 'thinking' task that potentially drives not only clinician-led verbal interventions but also eventual client-led ones independent of treatment settings.

A few fNIRS-based hyperscanning studies on verbal communication have recently been conducted to examine the neural underpinnings of dynamic coupling between people during natural dialog (e.g., Cañigueral et al., 2021; Hirsch et al., 2018; Hirsch et al., 2021; Y. Liu et al, 2017; N. Liu et al., 2016, Nozawa et al., 2016), with common findings in subregions that have long been implicated in speech production and comprehension such as Broca's and Wernicke's areas, respectively, as well as in the PFC subregions mentioned above. Interpersonal synchronization has tended to be significantly greater between people during these verbal interactions as compared to random pairings of participants who nevertheless conversed, but not with each other. However, no study to our knowledge has developed an experimental design that can be adapted to different clinical settings to specifically assess the inter- and intra-neural dynamics of verbal exchanges in clinical situations, particularly their epochs (e.g., speaking, listening, and thinking), nor have such exchanges been compared to non-clinical verbal communication to assess what is unique about clinical interactions that make the clinician successful or the interaction compelling to the client.

Accordingly, the aim of this work was to use a ‘real-world’ approach to developing a neuroimaging paradigm that addresses these theoretical and practical lacunae. It was predicted that, because clinical situations are inherently more interactive and normative than everyday instances of verbal communication, clinical interpersonal interactions will elicit greater cross-brain coherence in paired participants engaging in the roles of clinician and client compared to a control condition, and that within-brain contrasts will show cognitive resource consumption predominantly across the PFC. Moreover, since the tasks of clinicians in real-world treatment settings are much less passive than those involved in everyday discourse, it was hypothesized that periods of verbal intervention, in which clinicians are required to dispute dysfunctional cognitions about the self, others, and world, should demonstrate changes in activity above and beyond normal speaking demands, particularly in rostral PFC (area 10) and more posterior areas related to the semantic network. It was further expected that, perhaps to a greater degree, this pattern of activity will also be demonstrated prior to verbal intervention when clinicians covertly reason about dysfunctional cognitions, namely in rostral PFC and right middle frontal gyrus (area 46).

5.2 Method

5.2.1 Participants

Thirty healthy adults (15 pairs; 80% female; mean age = 30.17 ± 12.68 years; 97% right-handed participated in the study (Oldfield, 1971). All participants provided written informed consent in accordance with guidelines provided by the Yale Human Investigation Committee (HIC #1501015178), were reimbursed for participation. Dyads were assigned in order of recruitment and no individual participated in more than one dyad. Eligibility of participation was determined using two screening tasks, namely a right-handed finger-thumb tapping task and passive viewing of a reversing checkboard whilst fNIRS signals were acquired. A participant was selected for the hyperscanning experiment if counter-correlated HbO_2 and HbR signals were observed in the left motor hand-area for the finger-tapping task ($p < .05$) and in the bilateral occipital lobe for the passive viewing task ($p < .05$). This screening procedure attempted to ensure that the fNIRS signals of the sample were reliable and not confounded by irregularities in skull thickness, fat deposits, bone density, and blood chemistry (Owen-Reece, Smith, Elwell, & Goldstone, 1999; Okada & Delpy, 2003; Cui, Bryantm & Reiss, 2012).

5.2.2 Experimental paradigm

Participants were seated approximately 140 centimeters across a table and with a full field of vision of each other in a normal room (Figure 5.2). A computer screen was also positioned approximately 45° to the side of this face-to-face orientation and 70 centimeters from each participant’s face; so, the participants in each dyad had their own computer screens from which to view stimuli and that only they could see, and at which they needed not to turn their heads to look.

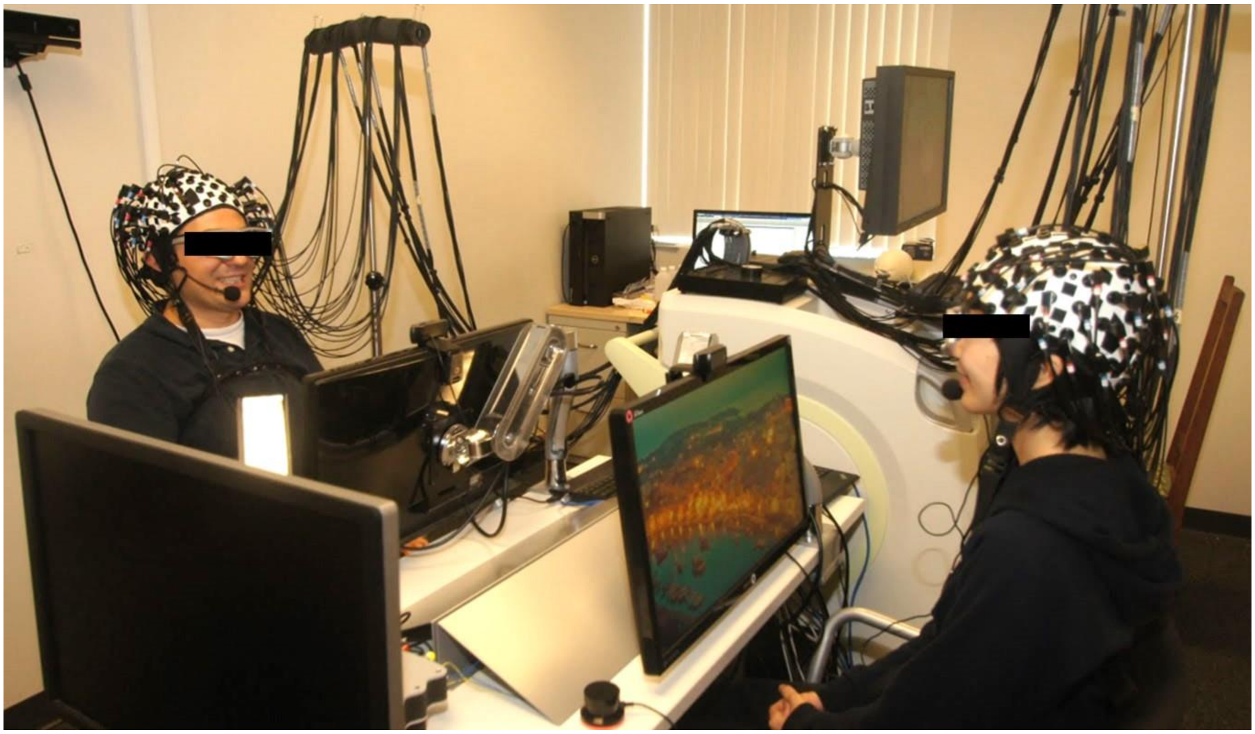

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Figure 5.2. Paradigm setting. Pairs of participants were seated across a table with a full field of vision of each other in a normal room, with no obstructions to natural facial information during verbal communication.

Participants engaged in four conditions (counterbalanced). The two factors classifying them were ‘situation’ and ‘role’. In the clinical situation, each participant was able to act as both the clinician and client; in the control condition, each participant was able to act as the speaker and responder. No participant was used more than once and each partner in a dyad was always different. The experimental design was therefore blocked and adopted a repeated-measures approach (Figure 5.3).

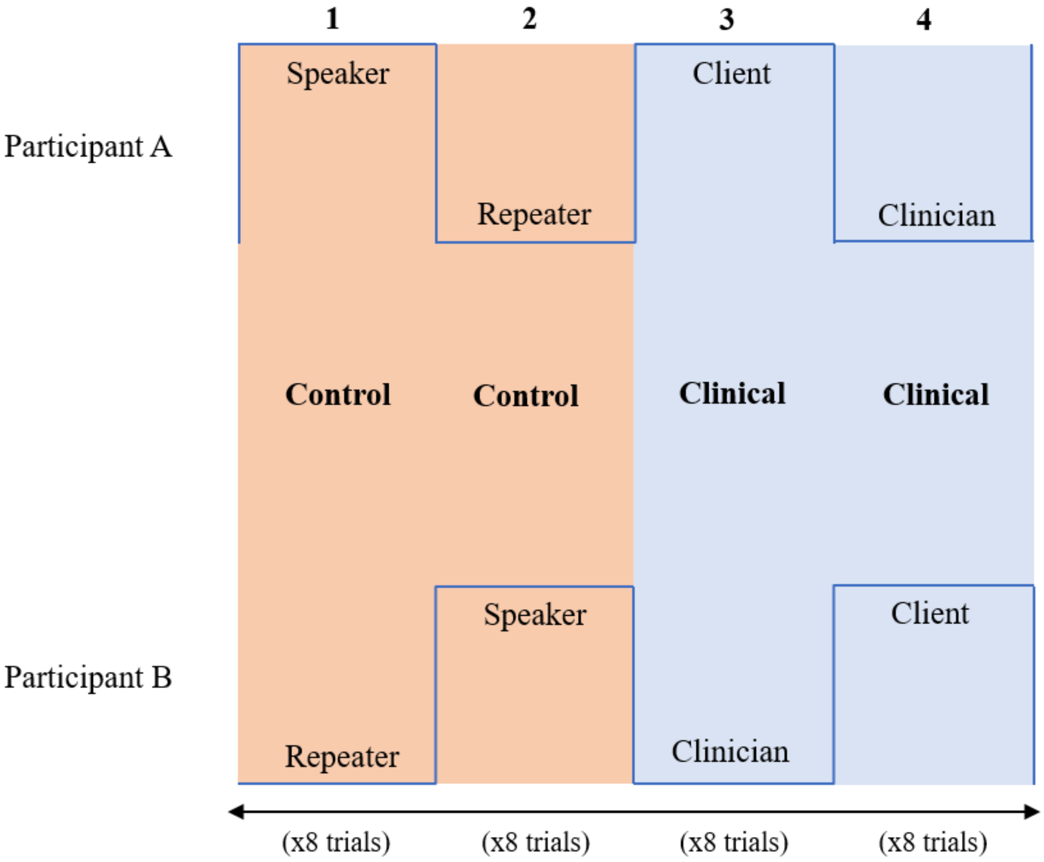
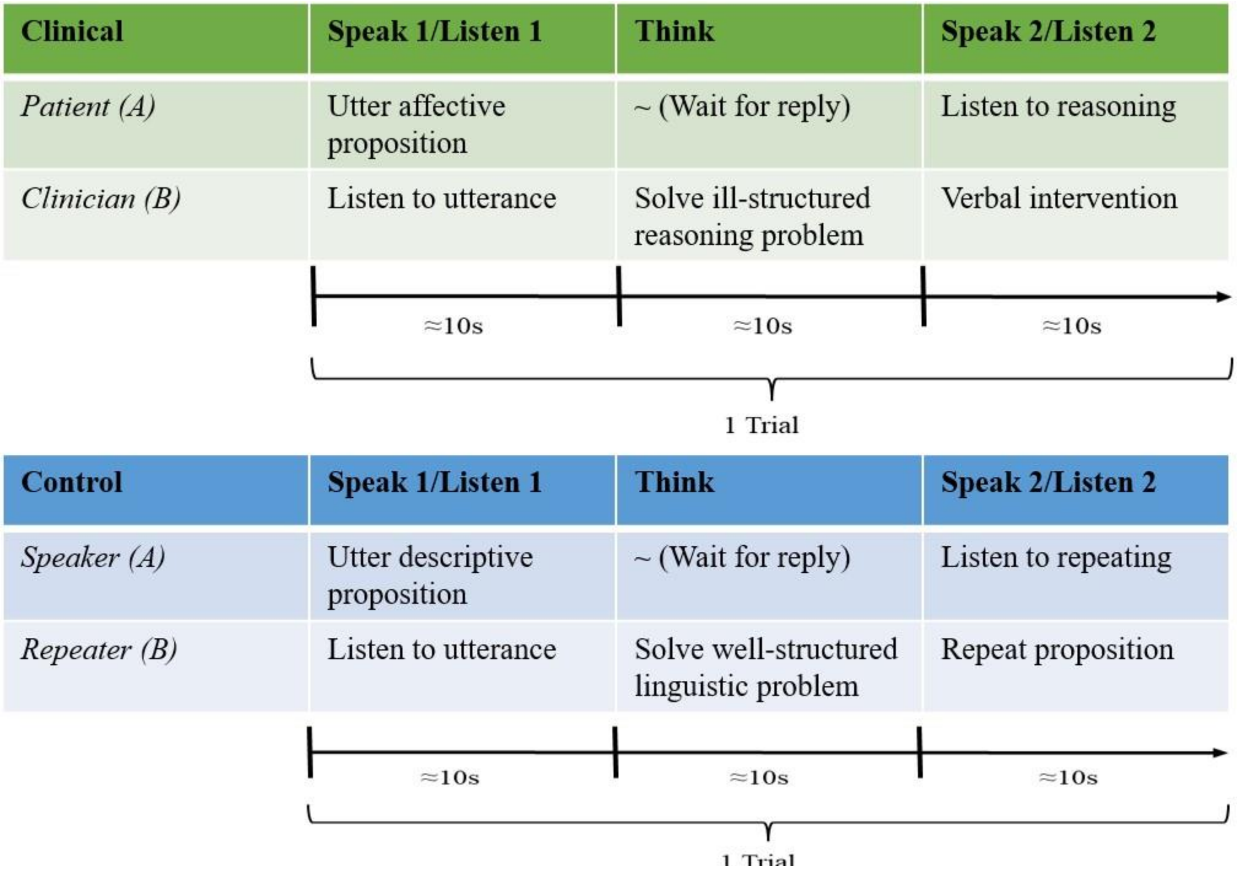


Figure 5.3. Experimental design. Participants alternated between roles within clinical (clinician, patient) and control (speaker, repeater) blocks (counterbalanced). Each block consisted of 8 trials, and each trial comprised of 3 types of epoch: speaking, listening, and thinking.

The subtasks across these conditions and within dyads included speaking, listening, and thinking epochs. (Figure 5.4). These subtasks, together with the stimuli, varied in nature depending on whether the interpersonal interaction was clinical. Namely, all stimuli shown on the computer screens were linguistic propositions, but in clinical blocks they were affective, or *hot*, conceptual valuations (Ochsner & Gross, 2014) (i.e., cognitive appraisals [Scherer et al., 2010]) and, more specifically, were dysfunctional in in that they were irrational and unrealistic in terms of being ungrounded in logic, empiricism, and pragmatism (David et al., 2010), representing a conjunction of the major types of irrational thinking (e.g., catastrophizing, self-downing, demandingness, etc.). For example: “My friends must always treat me fairly,” whereas the propositions in control blocks were purely descriptive facts about the world, containing no evaluative or normative component: “It is cheaper to buy produce from a farmers market.”



Clinical	**Speak 1/Listen 1**	**Think**	**Speak 2/Listen 2**
Patient (A)	Utter affective proposition	~ (Wait for reply)	Listen to reasoning
Clinician (B)	Listen to utterance	Solve ill-structured reasoning problem	Verbal intervention

Control	**Speak 1/Listen 1**	**Think**	**Speak 2/Listen 2**
Speaker (A)	Utter descriptive proposition	~ (Wait for reply)	Listen to repeating
Repeater (B)	Listen to utterance	Solve well-structured linguistic problem	Repeat proposition

Figure 5.4. Epochs. In a single trial of a clinical block, the patient read a statement representing an affective valuation whilst the clinician listened. The clinician was required to first silently reason (recogitate) about how the statement was dysfunctional and, then, explain this reasoning whilst the patient listened. In a single trial of a control block, the speaker read a statement representing a descriptive proposition whilst the repeater listened. The repeater was required to first silently solve a problem relating to the language of the statement and, then, repeat the statement multiple times.

In clinical blocks, the task of the person designated as the client was to utter the former class of proposition from the computer screen to the person designated as the clinician and then attend to the clinician for a reply. Clients were instructed to utter the proposition two times at a normal speaking pace to ensure that the other person heard it clearly and that this speaking epoch was sufficiently long to capture a hemodynamic response function. The clinicians' task was to carefully listen to this utterance and then to silently think of at least two ways in which it is an irrational belief—what it is about the sentence that makes it unrealistic and tenuous—after which their task was to verbally respond with this reasoning whilst the client listened. This interpersonal exchange of speaking (client), listening (clinician), thinking (clinician), speaking (clinician), and listening (client) constituted a single trial. So, once the second simultaneous epoch of speaking and listening concluded, a new affective valuation would appear on the client's screen. This clinical interpersonal interaction was repeated for eight trials. The second clinical block in the experimental design was exactly the same as the first, but with the only differences being that the roles of the participants were reversed and the stimuli were novel to the dyad.

Similar to the clinical condition, the control blocks consisted of the same subtasks of speaking (speaker), listening (responder), thinking (responder), speaking (responder), and listening (speaker). Namely, the person designated as the speaker was tasked with uttering a descriptive proposition two times to the person designated as the responder and then listening for a reply. The responder listened to the sentence and covertly determined which word in it was the second longest and then shortest. Once the responders performed this linguistic thinking task, they were required to repeat the whole sentence back to the speaker three times at a normal speaking pace. Piloting suggested that this was the appropriate amount of repeating to match temporally with the verbal intervention epoch of the clinical condition. The second control block was exactly the same as the first, but with the only differences being that the roles of the participants were reversed and the stimuli were novel to the dyad.

5.2.3 Signal acquisition and optode localization

Functional NIRS signal acquisition of hemodynamics was acquired using an 80-fiber (108-channel) continuous-wave fNIRS system (LABNIRS, Shimadzu Corp., Kyoto, Japan) configured for hyperscanning (54 channels per person) and sampled at a rate of 27 Hz at three wavelengths of light (780, 805, and 830 nm). A light-emitting diode probe (Daiso Crop., Hiroshima, Japan) was used to achieve an orthogonal connection between the fNIRS optodes and scalp (i.e., to displace hair in the cap). Anatomical locations of optodes in relation to standard head landmarks, including inion and top center (Cz) and left and right tragi, were determined using a Patriot 3D Digitizer (Polhemus, Colchester, VT) and linear transform techniques (Eggebrecht et al., 2014; Eggebrecht et al., 2012; Ferradal, Eggebrecht, Hassanpour, Snyder, & Culver, 2014; Okamoto & Dan, 2005; Singh, Okamoto, H. Dan, Jurcak, & I. Dan, 2005). Montreal Neurological Institute (MNI) coordinates (Mazziotta et al., 2001) for each channel were obtained using NIRS-SPM software (Ye, Tak, K. Jang, Jung, & J. Jang, 2009) with MATLAB (Mathworks, Natick, MA).

5.2.4 Regions of interest (ROIs)

The anatomical coverage of the channel configuration was corresponded with eleven bilateral ROIs (Figure 5.5; see Tables 6.1 & 6.2): rostral PFC (Brodmann’s area [BA] 10), middle frontal gyrus (BA46/9), inferior frontal gyrus (BA44/45/47), angular gyrus (BA39), supramarginal gyrus (BA40), middle temporal gyrus (BA21), superior temporal gyrus (BA22), somatosensory cortex (BA1/2/3), premotor and supplementary motor cortex (BA6), subcentral area (BA43), and primary auditory cortex (BA42). These ROIs were specified *a priori* based on recent hyperscanning research on human-to-human verbal communication (Hirsch et al., 2018; Y. Liu et al, 2017; N. Liu et al., 2016, Nozawa et al., 2016, Cañigueral et al., 2021; Hirsch et al., 2021), neuroimaging and cortical brain stimulation meta-analyses in emotion regulation (e.g., reappraisal [Buhle et al., 2014; Diekhof et al., 2011; Kohn et al., 2014; Messina et al., 2015]), and neuroimaging and neuropsychological research on frontal lobe functions (Shallice & Cipolotti, 2018, Shallice & Cooper, 2011; Knight & Stuss, 2013), particularly on the activation biasing of stimulus-independent attention (Burgess, Dumontheil, Gilbert, 2007) in favor of generating novel strategies (Cipolotti et al., 2016; Goel & Grafman, 2000; Geol et al., 2007; Goel & Vartanian, 2005; Roca et al., 2011; Seyed-Allaei, Avanaki, Bahrami, Shallice, 2017). That is, the channel configuration was designed to achieve coverage only over these theoretically constrained ROIs (see Poldrack, Mumford, & Nichols, 2012).

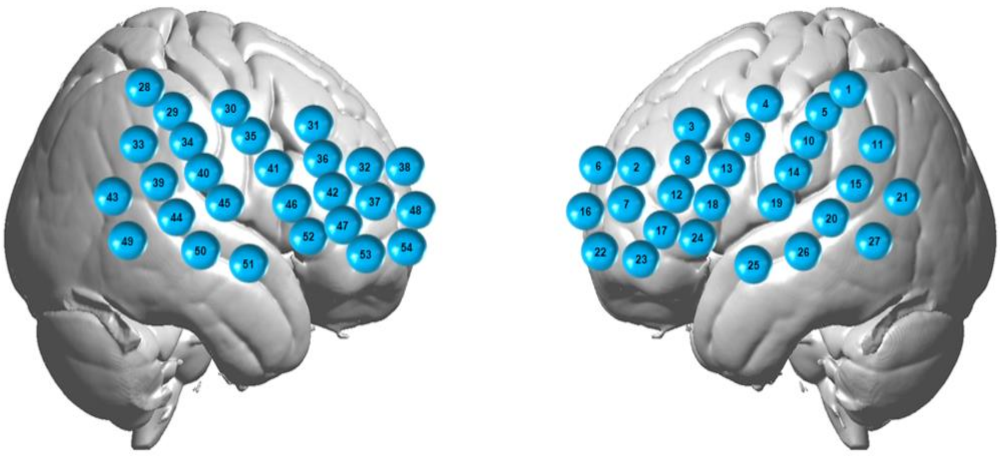


Figure 5.5. Layout of fNIRS channel configuration. The 108 channels were split between each participant in a dyad (54 channels per person), with 27 channels on both the right and left hemispheres of each brain.

Table 5.1

Group Median Coordinates, Anatomical Regions, and Atlas Probabilities of Channels (Left Hemisphere)

Channel #	Coordinates	Anatomical Region	BA	Probability
1	-49, -44, 57	Supramarginal Gyrus	40	0.97
2	-45, 38, 32	Middle Frontal Gyrus	46	0.68
3	-54, 14, 38	Middle Frontal Gyrus	9	0.78
4	-58, -11,47	Pre-Motor Cortex	6	0.7
5	-58, -36, 51	Supramarginal Gyrus	40	0.82
6	-16, 60, 34	Middle Frontal Gyrus	9	0.54
7	-44, 48, 22	Middle Frontal Gyrus	46	0.52
8	-57, 24, 21	Inferior Frontal Gyrus	45	0.54
9	-62, -2, 35	Pre-Motor Cortex	6	0.92
10	-64, -25, 41	Supramarginal Gyrus	40	0.26
11	-61, -51, 40	Supramarginal Gyrus	40	0.99
12	-55, 32, 12	Inferior Frontal Gyrus	45	0.57
13	-63, 6, 19	Pre-Motor Cortex	6	0.5
14	-68, -16, 27	Subcentral Area	43	0.27
15	-67, -41, 30	Supramarginal Gyrus	40	0.96
16	-19, 71, 13	Rostral Prefrontal Cortex	10	1
17	-53, 42, 1	Inferior Frontal Gyrus	47	0.53
18	-58, 17, 2	Superior Temporal Gyrus	22	0.29
19	-67, -9, 13	Subcentral Area	43	0.35
20	-69, -32, 18	Superior Temporal Gyrus	22	0.4
21	-66, -55, 17	Superior Temporal Gyrus	22	0.67
22	-32, 66, -1	Rostral Prefrontal Cortex	10	0.97
23	-48, 49, -6	Inferior Frontal Gyrus	47	0.54
24	-54, 27, -8	Inferior Frontal Gyrus	47	0.87
25	-66, -4, -11	Middle Temporal gyrus	21	1
26	-70, -24, 0	Middle Temporal gyrus	21	0.49
27	-69, -46, 4	Superior Temporal Gyrus	22	0.52

Table 5.2

Group Median Coordinates, Anatomical Regions, and Atlas Probabilities of Channels (Right Hemisphere)

Channel #	Coordinates	Anatomical Region	BA	Probability
28	53, -48, 55	Supramarginal Gyrus	40	1
29	62, -38, 48	Supramarginal Gyrus	40	0.9
30	63, -15, 45	Pre-Motor Cortex	6	0.53
31	60, 8, 38	Pre-Motor Cortex	6	0.46
32	50, 33, 31	Middle Frontal Gyrus	46	0.7
33	61, -53, 38	Supramarginal Gyrus	40	0.96
34	67, -27, 40	Supramarginal Gyrus	40	0.46
35	66, -4, 37	Pre-Motor Cortex	6	0.99
36	60, 20, 25	Inferior Frontal Gyrus	45	0.42
37	50, 43, 22	Middle Frontal Gyrus	46	0.8
38	29, 56, 33	Middle Frontal Gyrus	9	0.6
39	68, -41, 29	Supramarginal Gyrus	40	0.94
40	70, -18, 30	Primary Somatosensory Cortex	2	0.21
41	66, 5, 23	Pre-Motor Cortex	6	0.55
42	59, 30, 16	Inferior Frontal Gyrus	45	0.56
43	65, -56, 17	Superior Temporal Gyrus	22	0.6
44	71, -32, 20	Supramarginal Gyrus	40	0.42
45	70, -9, 18	Subcentral Area	43	0.44
46	63, 13, 10	Inferior Frontal Gyrus	44	0.51
47	56, 40, 7	Middle Frontal Gyrus	46	0.52
48	31, 67, 12	Rostral Prefrontal Cortex	10	1
49	70, -47, 6	Superior Temporal Gyrus	22	0.63
50	73, -24, 4	Superior Temporal Gyrus	22	0.45
51	68, -4, -2	Middle Temporal gyrus	21	0.62
52	59, 27, 1	Inferior Frontal Gyrus	47	0.62
53	53, 47, 0	Inferior Frontal Gyrus	47	0.48
54	40, 63, 1	Rostral Prefrontal Cortex	10	1

5.2.5 Signal processing

Pre-processing of raw fNIRS signals consisted of removing global systemic effects such as respiration, heart rate, and blood pressure (Tachtsidis & Scholkmann, 2016) using a principal component analysis (PCA) spatial filter (Zhang, Noah, Dravida, & Hirsch, 2017; Zhang, Noah, & Hirsch, 2016), a technique which uses the distributed optode coverage to distinguish signal components originating from local and distal (i.e., extracerebral) sources. Onsets and durations of the epochs of each trial of each block were extracted to generate the stimulus design, with which the canonical hemodynamic response function was then convolved using NIRS-SPM. A general-linear model (GLM) analysis then fitted these predicted signals to the data, yielding beta estimates for each parameter in the single-subject design matrices. The contrast effects of these data were then reshaped into 3-D volume images using SPM and normalized to standard MNI space using linear interpolation. The results of second-level, random-effects analyses via summary statistics (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007) based on these estimates and effects were rendered on a standard MNI brain template. Anatomical locations of peak voxel activity were identified using NIRS-SPM. Since the present study collected data only from the ROIs, and there were no whole-brain contrasts, corrections were not applied to the results; the false-discovery rate, for example, would have been too conservative for the nature of the study.

Inter-brain synchronization (cross-brain coherence) was evaluated across dyads (n = 30) for the comparison of the clinical and control interpersonal interactions using the wavelet analysis approach described in Zhang, Noah, Dravida, & Hirsch, 2020. Wavelet analysis assesses the extent to which two or more brains (i.e., hemodynamic signals) are correlated over time (Cui et al., 2012, Torrence & Compo, 1998), an indirect measure of non-symmetric coupled dynamic systems (Hasson & Frith, 2016). The wavelet function was the Complex Gaussian 2 from the MATLAB wavelet toolbox, because of its proximity to the hemodynamic response function. The number of octaves was 4 and the range of frequencies was 0.4 to 0.025 Hz. The number of octaves was also four; so, there were 16 scales for which the wavelength difference was 2.5 s. Task regressors were also removed according to PsychoPhysiological (PPI) analysis convention (Friston, 2011) to examine coherence that was not related to task-specific processes, but rather to dynamic coupling processes. Neural synchrony of the wavelet components of these residuals was explored also for scrambled dyads (randomly matched pairs) to control for potential effects of shared component processes that were not unique to paired participants. As with the within-brain analyses, channels were grouped into anatomical regions (i.e., 11 ROIs) based on shared anatomy for wavelet analysis. Lastly, all analyses were conducted on both HbO_2 and HbR, but the interpretation of results was based on research suggesting that HbR signals are less affected by systemic confounds (Dravida, Noah, Zhang, & Hirsch, 2017). For example, fNIRS paradigms involving overt as well as covert speech tasks produce changes in arterial CO_2 that, likely due to changes in respiration, alter the HbO_2 signal to a greater degree than HbR (Scholkmann, Gerber, M. Wolf, & U. Wolf, 2013, Scholkmann, M. Wolf, & U. Wolf, 2013).

5.3 Results

5.3.1 Contrast effects: ROIs

Within-brain statistical comparisons of ROIs that were determined *a priori* for situation and role types and the relative subtasks of these conditions were conducted at the threshold of $\alpha = .01$. Examining the effects of clinical discourse interactions compared to non-clinical interpersonal interactions [Clinical > Control], collapsed across all subtasks and roles, revealed significant differences in orbitofrontal cortex (BA11), $p < .001$, $t(28) = 2.93$, inferior frontal gyrus (BA47), $p < .001$, $t(28) = 3.08$, rostral PFC (BA10), $p < .001$, $t(28) = 3.05$, and supramarginal gyrus (BA40), $p < .001$, $t(28) = 2.64$ (Figure 5.6).

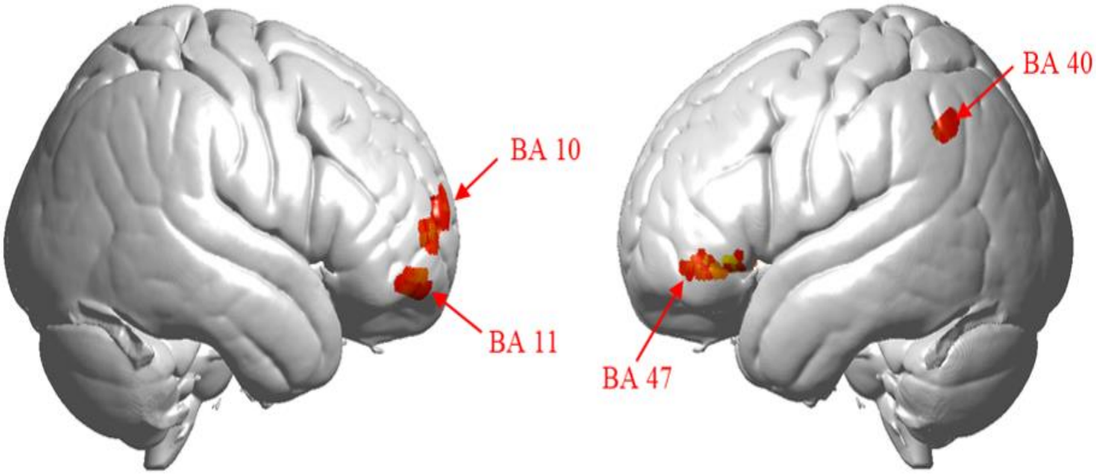


Figure 5.6. Clinical topic interaction. Contrast comparison of situation type [Clinical > Control] collapsed across role type and all subtasks for the ROIs (n = 30). Greater activation during the clinical blocks is represented in red. The clinical situation uniquely elicited right orbitofrontal cortex (BA11) and rostral PFC (BA10), and left inferior frontal gyrus (BA47) and supramarginal gyrus (BA40). See Table 5.3.

Table 5.3

Voxel-Wise GLM Contrast Comparisons (deOxyHb signals) of Situations Type

Contrast	Threshold	Coordinates[1]	t value	p	df[2]	Anatomical Regions in Cluster	BA[3]	Probability	Voxels
Situation [Clinical > Control]	p = 0.01	(38, 50, -8)	2.93	0.003	28	Orbitofrontal Area	11	0.63	28
						Rostral Prefrontal Cortex	10	0.27	
						Inferior Frontal Gyrus	47	0.10	
		(-54, 38, -4)	3.08	0.002		Inferior Frontal Gyrus	47	0.71	24
						Inferior Frontal Gyrus	45	0.15	
		(34, 53, 4)	3.05	0.002		Rostral Prefrontal Cortex	10	0.99	29
		(-60, -52, 38)	2.64	0.005		Supramarginal Gyrus	40	0.87	10
						Angular Gyrus	39	0.13	
Situation [Control > Clinical]	p= 0.01	(66, -22, 16)	-2.63	0.007	28	Primary Auditory Association Cortex	42	0.39	18
						Supramarginal Gyrus	40	0.18	
						Subcentral Area	43	0.18	
						Superior Temporal Gyrus	22	0.15	

Note. [1]Coordinates are based on the MNI system and (-) indicates left hemisphere. [2]df = degrees of freedom. [3]BA= Brodmann's Area.

Subtracting the activation in the thinking substask of Repeaters in the control condition from that of the thinking substask of Clinicians in the clinical condition [Clinical thinking > Control thinking] demonstrated a significant increase in the recruitment of left rostral PFC, *p* < .001, *t*(28) = 3.13, as well as in a cluster covering right middle frontal gyrus and inferior frontal gyrus, particularly pars orbitalis, *p* < .001, *t*(28) = 3.21, and in a cluster over the subcentral area (BA43) and primary auditory cortex, *p* < .001, *t*(28) = 3.18 (Figure 5.7).

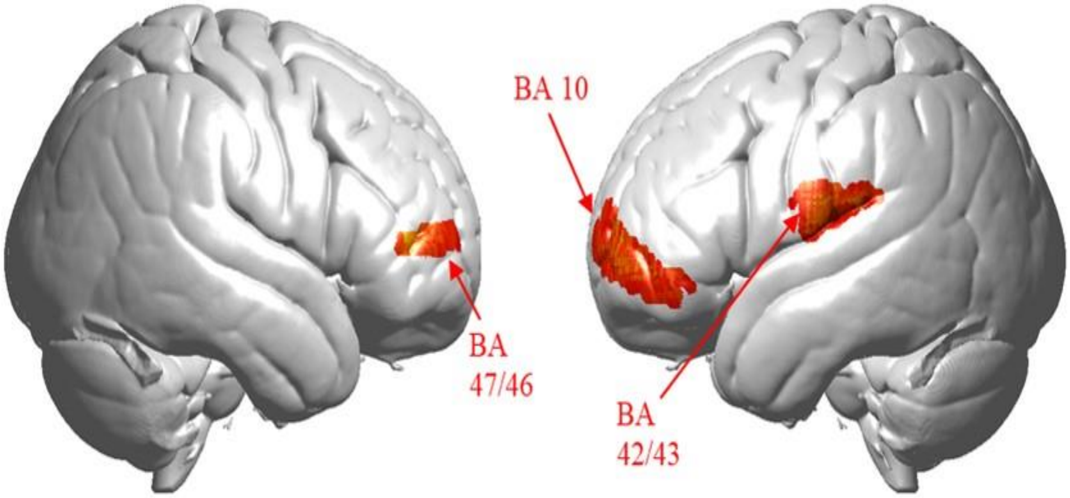


Figure 5.7. Recogitation. Contrast comparison of the thinking subtask of the clinical condition (i.e., internal reasoning about dysfunctional appraisals) [Clinical thinking > Control thinking] for the ROIs (n = 30). Greater activation during the thinking subtask of the clinical condition is represented in red. The cognitive resource demands of this type of recogitation (Crum, 2020) significantly recruited left rostral PFC (BA10), subcentral area (BA43), and primary and auditory association cortex (BA42), and right pars orbitalis (BA47) and middle frontal gyrus (BA46). See Table 5.4.

Table 5.4

Voxel-Wise GLM Contrast Comparisons (deOxyHb signals) of Reasoning Task

Contrast	Threshold	Coordinates[1]	t value	p	df[2]	Anatomical Regions in Cluster	BA[3]	Probability	Voxels
Thinking [Clinical > Control]	p = 0.01	(-32, 52, 0)	3.13	0.002	28	Rostral Prefrontal Cortex	10	0.97	305
		(46, 38, 6)	3.21	0.002	28	Middle Frontal Gyrus	46	0.49	58
						Inferior Frontal Gyrus	47	0.24	
						Inferior Frontal Gyrus	45	0.17	
						Rostral Prefrontal Cortex	10	0.11	
		(-66, -14, 18)	3.18	0.002	28	Primary and Auditory Association Cortex	42	0.25	188
						Subcentral Area	43	0.22	
						Superior Temporal Gyrus	22	0.14	
						Pre and Supplementary Motor Cortex	6	0.11	
Thinking [Control > Clinical]	p = 0.01	(-52, 34, 20)	-3.17	0.002	28	Middle Frontal Gyrus	46	0.71	17
						Inferior Frontal Gyrus	45	0.28	
		(50, 38, 20)	-2.85	0.004	28	Middle Frontal Gyrus	46	0.72	13
						Middle Frontal Gyrus	9	0.17	
		(-34, 26, 34)	-3.45	0.0009	28	Middle Frontal Gyrus	9	0.76	57
						Frontal Eye Fields	8	0.24	
		(-64, -26, 42)	-2.80	0.005	28	Supramarginal Gyrus	40	0.41	10
						Primary Somatosensory Cortex	2	0.23	
						Pre and Supplementary Motor Cortex	6	0.12	
						Primary Somatosensory Cortex	1	0.11	
		(-58, -12, 44)	-2.70	0.006	28	Pre and Supplementary Motor Cortex	6	0.59	10
						Primary Somatosensory Cortex	3	0.18	
						Primary Somatosensory Cortex	1	0.10	

Note. [1]Coordinates are based on the MNI system and (-) indicates left hemisphere. [2]df = degrees of freedom. [3]BA= Brodmann’s Area.

Comparing the verbal intervention subtask of Clinicians in the clinical condition against the repeating substask of Repeaters in the control condition [Intervention > Repeating] that occurred subsequent to the ‘thinking’ epochs showed significant—albeit less—activation in rostral PFC, *p* < .001, *t*(28) = 2.91, angular and supramarginal gyri (BA39) , *p* < .001, *t*(28) = 2.58, and pre-motor and supplementary motor cortex, *p* < .001, *t*(28) = 3.02 (Figure 5.8). Results including cluster sizes, MNI coordinates, probability estimates, and hemispheric localizations of these contrasts are presented in Tables 6.3-6.5.

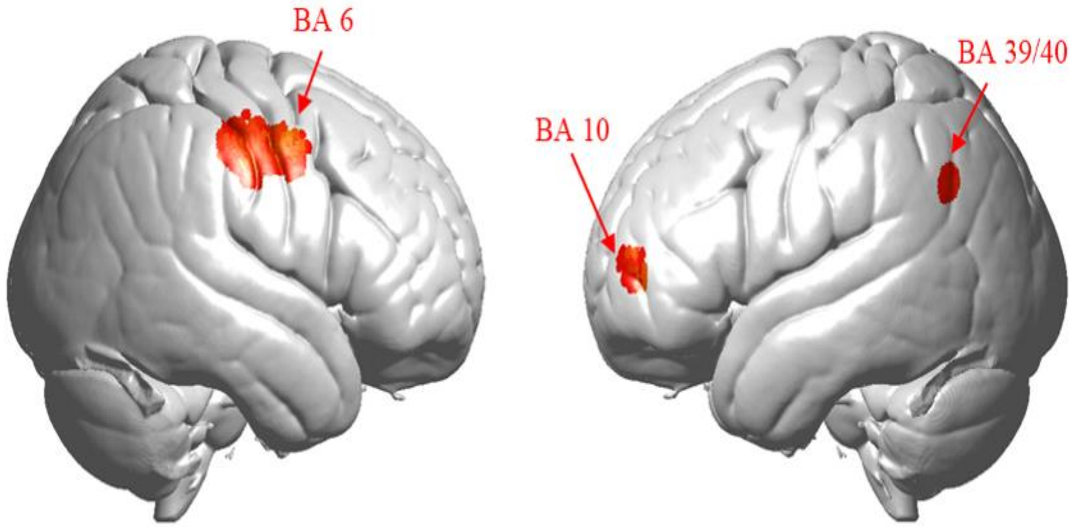


Figure 5.8. Verbal intervention. Contrast comparison of verbal intervention [Intervention > Repeating] for the ROIs (n = 30). Greater activation during verbal intervention in the clinical condition is represented in red. The cognitive resource requirements of verbal reasoning about dysfunctional appraisals significantly recruited left rostral PFC (BA10), angular gyrus (BA39), and supramarginal gyrus (BA40), and right pre-motor and supplementary motor cortex (BA6). See Table 5.5.

Table 5.5

Voxel-Wise GLM Contrast Comparisons (deOxyHb signals) of Verbal Task

Contrast	Threshold	Coordinates[1]	t value	p	df[2]	Anatomical Regions in Cluster	BA[3]	Probability	Voxels
Intervention [Verbal Intervention > Verbal Repeating]	p = 0.01	(-44, 52, 6)	2.91	0.003	28	Rostral Prefrontal Cortex	10	0.36	31
						Middle Frontal Gyrus	46	0.20	
						Inferior Frontal Gyrus	47	0.17	
		(-52, -56, 30)	2.58	0.008	28	Angular Gyrus	39	0.49	10
						Supramarginal Gyrus	40	0.49	
		(50, 0, 42)	3.02	0.003	28	Pre- and Supplementary Motor Cortex	6	0.80	326
Intervention [Verbal Repeating > Intervention]	p = 0.01	(-66, -4, 18)	-2.92	0.003	28	Pre- and Supplementary Motor Cortex	6	0.36	12
						Subcentral Area	43	0.20	
						Superior Temporal Gyrus	22	0.17	

Note. [1]Coordinates are based on the MNI system and (-) indicates left hemisphere. [2]df = degrees of freedom. [3]BA= Brodmann's Area.

5.3.2 Dynamic neural coupling

Cross-brain coherence between dyads during clinical discourse interactions [Clinical situation > Control situation] significantly increased between inferior frontal gyrus (BA44) and supramarginal gyrus, *p* = .002, *t*(29) = 3.35 (uncorrected; see Figure 5.9). Changes in coherence (y-axis) are plotted over 30 second periods of time (x-axis). This coherence was not observed when the partners were computationally shuffled (right panel): that is, randomly paired with every participant except the original partner, which is consistent with the idea that neural coupling is dyad-specific.

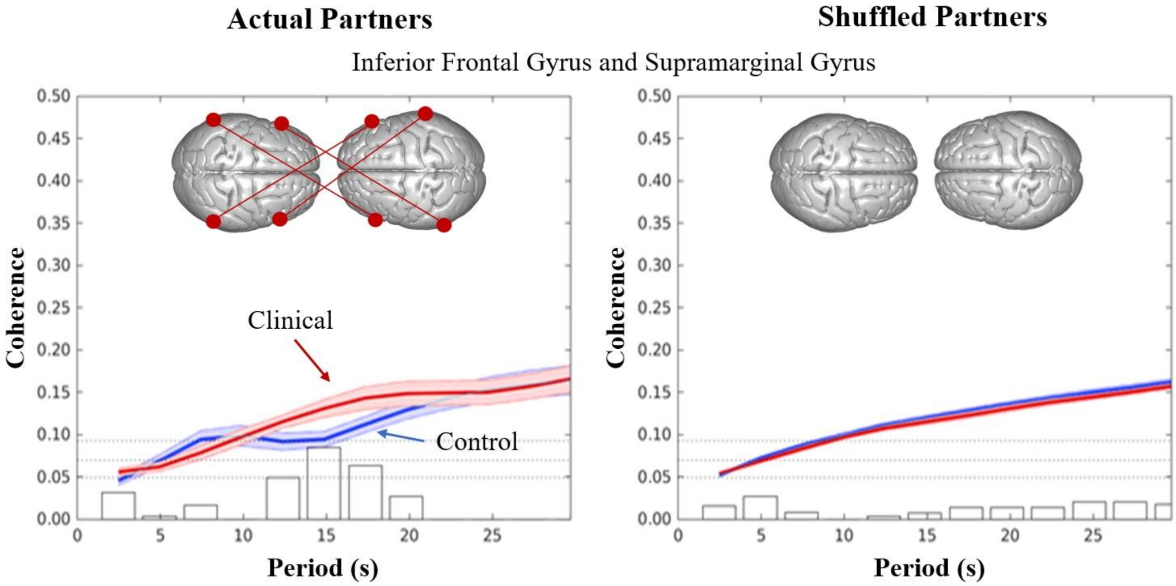


Figure 5.9. Neural synchronization. Coherence of brain-to-brain signals between clinical and control blocks collapsed across all roles and subtasks (n = 30). Signal coherence between dyads (y-axis) is plotted against the period (x-axis) for the clinical (red) and control (blue) conditions. Bar graphs indicate significance levels for the separations between the two conditions for each of the period values on the x-axis. The upper horizontal dashed line indicates ($p \leq 0.01$) and the lower line indicates ($p \leq 0.05$). Left panel shows coherence between actual partners and right panel shows coherence between shuffled partners. Cross-brain coherence is greatest in the clinical condition between inferior frontal gyrus and supramarginal gyrus.

5.4 Discussion

This study adapted the recent approaches of multi-person neuroscience paradigms investigating aspects of verbal communication (e.g., Cañigueral et al., 2021; Hirsch et al., 2018; Hirsch et al., 2021; Liu et al., 2017; Liu et al., 2016; Nozawa et al., 2016) to capture human-to-human interactions that might be clinically significant. The development and application of this novel paradigm constitute a proof of principle, but the results were surprisingly consistent with the prediction that interpersonal interactions in the context of psychotherapy place unique demands on neural systems that normal verbal communication does not. More specifically, the within- and cross-brain coherence evidence found in the clinical condition exhibited a pattern of mutual engagement of subregions along the anterior-posterior axis of the lateral surface of the cerebral cortex, particularly in the PFC and inferior parietal lobule. That the clinical condition showed greater dynamic neural coupling between pairs of participants is consistent with other observations of physiological synchronization (heart and breathing rates) between clinicians and clients (Anzolin et al., 2020; Ellingsen et al., 2020; Palumbo et al., 2017; Tschacher & Meier, 2019), which stresses the need for a more multi-modal approach. Indeed, additional neuroimaging techniques could complement temporal and spatial resolutions and other dependent measures such as eye-gaze and facial-cues could enhance researchers' ability to index coupling between systems during clinical interactions (Chen et al., 2019; Noah et al., 2020). One explanation for these findings is that they might derive from normative nature of the commutation; it was largely dialectical and discourse in everyday life is typically not. An additional element worth considering is the prosocial efforts on the part of the clinician to positively influence the dysfunctional information processing of the client, which could be a more specific source of influence on the strength of interactivity between individuals in these situations.

Interestingly, the within-brain findings support the role of specific PFC subregions in carrying out the task of clinicians to verbally intervene and restructure clients' dysfunctional thinking. Significant activation was observed in left rostral PFC (BA10) and right middle frontal gyrus (BA46) during the clinical thinking task, with the largest cluster being recruited in BA10 (-32, 52, 0). These results are in line with the postulation that this task largely depends on a cognitive ability (i.e., recogitation) that reasons about propositional attitudes in open-ended situations to produce changes that are conducive to well-being (Crum, 2021). Such an ability should place marked demands on stimulus-independent operations that support self-initiated procedures for generating and testing novel hypotheses about linguistic propositions (Goel & Grafman, 2000; Goel, Stollstorff, Nakic, Knutson, Grafman, 2009; Goel et al., 2007; Goel, Vartanian, 2005; Robinson et al., 2015; Volle et al., 2012; Roca et al., 2011; Seyed-Allaei et al., 2017; see Shallice & Cipolotti, 2018; Knight & Stuss, 2013). If this is the case, then it makes sense that such a manipulation of self-generated information would rely on sustained activation biasing in the rostral attentional gateway (Burgess et al., 2007). The actual testing and rejecting of thought hypotheses are potentially mediated by dorsolateral PFC (right BA46) in checking whether semantic criteria—stored in more posterior areas such as BA39 and BA40—are satisfied; it is also possible that dorsal anterior cingulate cortex might be involved in this procedure (Bush et al., 2002). Future research might explore these possibilities.

The findings relating to periods of verbal intervention support not only the importance of the PFC but also that of more posterior subregions of the inferior parietal lobule, namely angular gyrus (BA39) and supramarginal gyrus (BA40). These two subregions comprise what is often termed Geschwind's territory in the language literature, which is an area associated with multi-sensory integration of information such as sight, sound, and body sensation, and it is thicker in humans than in other primates and one of the last areas of the brain to mature—other than rostral PFC (Carter, Aldridge, Page, & Parker, 2019); it also mediates bidirectional information processing between Broca's and Wernicke's areas via the arcuate fasciculus (Catani & Jones, 2005). What is unique about these regions having been recruited is that the clinicians' pattern of activation strongly reflects that which is typically found in the participants of emotion regulation paradigms, particularly ones involving cognitive reappraisal (see Ochsner & Gross, 2005, 2008; Ochsner, Silvers, & Buhle, 2012, for reviews). It appears that, whilst restructuring the dysfunctional cognitions of others', clinicians engaged the same brain regions associated with the semantic network in modifying conceptual valuations during cognitive change strategies (reappraisal). In other words, clinicians are experts at engaging the same systems that clients are trained to use. This possibility raises two interesting questions. First, would it be possible, then, to distinguish between experienced and inexperienced clinicians? Indeed, recent research has shown interesting differences between novice and expert surgeons (Leff, Orihuela-Espina, Atallah, Darzi, & Yang, 2007). Such an investigation in the context of psychotherapy might have implications for developing training programs. Second, could examining discrepancies in patterns of activation between healthy populations (e.g., clinicians) and clinical ones lead to insights that would inform efforts to reduce these differences (e.g., cognitive training paradigms to help clients recogitate their dysfunctional thoughts)? Changes in such functional variations might serve as reliable biomarkers for how clients respond to treatment at the level of the brain and be predictive of treatment outcome measures. These possibilities are in line with recent literature on the potential applications of multi-person neuroscience to neuropsychiatry (Schilbach, 2016; Schilbach et al., 2013). In addition, within the framework of the Interactive Brain Hypothesis[95], inter-brain synchronization—or lack thereof—in clinical situations might be interpreted as a 'dialectical misattunement' of coupled, dynamical systems (Bolis, Balsters, Wenderoth, Becchio, & Schilbach, 2018; see Hasson, Ghazanfar, Galantucci, Garrod, & Keysers, 2012). Clearly, these possibilities warrant further research and there is yet much to learn from the brains of clinicians (Crum, 2021a).

That the present sample did not consist of licensed clinicians suggests something more general about the findings, namely that the evidenced neural systems represent aspects of the normal human functions that work towards modifying propositional attitudes; clinicians are simply a population of experts at engaging these systems. Some of these functions are individually well-understood in the areas of language, social interaction, emotion regulation, and executive function, but less-well understood in their confluence towards achieving the recogitation of not only dysfunctional cognitions but also everyday thoughts people have about the world, others, and self. The present study has shown that aspects of rostral PFC, inferior and middle frontal gyri, and supramarginal and angular gyri are potentially key to this general network. The sample also did not consist of clients with real diagnoses, and so it will be important when working with a clinical sample to assess the ways in which activation trends might differentiate from healthy participants during verbal intervention (e.g., Husain et al., 2020). However, it is worth noting that clinicians and clients should be able to interact naturally whilst neuroimaging data are collected—without computer-mediation. To achieve this, interpersonal interactions could be fractionated in similar ways to the epochs of the present design, but with brain-first approaches to extracting the stimulus design whereby significant functional events in particular brain regions are estimated from observed HbO_2 and HbR signals (Pinti et al., 2017). Portable and wireless neuroimaging devices (Pinti et al., 2018b) seem also to be a prerequisite to collecting data in authentic clinical settings (Crum, 2021b). Moreover, it will be important to include additional measures of people’s phenomenological experience of clinical settings in which neuroimaging data are collected to account for factors that might influence the information-processing systems of interest, such as nervousness, novelty, attitudes toward the ‘therapeutic alliance’, and so forth.

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Chapter 6: Interrelations of Executive Functions, Physical Activity, and Mental Health

6.1 Introduction

6.1.1 Executive deficits in emotion dysregulation

The previous two chapters introduced and explored the idea that the neurocognitive mechanisms driving explicit, conscious strategies to downregulate negative emotion (see Braunstein, Gross, Ochsner, 2017, for review) as well as those potentially mediating the effects of non-pharmacological mental health interventions (i.e., recogitation; Crum, 2021a,b) are predominantly executive in nature. This raises an important issue regarding the negative link between performance on executive function tasks and psychopathological symptomology (see Joormann & Vanderlind, 2014; Rock, Roiser, Riedel, & Blackwell, 2014, for reviews). For example, in the case of depression, greater symptom severity and maladaptive strategies for downregulating negative emotion are associated with worse performance on tasks requiring response inhibition (e.g., Joormann & Gotlib, 2010; Joormann, Levens, & Gotlib, 2011), dynamic updating (e.g., Meiran, Diamond, Toder, & Nemets, 2011), and attentional switching (e.g., Malooly, Genet, & Siemer, 2013). The most prevalent maladaptive strategy is rumination, a trait-like proclivity to think repetitively about goal-incongruent and mood-congruent information (Nolen-Hoeksema, 1991; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). This places particular demands on attention, consequently leaving fewer resources available for adaptive strategies such as reappraisal (see Joormann & Siemer, 2014, for review). Whether this or similar deleterious tendencies (e.g., suppression; Campbell-Sills, Barlow, Brown, & Hofmann, 2006) is integral to the pathogenesis of psychopathological symptoms (Wells & Matthews, 1994) or a product of them, or result of other interactions with factors such as socioeconomic status and malnutrition, it is clear that such propensities are concurrent with diminished mental health and that the global tax they place on the cognitive system challenges the ability of affected systems to achieve amelioration. The clinical implication is that deficits in executive functions might detract from the effectiveness of mental health interventions (Roiser & Sahakian, 2013), which raises the interesting question of whether improving the performance of executive functions localized in the prefrontal cortex (PFC) would augment the effects of these control operations on changes in mental health. The present work posits that a better understanding of certain behaviors that affect executive functions (e.g., physical activity) will have far-reaching theoretical and practical implications in the clinical domain that will potentially help to overcome the negative link between psychopathological symptoms and executive performance.

6.1.2 Cognitive training

Empirical investigation of behaviors that improve executive performance requires that the cognitive ability or function of interest is the object of intervention, which brings this vein of enquiry in line with recent approaches in cognitive neuroscience to improve aspects of cognition. For example, some research has suggested that so-called ‘cold cognition’ can be enhanced as a function of cognitive training (see Ballesteros, Voelcker-Rehage, Bherer, 2018; Jaeggi, Buschkuehl, Jonides, & Shah, 2011, for reviews). Cognitive training paradigms typically focus on working memory tasks (e.g., n-back), but other research has started to explore whether training on more complex tasks that recruit many different executive functions (e.g., video games) transfer into long-term increases in performance on different yet equally complex tasks (see Boot, Blakely, & Simon, 2011; Pallavicini, Ferrari, Mantovani, 2018, for reviews). So, cognitive training experiments are an approach to enhancing or retaining the integrity of the brain and, more specifically, they fall into a ‘top-down’ class of approach whereby directly exercising, as it were, the cognitive operations of interest improves their efficiency. For example, in the area of aging and neurodegenerative diseases, some plasticity paradigms have shown that cognitive training reduces neural compensation in older adults (e.g., Iordan et al., 2020). Neural compensation refers to the tendency of older adults to recruit greater activation in the brain than younger adults to achieve comparable performance on low demand tasks, which leaves fewer resources available in an analogous fashion to rumination when task demands are marked, in which case there is a ceiling effect of having insufficient resources to achieve comparable performance (i.e., the Compensation Related Utilization of Neural Circuits [CRUNCH] Hypothesis; Reuter-Lorenz & Cappell, 2008). Some meta-analyses have suggested that cognitive training leads to small, long-lasting improvements to cognition in people with mild cognitive impairment and dementia cognitive training (Bahar-Fuchs, Martyr, Goh, Sabates, & Clare, 2019).

As regards mental health, meta-analyses generally supporting the effectiveness of attention-bias modification tasks in reducing symptoms common to anxiety and mood disorders (e.g., Cristea, Kok, & Cuijpers, 2015; H. Liu, Li, Han, & X. Liu, 2017). For example, some studies have shown decreases in depressive symptoms following cognitive training that targets the ability of people to attend away from negative stimuli (Preiss, Shatil, Čermáková, Cimermanová, & Ram, 2013; Siegle, Ghinassi, & Thase, 2007). There is also some evidence for the effectiveness of transcranial direct current stimulation in reducing depressive symptoms (e.g., Katz et al., 2017; Ruf, Fallgatter, & Plewnia, 2017), which represents a more ‘bottom-up’ approach. However, the findings of cognitive training paradigms are often mixed in the sense that there are marked individual differences within samples; training works differently for different people. Accounting for these differences likely requires training programs to be customized to the individual rather than to a particular group. It is also worth noting that the tasks in which people are trained need to make sense in terms of the outcomes to which they purportedly transfer; for example, it would make little sense to train people on a n-back test or Tower of London task and expect the learning that occurs to translate into better performance in a complex video game. So, there is a growing interest in whether cognitive functions can be improved through top-down training approaches, and although the evidence crossing into the clinical domain is promising, it is still marginal and further research is necessary. At the moment, such approaches should only be considered as a complement rather than a replacement for treatments that have long been established as efficacious.

6.1.3 Exercise-affect interactions

It is plausible that some bottom-up approaches to improving cognition might be more practical and able to circumvent the challenges of targeting specific cognitive functions by having global effects on the brain. For example, one potential approach is medication; however, evidence for the effectiveness of medication in improving cognition in clinical populations is not strong (Halahakoon and Roiser, 2016; Shilyansky et al., 2016). Another possibility is one of the most predominant means by which to improve physical well-being in everyday life: physical activity. Cognitive training and exercise (chronic and acute) appear to benefit brain function, especially when used together (e.g., Zhu et al., 2016), but do these improvements to ‘cold’ cognition benefit psychological well-being in turn? In short, they probably do, but some things remain unclear from a cognitive neuroscience perspective. Cognitive training paradigms have been linked to improvements in mental health (see Keshavan et al., 2014), such as attention bias modification for anxiety and mood disorders (e.g., Beard, Sawyer, & Hofmann, 2012; Deckersbach et al., 2010; Hakamata et al., 2010). At the same time, physical activity has been associated with improvement in mental health (Hallgren et al., 2016; Harvey, Hotopf, Øverland,

& Mykletun, 2010; Mammen & Faulkner, 2013, Song et al., 2012, Teychenne et al., 2008), and it appears that any level of intensity works to change mood (Helgadóttir et al., 2016). Unsurprisingly, then, exercise has been explored as an alternative treatment for mild to moderate depression (Parker and Crawford, 2007), as well as other disorders (see Stathopoulou, Powers, Berry, Smits, & Otto, 2006). More appropriately, using exercise in combination with CBT has shown improvements in outcome measures relative to CBT with no exercise program complementing it (e.g., McArdle, McGale, & Gaffney, 2011, 2012). However, this raises some theoretical issues.

Because cognitive training techniques such as attentional bias modification target the ‘attentional deployment’ step of the emotion regulation model, which essentially cultivates the marginally efficacious strategy of distraction, rather than that of ‘cognitive change’ (Gross, 1998, 2014), dysfunctional appraisal processes are not targeted as they are in CBT. This is why such cognitive training paradigms cannot viably act as a substitute for this form of psychotherapy: They might target important aspects of attention and memory, but they do not explicitly train the systems uniquely engaged during CBT. And, even if techniques were developed to train the systems underpinning reappraisal and recogitation to act on maladaptive schemas and appraisals, they should probably still be used in combination with psychotherapy, since they would lack other important factors that contribute to mental health (e.g., interpersonal interactions that build the therapeutic alliance). In fact, both cognitive training and exercise should probably be used together to augment the effects of CBT on mental health. Perhaps the best approach might be one that is the most holistic and customizable, such as by including protocols for not only exercise but also nutrition and sleep. Whatever the optimal approach to cultivating mental health, the particular means by which exercise accomplishes its role is unclear.

That physical activity facilitates the release of endorphins and dopamine (e.g., ‘runner’s high’) is well recognized, but also is the transient nature of these effects (see Dishman & O’Connor, 2009). Although these low-level neurobiological effects might be useful in boosting mood and decreasing anxiety, they might have little impact on sustained changes in mental health. Instead, any sustained effects might be due to changes in executive functions. In other words, positive affect from low-, state-level effects relating to exercise or otherwise is not what drives current or future applications of cognitive strategies to downregulate negative emotion: Executive functions largely underpin this downregulation (see Gross, 2014). Therefore, profound changes in long-term mental health might be more closely related to the acute and chronic effects of exercise on the executive functions that comprise the subsystems carrying cognitive restructuring. However, the understanding in cognitive neuroscience of the nature of these basic effects on the functions of the PFC, and whether they vary with psychopathological symptoms, remains poor. Aspects of this understanding ought to be improved if researchers are to take full advantage of the clinical applications of physical activity. The following discusses the state of the subfield which concerns itself with brain-body interactions related to exercise and exertion: exercise neuroscience.

6.1.4 Exercise-function interactions

Because physical exercise has well-known effects on physiological systems that are positive (e.g., lower risk of diabetes, breast cancer, colon cancer, heart disease, and stroke; Kyu et al., 2016), and because the mind is realized through such a system (a neural substrate), physical activity might have similar effects on cognition that could be clinically significant. Exercise neuroscience researchers have been steadily studying the idea that physical movement and exertion interact with cognition for a few decades, with the last two decades seeing a marked increase in the frequency of investigations adopting cognitive neuroscientific methods (see Pontifex et al., 2019, for review). A convenient historical starting point for theorizing in this field is Yerkes and Dodson's (1908) postulation that the interaction between arousal and performance follows an inverted-U curve, according to which performance increases as arousal increases, but only to a certain point: Too much arousal for too long detracts from performance.

In information-processing terms, Kahneman (1973) argued that increases in physiological arousal increases the availability of cognitive resources for tasks, and it is this effect which mediates the relationship between physical activity and cognitive performance. Theories accounting for the multidimensional interrelationships between arousal, cognition, and performance are referred to as 'cognitive-energetical' and 'allocatable resources' theories (e.g., McMorris & Graydon, 1996; Sanders, 1983; see McMorris, 2016, for review of historical accounts of the study of brain-body interactions related to exercise). More specifically, these approaches predict that task performance should improve if there is a greater availability of resources, because this facilitates the efficiency with which they can be allocated to the cognitive operations required of a task (e.g., Hockey, 1997). In supervisory terms, this might suggest that exercise particularly upregulates energization in medial PFC, together perhaps with the 'care' subsystem that ascribes a level of 'aspiration' (i.e., cognitive effort that should be committed) to tasks.

However, a competing account, termed the 'reticular-activating hypofrontality model' (Dietrich & Audiffren, 2011), is predicated on the distinction between control and automatic cognitive processes and the prediction that acute bouts of aerobic activity have differential effects on automatic and controlled information-processing systems in the brain. On this view, exercise is so inherently taxing on the systems supporting movement and balance that any upregulation of resources is preferentially allocated to these systems, reducing the resources available for executive functions; consequently, tests of executive function should result in worse performance during and shortly after exercise, as well as in local deactivations within PFC. However, predictions from the reticular-activating hypofrontality model have not been consistent with either findings from studies examining the acute effects of exercise on executive functions, and cognition more generally, nor from studies of cerebral oxygenation and blood flow (see Rooks, Thorn, McCully, & Dishman, 2010, for review).

The positive association between chronic physical activity levels and cognition is well established, such as in populations of older adult and children (see Etnier, Shih, Piepmeier, 2016, for review). However, correlational analyses may always be subject to effects from mediating factors such as socioeconomic or nutritional influences, and the number of well-controlled longitudinal studies examining chronic changes in cognition as they track physical activity or fitness levels within subjects is not substantial. The evidence of acute effects of exercise is more extensive, but evidence relating to the brain mechanisms in humans through which acute physical activity can provide a boost—or ‘buff’, as it were, in the modern parlance of video games—to cognitive functions is severely lacking. Studies have suggested that there are acute effects of exercise on multiple areas of cognition from just a single bout (Hillman et al., 2003, 2009; Kamijo et al., 2009; Kamijo, Nishihira, Higashiura, & Kuroiwa, 2007; O’Leary, Pontifex, Scudder, Brown, & Hillman, 2011; Pontifex, Saliba, Raine, Picchietti, & Hillman, 2013). The quality and degree of these improvement tend to be transient; they remain for a limited window of time: for example, meta-analyses suggest they can last up to two hours, but also that the largest effects reduce within a 15-20 minute period (Chang et al., 2012; Lambourne & Tomporowski, 2010). There is some evidence that acute exercise-cognition interactions are especial to executive functions (McMorris, 2016), so the mental tasks that have been used to index aspects of these interactions have often been traditional cognitive control ones such as the flanker task (Eriksen & Eriksen, 1974), Simon task (Simon, 1969), Stroop task (Stroop, 1935), go/no go task (Donders, 1969), stop signal task (Logan & Cowan, 1984), Wisconsin card sorting task (Berg, 1948), Tower of London task (Shallice, 1982), random number generation task (Baddeley, 1966), trail making test (Reitan, 1958), and n-back test (Kirchner, 1958). Interestingly, meta-analytic findings have suggested that go/no go tasks index supervisory monitoring rather than simple response inhibition, since participants first check the stimuli before inhibiting an associated action on a given trial, and the general findings of activation in right dorsolateral PFC support this (see Criaud & Boulinguez, 2013).

In addition to task type, the type of exercise and its intensity have also varied in this domain of research. Exercise interventions typically consist of aerobic exercises, which involve continuous activities such as walking, running and cycling, where the intensity can be defined into three categories: mild, moderate, and heavy. More specifically, mild, moderate, and heavy exercise are specified as <40% VO_2max, >40-79% VO_2max, and >=80% VO_2max, respectively (see McMorris, 2016), where VO_2max refers to the maximum oxygen (O_2) uptake achieved during incremental exercise to exhaustion. This is the gold standard measure of aerobic capacity and is directly linked to an individual’s physical fitness and health. The main findings of research focusing on cognitive control are that, during and just after moderate exercise (e.g., Kamijo et al., 2004), it generally improves the ‘speed of processing’ across executive functions (e.g., McMorris & Hale, 2012), with some reductions in accuracy depending on the type of task and if the exercise was strenuous. In other words, the most oft-repeated finding is a decrease in reaction times (i.e., people respond more quickly) on cognitive tests with changes in error rate being rather more situation- and task-dependent. This seems to fit with the present interpretation—and, indeed, prediction—that the energization of supervisory systems in medial PFC is probably a key recipient of the bottom-up effects of exercise.

6.1.5 An evolutionary perspective

But why are there positive interactions between exercise and cognition at all? And, more specifically, is the postulation that cognitive control should be reduced during and shortly after exercise (Dietrich & Audiffren, 2011) incorrect because an upregulation to these resources was adaptive rather than maladaptive? Raichlen and Alexander (2018) argue from an evolutionary-neuroscience perspective that "links between exercise and the brain likely evolved to improve foraging success in our ancestors, and a lack of either exercise in general or cognitive demands during exercise may lead to capacity reductions or sub-optimal capacity maintenance in the brain similar to those seen in other organ systems." For example, some inactivity-induced capacity reductions include reductions in bone density, muscle mass, peripheral capillary density in the heart, lung mass, and so forth. Similar reductions can occur in the brain (e.g., atrophy), constituting risk factors for neurodegenerative diseases and highlighting the importance of physical activity in combating age-related cognitive decline. So, physical activity was not only advantageous for well-being and survival during early human evolution but also a behavior that was seldom carried out in isolation—that is, in the absence of a broader, complex cognitive task (e.g., hunting, foraging). Such behavior is in stark contrast to that of starring at a wall whilst running on a stationary treadmill, where the only active cognitive functions are those relevant to the exercise. Thus, early hominids evolved to maintain survival by using their bipedal adaptation to find more distant food sources, such as to physically hunt other animals, which means that they were carrying out an essential, complex behavioral task that called for the careful execution of a host of mental functions, including control operations (e.g., those of prospection). So, a common pairing throughout evolutionary epochs were the taxing physical demands of early hominids—what is now considered vigorous aerobic exercise (≥80% VO2max; McMorris, 2016)—and the executive functions that supported long-term survival. A reduction in the performance of executive functions during vigorous exercise was probably not evolutionarily advantageous. It therefore makes sense to infer that there remains in the modern human brain the constitution for completing difficult tasks during vigorous exercise without a significant reduction in how successfully they are carried out.

In fact, the brain might stand to benefit more from physical activity that is not solely sensorimotor and, instead, requires multitasking. For example, running on a treadmill might be too “cognitively impoverished” compared to running through an urban environment in which attention needs to be continuously or periodically directed towards the route, pedestrians, vehicles, signals, animals, and so on. The incoming novel information might be key to maximizing the effects of exercise on cognition (Kempermann, 2008), such that running the same route is not as optimal as exploring new ones. So, the effects of physical activity on the brain are potentially optimized when exercise is combined in some way with cognitive demands akin to the hunting and gathering tasks of early humans. This prediction appears to be consistent with meta-analytic findings that interventions combining exercise and cognitive training paradigms produce improvements in cognition in healthy older adults over and above exercise alone (Zhu, Yin, Lang, He, & Li, 2016). However, it is worth noting that the future research for which these predictions clearly call could face some difficulties with disentangling executive functions. Namely, although running and cycling on stationary machines might not place the same exogenous demands on executive functions as naturalistic exercises (e.g., hiking a novel route on a mountain), these ‘boring’ activities might still tend to co-occur with self-initiated, endogenous mental activities that carry significant executive demands—perhaps following an opportunistic, evolutionary disposition for engaging more in SIT-based mental tasks during moments of little to no exogenous stimuli. Indeed, running at the local gym is an opportunity to be mentally productive (e.g., plan for the future). Future exercise neuroscience research might consider controlling for endogenous factors if using ‘no cognitive task’ conditions during exercise. For more evolutionary perspectives, see Wallace, Hainline, and Lieberman (2018).

6.1.6 Exercise-structure interactions

Because cognition reduces to brain states, it makes sense to enquire into the neurobiological underpinnings of exercise-cognition interactions. Although the precise orchestration of neurobiological mechanisms engendering enhanced cognitive functioning remains unclear, research has elucidated a few effects that might be key. Observations from behavioral neuroscience have shown structural changes related to chronic exercise in rodents, such as increases in the total number of neurons, synapses, dendritic complexity, and spine density in a number of brain regions. For example, these structural changes have been especially observed within the hippocampus, particularly the dentate gyrus (van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999), which is a central hub for integrating sensory information to form unique memory representations. An effect of this exercise-evoked neurogenesis is increased cortical volume (e.g., new granule neurons in the dentate gyrus add to its granule layer, increasing its mass; Clark et al., 2009). It is worth noting that these findings are clinically relevant, because the dentate gyri of the hippocampi are the first brain regions affected by neurodegenerative diseases such as Alzheimer’s disease (Rodriguez & Verkhratsky, 2011; Varela-Nallar, Aranguiz, Abbott, Slater, & Inestrosa, 2010). Importantly, these findings have been replicated in humans (e.g., Erickson et al., 2011). In this area of neuroscientific research, increases in cortical volume has been evidenced not only in the hippocampus but also the frontal lobe, particularly the PFC (Erickson & Kramer, 2009). Another interesting finding is that the observed increases in cortical volume in the PFC might relate to marked changes in the proliferation of astrocytes (Li et al., 2005). See Hamilton and Rhodes (2016) for further review of the structural effects of chronic exercise. Such exercise-structure interactions could help to explain the above discussed exercise-function interactions, but what are the acute, constituent effects potentially leading to these structural changes?

6.1.7 Notable metabolic mechanisms

Behavioural neuroscience studies into the acute effects of exercise have found that physical activity raises the concentration of neurotrophic factors such as fibroblast growth factor 2 (Gomez-Pinilla, Dao, & So, 1997), insulin-like growth factor 1 (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006), brain-derived neurotrophic factor (BDNF; Neeper, Gomez-Pinilla, Choi, & Cotman, 1996), and vascular endothelial growth factor (Uysal et al., 2015). BDNF has drawn great interest from researchers because of its role in facilitating neurogenesis and neuroplasticity (Cotman & Berchtold, 2002). More specifically, it is a basic protein of 252 amino acids that is coded by the BDNF gene, which is on band p13 of chromosome 11 (see Knaepen, Goekint, Heyman, & Meeusen, 2010, for review), and moderate to rigorous physical activity has been linked to increases in its concentration in the blood (i.e., serum BDNF; see Piepmeier & Etnier, 2015, for review). So, repeated increases in serum BDNF during acute bouts of exercise might explain the structural changes in the brain to which chronic exercise leads. However, the connection between these increases and improvements in cognition remains unclear, especially with respect to the executive functions of the PFC. For example, some studies have not found an association between exercise-induced BDNF and performance on executive function tasks (Ferris, William, & Shen, 2007; Tsai et al., 2016), and sometimes only those individuals who are already fit show significant increases in BDNF (Tsai et al., 2014). What is more is that there is an association between anaerobic exercise (e.g., strength training) and improved performance on executive function tasks, but changes in levels of BDNF do not mediate this relationship (Forti et al., 2014; Goekint et al., 2010). Interestingly, in line with the evolutionary perspective above, changes in BDNF are least significant when the same physical activities are repeatedly performed in environments that are not cognitively ‘enriched’ (Adlard, Perreau, & Cotman, 2005). Thus, negative findings might be due to paradigms relying too heavily on stationary exercises in environments that place few demands on cognition, or perhaps there are multiple roads—as it were—to enhanced cognition, such that there are different mechanisms at work in the case of strength training.

Although particular neurotrophic factors likely have some long-term role in improving cognitive functions through structural changes in the brain and might be involved in facilitating the acute effects of exercise on cognition (see Huang, Larsen, Ried-Larsen, & Anderson, 2014, for further review), structural changes are likely not mediating the latter interaction. Such physical changes are more likely to accrue over a relatively long period of time (Kandell, Koester, Mack, & Siegelbaum, 2021) rather than within the span of an acute bout of exercise. What, then, is occurring during exercise that improves cognition *in situ* and cascades into the near future? One possibility is the upregulation of certain neurotransmitters such as dopamine, since its concentration in the blood is transiently increased during exercise (see Meeusen et al., 1997). Indeed, exercise tends to acutely raise the levels of many different neurotransmitters in the blood, such as epinephrine, norephenphine, serotonin, and acetylcholine (Kurosawa, Okada, Sato, & Uchida, 1993). A greater availability of neurotransmitters could explain the composite finding of executive function studies that speed of processing is generally enhanced, provided this availability is corresponded with greater usage. However, research has shown a weak relationship between exercise-related increases in concentrations of catecholamines in the blood and their usage in the brain (McMorris, Collard, Corbett, Dicks, & Swain, 2008), and that baseline concentrations of catecholamines poorly predict post-exercise changes in cognitive performance (McMorris et al., 2003), suggesting a more indirect than direct relationship between the release of catecholamines in the sympathoadrenal system and improvement in cognition.

Another explanation involves considering the chief factor on which both exercise and cognitive functioning directly depend: hemodynamics. After all, exercise is a cognitive task and all cognitive tasks depend on the brain regions supporting them to receive the oxygen they need for continued activation. So, does the upregulation of cerebral blood during physical activity explain interactions involving cognition? The evidence for this view is somewhat strong. Meta-analytic findings have supported the idea that cerebral blood flow increases during exercise, particularly when the activity is moderate to heavy (Rooks et al., 2010). More specifically, this upregulation consists of both increases in cerebral blood velocity, as measured by transcranial doppler ultrasound (Lupetin, Davis, Beckman, & Dash, 1995), and oxygenation, as measured by functional near-infrared spectroscopy (fNIRS). For example, exercise acutely increases regional levels of oxygenated hemoglobin (HbO_2) in premotor, motor, and prefrontal cortices (Subudhi, Miramon, Granger, Roach, 2009). In other words, the velocity and oxygen concentration of blood flow is increased within arteries during exercise, but the arterial pressure of cerebral autoregulation does not exceed normal parameters (60-150 mm Hg). However, this renders the investigation of changes in HbO_2 that are due to a cognitive task during exercise difficult, because the upregulation of extra- and intra-cerebral blood flow washes it out, and artifacts of motion also increase the noise in signals purporting to show changes in concentrations of HbO_2 and deoxygenated hemoglobin (HbR) that are related to neuronal activity (Ekkekakis, 2009). Moreover, cerebral oxygenation is modulated by the respiration demands of physical activity (Zhang et al., 2019). Therefore, studies examining aspects of cognition during exercise, especially those using fNIRS, should not only take great care in the pre-processing stages of data analysis (e.g., motion-artifacts), and rely more on HbR than HbO_2 for interpretation, but also account for heart and respiration rates so that their potential contamination of the signals can be removed when estimating single-subject design matrices.

Fortunately, there is a safer approach with respect to the integrity of data, and which allows for examination of whether exercise-induced increases in regional cerebral blood flow relate to the acute effects on cognitive performance that have been consistently demonstrated in experimental exercise psychology: Namely, measuring cognition before and after exercise. A repeated-measures approach does potentially raise the issue of learning upon the cognitive task, affecting performance of the cognitive tasks and the level and distribution of the supporting haemodynamic, but this can be largely addressed with counterbalancing tasks and stimuli and with a control group that does not exercise. Recent research using a repeated-measures approach to examine the acute effects of exercise-induced increases in cerebral oxygenation on cognitive performance have been consistent with the prediction that increased cerebral oxygenation supports the subsequent neural demands of cognitive tasks. For example, Endo and colleagues (2013) investigated the effects of different aerobic demands on response inhibition using the Stroop task. They found improvements in response inhibition (15 minutes post-exercise) were coupled with increases in PFC activation compared to measures taken before exercise. Faulkner, Lambrick, Kaufmann, and Stoner (2016) later replicated these findings using the same task and exercise (cycling) at 30 minutes post-exercise. Other researchers have also linked acute improvements on executive function tasks with increases in cerebral oxygenation to the PFC (Byun et al., 2014; Hyodo et al., 2012; Yanagisawa et al., 2010). These findings contradict the predictions of the reticular-activating hypofrontality model of acute exercise (Dietrich & Audiffren, 2011), and are more in line with Kahneman's (1973) idea that increases in physiological arousal increase the availability of cognitive resources for tasks, with 'availability', here, corresponding closely to oxygenation availability at the level of the whole brain. However, one question that remains unclear is whether this upregulation is *global* within the PFC or more *specific* to its subregions and their role in the tasks of interest. This is in part because some of the studies mentioned above obtained only partial coverage of the PFC, such that they only measured activity from part of the right hemisphere or only had a few channels over the forehead area, but reported effects on the PFC instead of on the subregion(s) their fNIRS channels covered. Reporting PFC effects as if they were global when data were only collected from specific subregions within a single hemisphere creates some ambiguity on question above. Coverage of multiple PFC subregions on both hemispheres should be able to better address this problem. See Ando (2016) for further review on cerebral oxygenation.

Interestingly, because there is some evidence showing a significant decrease in cerebral oxygenation during rigorous levels of exercise (i.e., >=80% VO_2max), which also persist shortly after exercise (Ando, Kokubu, Yamada, & Kimura, 2011), researchers tested whether cognitive performance is preserved under such conditions by varying the degree to which participants experienced hypoxia during exercise (i.e., fractions of inspired oxygen were manipulated and pulse oximetric saturation was monitored). Specifically, Ando and colleagues (2013) found that the performance of participants on the executive function task (go/no go task) was preserved, improved in fact. Moreover, they failed to observe a significant change in cognitive performance in the absence of exercise during hypoxic conditions. So, the upregulation of cerebral oxygenation during moderate exercise might lead to improvements in cognition and cascade into post-exercise behavior, but during strenuous exercise, this oxygenation is relatively decreased, and yet cognitive performance is nonetheless sometimes improved. Potentially key to explaining these findings is the term 'relatively', in that oxygenation might have been lower during heavy physical activity with respect to oxygenation during moderate exercise, but not with respect to baseline levels prior to exercise. That is, although cerebral oxygenation might vary depending on exercise intensity, any amount of exercise will upregulate blood flow and, therefore, potentially contribute to brain function.

However, this does not explain the metabolic mechanisms that might be helping to energize executive functions when there is less oxygen available in the brain. One explanation comes from what is already known about the rest of the body and how it functions under such conditions. Namely, a central feature of cell metabolism in the context of exercise is the production of lactate, a by-product of glycolysis, whose ultimate function is to convert glucose into energy (i.e., adenosine triphosphate) when local levels of O_2 are insufficient (Chen, Fry, Layton, 2017). Because synaptic activity in the brain is coupled with glycolysis (Pellerin & Magistretti, 1994), lactate might be an important, and indeed auxiliary, fuel source for brain metabolism during strenuous physical activity (Quistorff, Secher, Johannes, & Lieshout, 2008). For example, Ide, Schmalbruch, Quistorff, Horn, and Secher (2000) measured arterial-internal jugular venous concentrations of O_2 and lactate during maximal exercise and found that lactate uptake to the brain exceeded O_2 uptake, including after exercise. Linking this to cognition, and particularly to executive functions, Tsukamoto and colleagues (2016) showed that post-exercise improvements in response inhibition (Stroop task) were associated with accelerated lactate metabolism. That lactate becomes increasingly relevant to brain function as the demands of physical activity increase appears to be consistent with the important role of astrocytes in glycolysis (see Pellerin, 2005), and resonates with the observation that exercise increases the proliferation of astrocytes in the PFC (Li et al., 2005). Therefore, regarding Kahneman's (1973) idea that increases in physiological arousal increase the availability of cognitive resources for tasks, the terms 'availability' now perhaps more precisely corresponds not to O_2, but to the upregulation of metabolic mechanisms using O_2 and lactate to produce energy (e.g., glucose utilization in astrocytes).

6.1.8 The present study

The present work therefore investigated the effects of acute exercise on the PFC activity during executive function tasks in ways that address the shortcomings of previous studies, namely by using a repeated-measures design and a control group, as well as measuring physiological confounds (heart and respiration rates) and PFC activity from multiple subregions across both hemispheres. The central question was whether performing executive function tasks shortly after heavy exercise would result in neural activation that is largely global across the PFC or specific to the operational demands of its subregions that typically support these tasks. The specific executive functions that were examined were those which are potentially critical to recogitation, namely stimulus-independent and -dependent thought/attending (SIT & SOT, respectively; see Burgess, Dumontheil, & Gilbert, 2007, for review), as well as strategic monitoring during response inhibition. If exercise induces changes in the availability of cognitive resources, then cerebral upregulation might show a more generalized recruitment of the PFC on composite contrasts indexing factors that require support from many brain areas, such as ‘processing speed’ across multiple executive function tasks. Moreover, if greater resource availability also engenders greater efficiency in use, then resource consumption might appear more region-specific on individual tasks that have been developed to isolate a specific set of executive functions (e.g., attentional monitoring, attentional mode). These effects of exercise on the PFC were also hypothesized to correspond with improvements in behavioural performance, particularly decreases in response times.

What also remains to be seen is whether psychopathological symptoms such as depressed mood relate to the acute effects of exercise on PFC functional activation during these executive function tasks. The present work therefore aimed to investigate this question as well as whether one’s level of physical fitness, as measured by VO_2peak, impacts the reactivity of the PFC to exercise. Because of the link between depressive symptoms and deficits in executive functions, and because exercise positively affects executive functions, there might also be a link between depressed people’s neural reaction to exercise in the PFC. Thus, it was hypothesized that people with greater depressive symptoms might show weaker effects of exercise on the PFC, but that greater levels of cardiorespiratory fitness would show a stronger upregulation of the PFC as a function of exercise.

6.2. Method

6.2.1 Participants

Participants were voluntarily recruited and randomly allocated to an exercise group (n = 106; 73% male; age: 39 ± 9 years; weight 84.0 ± 19.7 kg; height 173.6 ± 20.2 cm), and a control group (n = 27; 97% male; age: 43 ± 6; weight 89.4 ± 18.6 kg; height 177.7 ± 9.4 cm). All participants completed a Physical Activity Readiness Questionnaire (PAR-Q; Pescatello, Riebe,

& Thompson, 2014) to screen for eligibility to undergo exercise test to volitional exhaustion; completed the Mood and Feelings Questionnaire (MFQ; Angold et al., 1995), a widely used self-report measure of depressive symptomology that has high internal reliability (Cronbach's alpha = 0.85); and provided written informed consent prior to participating in the study. Participants were excluded from the study if they were not law enforcement officers, if they presented any injury or illness that prevented them from exercising to exhaustion, if they had a neurological condition or if responded "yes" to any of the questions on the PAR-Q. Ethical approval was granted by the University College London Research Ethics Committee in line with the declaration of Helsinki (Ethics number: 13985/004).

6.2.2 Experimental paradigm

The experimental design consisted of a time manipulation (neurocognitive testing before and after exercise) and cognitive manipulations within each neurocognitive testing session (Figure 6.1). Participants were randomly allocated to an exercise group or a control group. While the exercise group completed neurocognitive testing before and after exercise, the control group completed neurocognitive testing before and after resting, and then underwent exercise testing after the cognitive testing was complete to gather their fitness data. Participants were fitted with Equivital (https://www.equivital.com/products/eq02-lifemonitor) to record heart rate and respiration rate, and with a continuous-wave fNIRS system (LIGHTNIRS, Shimadzu Corp., Kyoto, Japan) measure changes in hemodynamics.

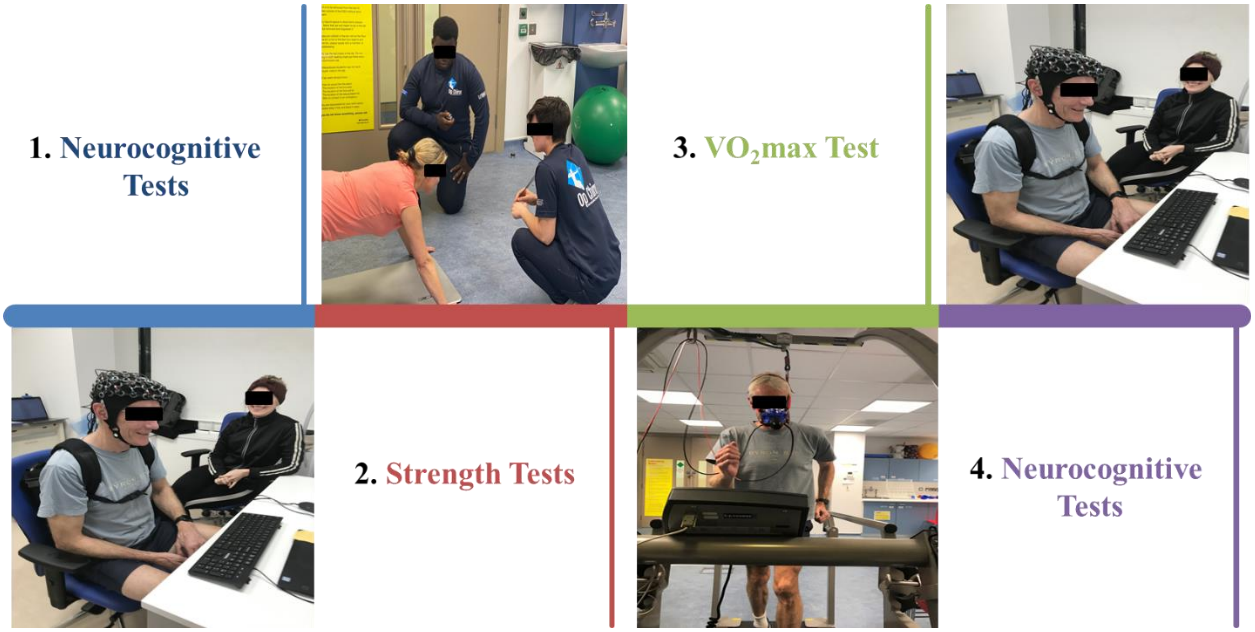


Figure 6.1. Experimental design. After participants completed several cognitive tests (**1**), they engaged in a battery of strength tests, including press-ups, hand-grip strength, and countermovement jump height (**2**). Next, they were required to complete a 15-minute bleep test of aerobic fitness, namely a VO2max test (**3**) and, after a cooldown period, completed similar cognitive tests (**4**).

6.2.3 Cognitive tasks

These data were collected whilst participants completed a set of cognitive tasks on a computer screen. The cognitive tasks were created in PsychToolbox, MATLAB (Mathworks, Natick, MA) to test aspects of executive function (inhibition and attention). Regarding response inhibition, there were 3 blocks that varied from low, moderate, to high inhibition. Namely, the low inhibition condition was a simple reaction time (SRT) task in which they were required to respond (press the spacebar) each time an image appeared on the screen, and to not respond when a fixation cross was shown. The moderate inhibition condition was the same as the previous one, with the exception that they were instructed to not respond to specific images, particularly kittens: “Do not ‘shoot’ the kittens” (Figure 6.2) The high inhibition condition was the same as the moderate one, with the exception that a loud auditory noise would randomly occur (a gunshot) by which they were asked not to be distracted.

Figure 6.2. Example trials of the Go/No-Go condition of the response inhibition task (images: Public Domain).

Regarding mode of attending, these tasks also consisted of 3 blocks and required participants to respond in particular ways depending on whether they were attending to stimuli on the computer screen (i.e., exogenous attending) or to stimuli independent of it—i.e., in their minds only (i.e., endogenous attending). More specifically, the first of these conditions was a stimulus-oriented thought (SOT) task in which participants pressed one of two keys depending on whether a given letter in the alphabet that was presented on the screen contained any curved lines. The next condition was a stimulus-independent thought (SIT) task in which they were required to respond in the same way as the previous task to each letter in the alphabet, but no letters were shown on the screen; they needed to represent them mentally (Figure 6.3). Lastly, the third mode of attending condition was also a SIT task that was exactly the same as the previous one, with the exception that distractor letters were shown on the screen in each trial (see Burgess et al., 2007, for background of SOT/SIT tasks).

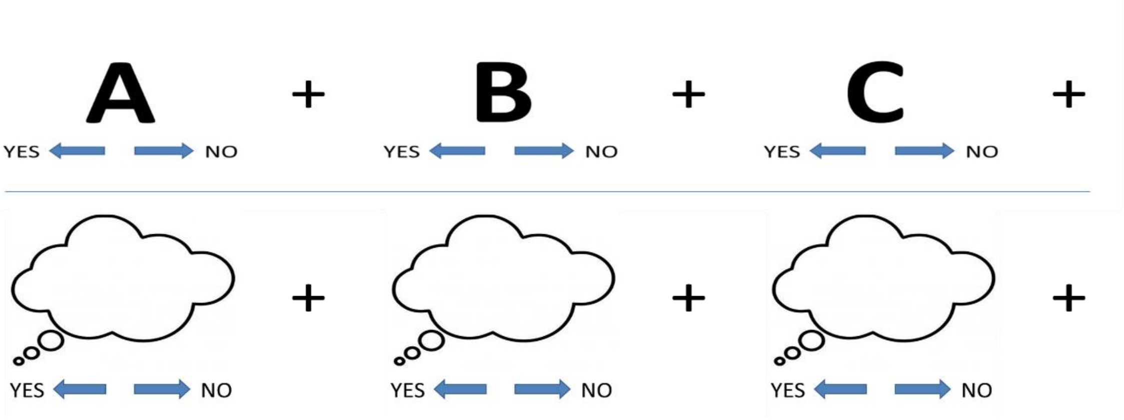


Figure 6.3. Example trials of the SOT (upper row) and SIT (lower row) tasks.

After this first testing session, the exercise group completed four strength tests and a VO_2max test (described below), whereas the control group passively viewed a television program for 30 minutes, which was equivalent to the amount of time required for the exercise group to complete the fitness tests. Immediately after terminating the VO_2max test on a treadmill, participants walked for 3 minutes at 6kph, they were allowed a drink of water only and then returned immediately to the neurocognitive testing room to repeat the same cognitive tests. Fitting the fNIRS cap required 5 more minutes, while the participant sat quietly, giving a total recovery time of about 10 minutes between the end of the VO_2max test and the start of the second cognitive test battery. The second round of cognitive tests had counterbalanced blocks containing different stimuli. Systemic, fNIRS, and behavioral data were collected again.

6.2.4 Fitness and strength testing

Participants were instructed not to eat large meals for up to 2 hours before testing, and to not consume caffeine for 24 hours prior to testing. Anthropometric data (height and weight) were recorded prior to exercise testing. Body composition was analyzed via bioelectrical impedance on a Tanita MC980MA (Tanita Cooperation, Tokyo, Japan). The exercise testing consisted of a series of strength endurance tests and a VO_2max test. All exercises were demonstrated first by the researchers and participants were allowed familiarization trials. Participants first warmed up on a cycle ergometer at 60rpm for 5 minutes, at a rate of perceived exertion of 6/10. Four minutes rest were given between strength tests to prevent fatigue. Participants completed a push-up test, a triple hop jump, a counter-movement jump (CMJ) and a hand grip test. For the push-up test, participants were instructed to complete as many push-ups as possible in one minute without breaking form. Correct press-ups initiated from a full plank with arms shoulder width apart, shoulders stacked over wrists, hands flat on the floor and toes on the floor, not knees. A full repetition was counted if a 90° bend at the elbows was achieved as the bottom, and a straight plank at the top. Next, for the triple hop jump test, participants were instructed to cover the farthest distance possible by hopping three times on one leg without stopping or stumbling. Three jumps were completed per leg, the farthest distance was recorded. For the CMJ, participants were instructed to place hands on hips, squat down and immediately jump up with straight legs maintaining hands on hips. Three CMJs were performed using a contact platform (Chronojump-Boscosystems, Bacelona, Spain), the highest jump was recorded. Hand grip strength was measured as the best of three trials with a T.K.K. 5001 grip strength dynamometer (Takei Scientific Instruments Co., Niigata, Japan). After the strength tests, participants completed a Bruce protocol test (Myers, Voodi, Umann, & Froelicher, 2000) on a treadmill (h/p/cosmos, Nussdorf, Germany).

The cardiovascular protocol began with 3 minutes walking (2.6 km/h) with no incline; every three minutes thereafter, the incline and speed of the treadmill are increased. Throughout the test, the participant is encouraged to continue exercising until volitional exhaustion, at which point the test is terminated, the treadmill returns to level at walking pace, the participant is instructed to walk slowly (2.6 km/h) for 3 minutes to recover fully. Participants who gave up to early did not receive a VO_2max score. Breath-by-breath gas analysis and heart rate were gathered through the Vyntus CPX Metabolic Cart (Vyaire Medical, Chicago, USA) throughout the test. The anaerobic threshold was determined using the v-slope method, as the point of departure from linearity of carbon dioxide output (VCO_2) plotted against oxygen uptake (VO_2) (Wasserman, Stringer, Casaburi, Koike, & Cooper, 1994). VO_2max (ml/kg/min) was determined as the highest recorded VO_2 value. VO_2max was identified if the gas analysis showed a plateau in the VO_2 values, if respiratory exchange ratio (RER) > 1.13, and if heart rate max reached approximately 220-age. Raw VO_2max values were recorded as ml/min/kg, VO_2max rating was determined as per the ACSM normative values (Pescatello et al., 2014), where scores are categorized into normative values according to age and gender. Once the participants completed their 3-minute recovery walk, they were allowed a drink of water and then prepared again for the cognitive tests. The total delay time between reaching maximal exertion and commencing the second round of cognitive tests was ~10 minutes.

6.2.5 fNIRS signal acquisition and regions of interest (ROIs)

Functional NIRS signal acquisition of hemodynamics was acquired using a 16-fiber (22-channel configuration: 8 sources & 8 detectors) continuous-wave fNIRS system (LIGHTNIRS, Shimadzu Corp., Kyoto, Japan) sampled at a rate of 13.33 Hz at three wavelengths of light (780, 805, and 830 nm) (Figure 6.4). A light-emitting diode probe (Daiso Crop., Hiroshima, Japan) was used to achieve an orthogonal connection between the fNIRS optodes and scalp (i.e., to displace hair in the cap). Due to the large sample size and need for rapid-testing, digitization was based on a single subject; researchers were then carefully trained to place the cap the same way for each participant. Anatomical locations of optodes in relation to standard head landmarks, including inion and top center (Cz) and left and right tragi, were determined using a Patriot 3D Digitizer (Polhemus, Colchester, VT) and linear transform techniques (Eggebrecht et al., 2014; Eggebrecht et al., 2012; Ferradal et al., 2014; Okamoto & Dan, 2005; Singh et al., 2005).

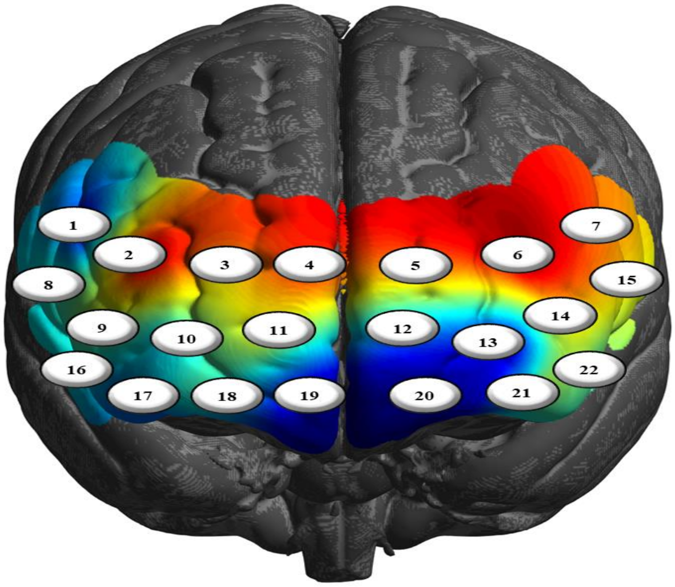


Figure 6.4. Channel-specific locations of the 22-channel (8 sources & 8 detectors) configuration overlaid onto a model brain mesh of the PFC with a default jet colour scheme.

Montreal Neurological Institute (MNI) coordinates (Mazziotta et al., 2017) for each channel were obtained using NIRS-SPM software (Ye, Tak, Jang, Jung, & Jang, 2009; https://www.nitrc.org/projects/nirs_spm/) with MATLAB (Mathworks, Natick, MA). The anatomical coverage of the channel configuration was corresponded with three bilateral ROIs (Table 6.1): rostral PFC (BA10), dorsolateral PFC (BA46/9), and ventrolateral PFC (BA44/45/47). These ROIs were specified *a priori* based on neuroimaging and neuropsychological research on frontal lobe functions (see Knight & Stuss, 2013; Shallice & Cooper, for reviews). Lastly, ECG signals were continuously collected at 256 Hz using two Equivital ‘eq02+ LifeMonitors’ (https://www.equivital.com/heart-rate-and-breathing-rate-monitor).

Table 6.1

Channels, Coordinates, and Anatomical Regions

Channel #	Anatomical Region	BA[1]	Coordinates[2]
1	Right Superior Frontal Gyrus	9	53, 26, 30
2	Right Middle Frontal Gyrus	46	41, 49, 23
3	Right Rostral PFC	10	25, 62, 21
4	Right Rostral PFC	10	4, 65, 21
5	Left Rostral PFC	10	-19, 63, 21
6	Left Middle Frontal Gyrus	46	-37, 52, 22
7	Left Superior Frontal Gyrus	9	-51, 28, 29
8	Right Inferior Frontal Gyrus	44	60, 15, 16
9	Right Inferior Frontal Gyrus	45	51, 43, 7
10	Right Rostral PFC	10	36, 60, 5
11	Right Rostral PFC	10	17, 68, 5
12	Left Rostral PFC	10	-8, 68, 5
13	Left Rostral PFC	10	-32, 62, 4
14	Left Inferior Frontal Gyrus	45	-47, 46, 7
15	Left Inferior Frontal Gyrus	44	-58, 17, 17
16	Right Inferior Frontal Gyrus	47	54, 30, -6
17	Right Rostral PFC	10	45, 51, -8
18	Right Rostral PFC	10	28, 64, -7
19	Right Rostral PFC	10	3, 67, -7
20	Left Rostral PFC	10	-22, 66, -8
21	Left Rostral PFC	10	-41, 54, -7
22	Inferior Frontal Gyrus	47	-51, 36, -3

Note. [1]BA = Brodmann's Area. [2]Coordinates are based on the MNI system and (-) indicates left hemisphere.

6.2.6 fNIRS signal processing

Signal processing of the fNIRS data was carried out in accordance with the quality control standards suggested by Yücel and colleagues (2021); data collection errors reduced the sample sizes of the exercise (n = 92) and control (n = 18) groups. The pre-processing of raw fNIRS signals was conducted according to the particular recommendations of Pinti, Scholkmann, Hamilton, Burgess, and Tachtsidis (2019) using functions developed in HOMER2 (https://homer-fnirs.org). Specifically, raw voltage intensities were converted from .OMM format to .TXT and, then, into .NIRS format. Next, these data were converted into optical density (OD) signals. Then, motion-artifact correction was conducted using wavelet convolution (iqr = 1.5), with a differential pathlength factor (DPF) that is conventionally used for continuous-wave fNIRS [6, 6, 6]. To further reduce sources of noise in the OD signals and isolate task-related components, these signals were temporally smoothed using a band-pass filter (FIR: order 1,000) [.01 .4 Hz]) to remove extracerebral, systemic effects. The cleaned OD signals were then converted into changes in concentrations of oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (HbR), and total hemoglobin (HbO_2 + HbR) using the the modified Beer-Lampert Law (see Dirnagl & Villringer, 1997). Channels that were faulty or remained poor in signal-to-noise ratio were removed from the analysis.

To further account for variance attributable to physiological confounds in these predicted signals, HR (n = 56) and RR (n = 52) were included as additional parameters in the single-subject design matrices (see Tachtsidis & Scholkmann, 2016). To achieve this, RR and HR needed to be extracted from the ECG data and temporally integrated into the appropriate testing sessions (i.e., during fNIRS acquisition). More specifically, waveform analysis calculated RR from the ECG data (Charlton et al., 2016). In particular, respiratory signals (a time-series dominated by respiratory modulation based on frequency) were identified using band-pass filters to remove high [.89 1.2 Hz] and low [.02 .16 Hz) non-respiratory frequencies (i.e., unrealistic breaths per minute, such as less than 4) and a QRS detector (Hamilton & Tomkins, 1986; Pan & Tompkins, 1985); R-waves and pulse peaks were detected as the maxima at or between detected beats. Beat-by-beat measurements were then detected using a feature-based extraction technique that calculates the time intervals between consecutive peaks (Orphanidou et al., 2013; Karlen et al., 2013). Auto-regressive all-pole modelling (order 8), with highest magnitude pole selected as the respiratory pole (Fleming et al., 2008), was then used to estimate RR from the respiration signals (see Charlton et al., 2016, for review). The intervals between R-wave peaks of QRS complexes—representing ventricular depolarization—were used to compute beats per minute (HR). Because most, but not all, of the physiological data were accounted for in the fNIRS sample (HR: 61%, RR: 57%), a comparison of the group results of the subsample for which there were physiological parameters against the whole sample, which included the additional fNIRS data sets for which there were no HR and RR, revealed no significant differences in the results below. Moreover, comparing the group results of this subsample with and without these physiological parameters showed significant changes in the results; therefore, accounting for the majority of physiological variance in the fNIRS sample was sufficient.

Onsets and durations of the epochs of each trial of each block were extracted to generate a stimulus design for each participant, with which a canonical hemodynamic response function (HRF) was then convolved. The HR and RR parameters as well as the predicted HRFs (HbO_2 and HbR) for each block were then down-sampled to 1 Hz using spline interpolation (Cohen, 2017) and a general-linear model (GLM) analysis, using SPM and NIRS-SPM functions, fitted these models to the observed data, yielding beta estimates for each parameter of the single-subject design matrices. The second-level analysis of the group data used a random-effects approach via summary statistics (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007; Poldrack, Mumford, & Nichols, 2011) and was channel-based. After false-discovery rate (FDR) correction ($q < 0.05$; Singh & Dan, 2006) was carried out, the group effects of each HbO_2 and HbR contrast for each channel were then projected onto a 3-D brain mesh using the sample digitization coordinates that were normalized to standard MNI space via linear interpolation. Lastly, although all signal analyses were conducted on both HbO_2 and HbR, the interpretation of the results was based on research suggesting that HbR signals are less affected by systemic confounds (Dravida, Noah, Zhang, & Hirsch, 2017), especially in fNIRS paradigms involving marked changes in arterial CO_2 due to changes in respiration (e.g., exercise, speaking, etc.), because such changes alter the HbO_2 signal to a greater degree than HbR in these cases (Sholkmann et al., 2013; Sholkmann et al., 2013).

6.3 Results

6.3.1 Exercise improved information-processing speed

Demographic information and fitness test outcomes are presented in Table 6.2.

Table 6.2

Fitness test outcomes

	Exercise Group	Control Group
N (male, female)	65, 27	16, 2
Height (cm)	173.6 ± 20.2	177.7 ± 9.3
Weight (kg)	84.0 + 19.7	89.4 ± 15.6
Fat %	25.2 ± 7.8	24.0 ± 5.0
Age (years)	39 ± 8	43 ± 6
Push-ups per minute (reps)	23.4 ± 16	No data
Counter-Movement Jump height (cm)	23.7 ± 7.7	No data
Counter-Movement Jump power (W)	874 ± 236	No data
Hand Grip (W)	46.2 ± 12.5	No data
VO_2 at Anaerobic Threshold (ml/min/kg)	27.3 ± 6.6	30.7 ± 7.1
VO_2max (ml/min/kg)	36.9 ± 9.1	40.1 ± 7.2
Heart Rate max (bpm)	170 ± 49	160 ± 51

Inferentially, there were improvements in performance for the exercise group. Reaction times (RTs) decreased across all tasks by an average of 22% after exercise (*M* = .53s, *SD* = .09) compared to before it (*M* = .66s, *SD* = .13), *t*(91) = 14.19, *p* < .001. There was no difference in accuracy. To assess the extent to which the improved performance of the experimental group was not due to potential learning effects, the change in RTs of the control group (*M* = -.09, *SD* = .07; 16% decrease in RTs) was compared against a random subsample of the exercise group (*M* = -.16, *SD* = .09; 26% decrease in RTs) of equal sample size (n = 18). This subsample consisted of the last few data sets; a second subsample was also used from the first 18 data sets as a reliability check. An independent-samples t-test was used, yielding a significant difference between the observed changes in RTs of the two groups *t*(34) = -2.63, *p* = .01, 95% CI [-.12, -.02], *d* = -.88 (Figure 6.5). That is, although some learning probably occurred in both groups of participants, exercise appears to have uniquely increased participants' information-processing speed by up to 10%.

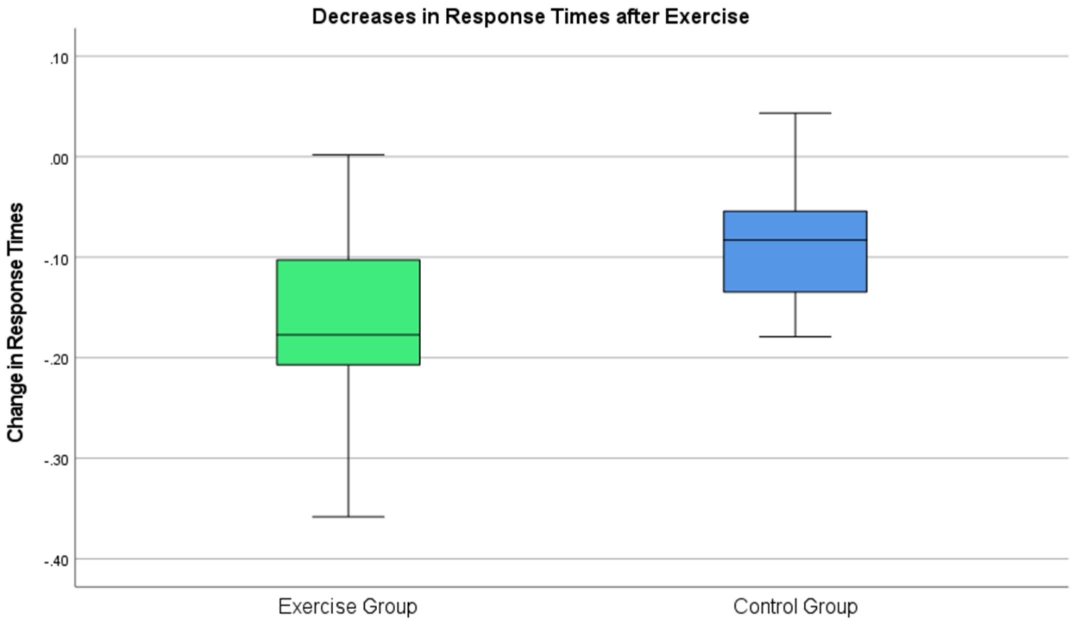
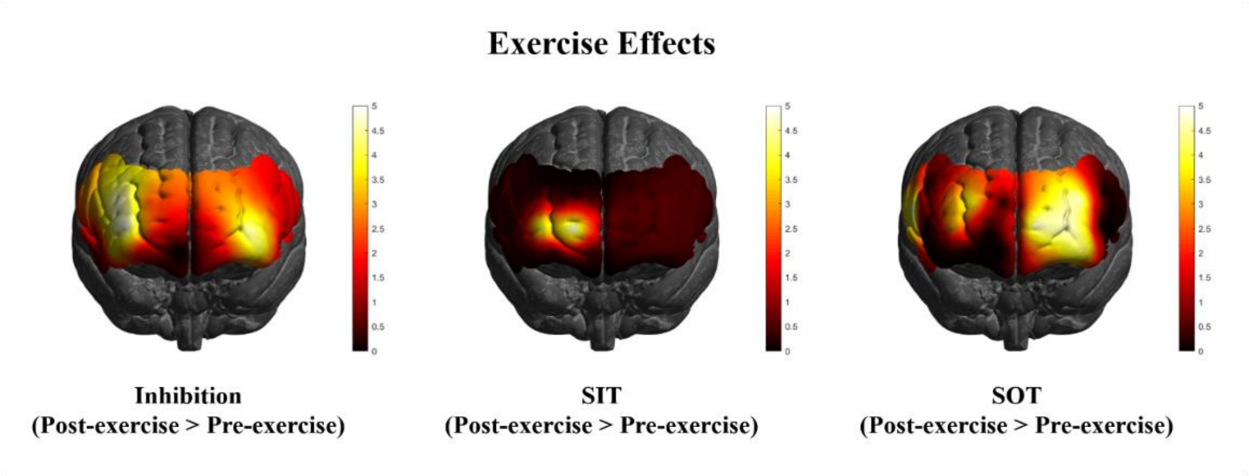


Figure 6.5. Decreases in Response Times after Exercise. The change in response times (RTs) between measures (post-exercise - pre-exercise RTs) indicated a decrease in the experimental subsample RTs (*M* = -.16, SD = .09) that was significantly larger than the control group (*M* = -.09, SD = .07).

6.3.2 Pre- versus post-exercise PFC hemodynamics

Within-brain statistical comparisons for the response inhibition and attentional modes tasks (i.e., subtractions of their pre-exercise conditions) showed significant increases in activation in PFC subregions (Figure 6.6). Namely, inhibition recruited bilateral dorsolateral (BA46/9), ventrolateral (BA44/45), and rostral (BA10) PFC, with greatest activation in right dorsolateral (BA46) and rostral PFC (Table 6.3). Regarding the attentional modes tasks, the SIT condition solely recruited right rostral PFC and the SOT condition showed increased activation in right ventrolateral PFC (BA44) and bilateral dorsolateral (BA46) and rostral (BA10) PFC.



Inhibition (Post-exercise > Pre-exercise)

SIT (Post-exercise > Pre-exercise)

SOT (Post-exercise > Pre-exercise)

Figure 6.6. HbR changes in the PFC as an acute effect of exercise (α < .05, FDR corrected). Greatest activation changes are represented in bright yellow and white, with little to no effects represented in dark red and black, respectively (t values of the images are scaled from 0-5+).

Table 6.3

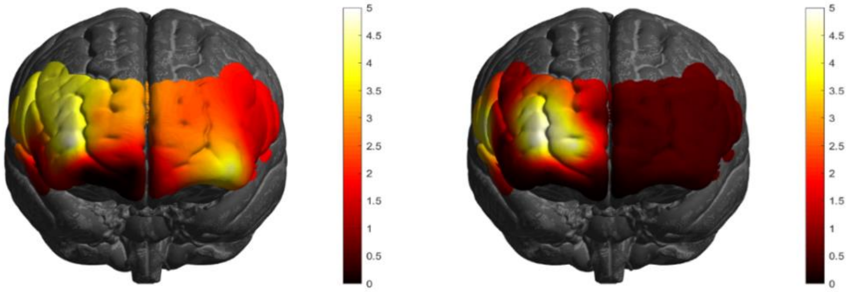
Channel-based Comparisons (HbR signals) of the Acute Effects of Exercise

Contrast	Channel	t value	p	BA[1]	Coordinates[2]
Inhibition	1	6.20	<0.001	9	(53, 26, 30)
	2	8.49	<0.001	46	(41, 49, 23)
	3	4.45	<0.001	10	(25, 62, 21)
	4	4.11	<0.001	10	(4, 65, 21)
	5	5.41	<0.001	10	(-19, 63, 21)
	6	4.58	<0.001	46	(-37, 52, 22)
	7	2.63	0.012	9	(-51, 28, 29)
	8	5.59	<0.001	44	(60, 15, 16)
	9	5.82	<0.001	45	(51, 43, 7)
	10	8.80	<0.001	10	(36, 60, 5)
	11	3.40	0.002	10	(17, 68, 5)
	12	2.88	0.006	10	(-8, 68, 5)
	13	8.23	<0.001	10	(-32, 62, 4)
	14	4.92	<0.001	45	(-47, 46, 7)
	15	3.05	0.004	44	(-58, 17, 17)
	17	6.36	<0.001	10	(45, 51, -8)
	18	3.12	0.003	10	(28, 64, -7)
	20	3.67	<0.001	10	(-22, 66, -8)
	21	7.44	<0.001	10	(-41, 54, -7)
	22	2.51	0.015	47	(-51, 36, -3)
SIT	10	2.93	0.023	10	(36, 60, 5)
	11	3.49	0.008	10	(17, 68, 5)
SOT	2	2.39	0.041	46	(41, 49, 23)
	3	3.41	0.003	10	(25, 62, 21)
	5	3.51	0.002	10	(-19, 63, 21)
	6	4.24	<0.001	46	(-37, 52, 22)
	8	4.55	<0.001	44	(60, 15, 16)
	10	2.93	0.010	10	(36, 60, 5)
	12	4.30	<0.001	10	(-8, 68, 5)
	13	4.19	<0.001	10	(-32, 62, 4)
	20	3.03	0.008	10	(-22, 66, -8)
	21	3.86	<0.001	10	(-41, 54, -7)

Note. [1]BA = Brodmann’s Area.[2]Coordinates are based on the MNI system and (-) indicates left hemisphere.

More generally, when the post-exercise tasks comprising the cognitive domains of ‘speed of processing’ (Speed: all experimental blocks) and ‘attentional control’ (Control: SIT and SOT blocks) were collapsed across conditions and subtracted from those of the pre-exercise tasks, Speed showed bilateral activation changes in dorsolateral (BA46/9), ventrolateral (BA44/45), and rostral (BA10) PFC, with the greatest changes occurring in right BA10 and BA46 (Figure 6.7). Control showed a significant increase in activation exclusively across right lateral PFC, namely BA10, BA46, and BA44, with the greatest changes occurring in right BA10 (Table 6.4).

Exercise Effects



Speed
(Post-exercise > Pre-exercise)

Control
(Post-exercise > Pre-exercise)

Figure 6.7. Composite HbR changes in the PFC as an acute effect of exercise (α < .05, FDR corrected). Greatest activation changes are represented in bright yellow and white, with little to no effects represented in dark red and black, respectively (t values of the images are scaled from 0-5+).

Table 6.4

Channel-based Comparisons (HbR signals) of the Acute Effects of Exercise (Composite)

Contrast	Channel	t value	p	BA[1]	Coordinates[2]
Speed	1	7.33	<0.001	9	(53, 26, 30)
	2	8.38	<0.001	46	(41, 49, 23)
	3	5.37	<0.001	10	(25, 62, 21)
	4	5.83	<0.001	10	(4, 65, 21)
	5	4.51	<0.001	10	(-19, 63, 21)
	6	4.38	<0.001	46	(-37, 52, 22)
	7	2.75	0.008	9	(-51, 28, 29)
	8	7.71	<0.001	44	(60, 15, 16)
	9	4.01	<0.001	45	(51, 43, 7)
	10	9.62	<0.001	10	(36, 60, 5)
	11	4.54	<0.001	10	(17, 68, 5)
	12	5.02	<0.001	10	(-8, 68, 5)
	13	5.95	<0.001	10	(-32, 62, 4)
	14	3.48	0.001	45	(-47, 46, 7)
	15	3.38	0.001	44	(-58, 17, 17)
	17	4.35	<0.001	10	(45, 51, -8)
	20	5.36	<0.001	10	(-22, 66, -8)
	21	8.37	<0.001	10	(-41, 54, -7)
	22	2.37	0.023	47	(-51, 36, -3)
Control	2	2.85	0.019	46	(41, 49, 23)
	3	2.65	0.029	10	(25, 62, 21)
	8	3.33	0.015	44	(60, 15, 16)
	10	3.21	0.015	10	(36, 60, 5)
	11	3.09	0.015	10	(17, 68, 5)

Note. [1]BA = Brodmann’s Area.[2]Coordinates are based on the MNI system and (-) indicates left hemisphere.

6.3.3 PFC hemodynamics of acute exercise: Control group comparisons

To assess the degree to exercise affects activity in these PFC subregions rather than the test-retest effect, comparisons of brain activity between the control group and an equally matched subsample of the exercise group (the random subsample used above for the behavioral data) were examined along the same contrasts (Figure 6.8). More specifically, the activation changes between testing sessions unique to the control group (n = 18) were subtracted from those of the exercise subsample (n = 18), yielding significant changes for the inhibition and attention conditions and for their composite factors of Speed and Control (Table 6.5). Namely, the greatest activation change for inhibition was found in right dorsolateral PFC (BA46). For both the SIT and SOT conditions, right rostral PFC (BA10) showed the greatest change in activation. As regards the composite variables of Speed and Control, Speed showed an increase in bilateral activation in dorsolateral (BA46/9) and rostral PFC, and the Control factor exclusively recruited right rostral, dorsolateral (BA46/9), and ventrolateral (BA45) PFC. The greatest change in activation for both of these factors was in right rostral PFC (channel 11).

Table 6.5

Channel-based Group Comparisons (HbR signals) of Exercise Effects

Contrast	Channel	t value	p	BA[1]	Coordinates[2]
Inhibition	2	4.95	<0.001	46	(41, 49, 23)
	6	3.87	0.005	46	(-37, 52, 22)
	9	3.23	0.019	45	(51, 43, 7)
SIT	11	3.72	0.007	10	(17, 68, 5)
SOT	5	3.25	0.019	10	(-19, 63, 21)
	11	4.31	0.002	10	(17, 68, 5)
Speed	1	3.62	0.007	9	(53, 26, 30)
	2	3.75	0.007	46	(41, 49, 23)
	3	2.86	0.031	10	(25, 62, 21)
	6	3.43	0.008	46	(-37, 52, 22)
	11	3.98	0.007	10	(17, 68, 5)
Control	1	2.87	0.026	9	(53, 26, 30)
	2	3.55	0.012	46	(41, 49, 23)
	3	3.21	0.017	10	(25, 62, 21)
	9	3.17	0.017	45	(51, 43, 7)
	10	3.07	0.018	10	(36, 60, 5)
	11	4.57	0.001	10	(17, 68, 5)

Note. [1]BA = Brodmann's Area. [2]Coordinates are based on the MNI system and (-) indicates left hemisphere.

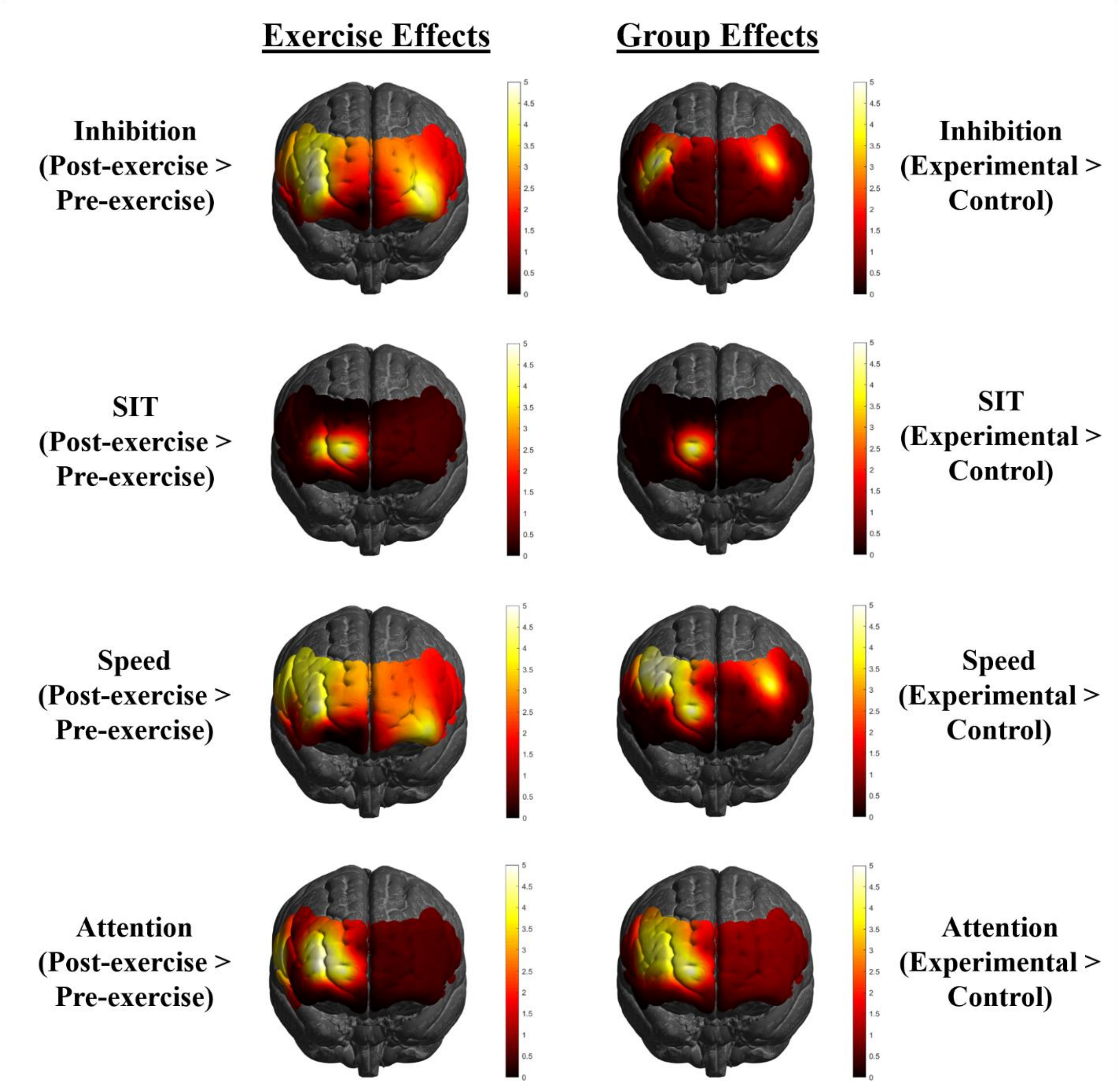


Figure 6.8. HbR changes in the PFC as an acute function of exercise (column 1) and differential activation of the control group compared to a random subsample of the exercise group (column 2) ($\alpha < .05$, FDR corrected). Greatest activation changes are represented in bright yellow and white, with little to no effects represented in dark red and black, respectively (t values of the images are scaled from 0-5+).

6.3.4 Exercise-related PFC activity predicted mood and fitness levels

To investigate whether the effects observed in these PFC subregions varied depending on level of depression symptomology (MFQ scores; *M* = 4.04, *SD* = 4.25), a multiple linear regression analysis resulted in three channels (8, 9, & 16) that explained the most variance in depression scores, $R^2 = .14$, $F(2, 89) = 4.59$, $p = .005$. Together, these channels form a spatial cluster approximately over right inferior frontal gyrus (IFG: BA44/45/47, respectively), so the values for these channels were transformed into Z-scores and summed to create an 'IFG' variable. Although the IFG data were normally distributed, a Shapiro-Wilk test showed that the depression scores were not normally distributed, $W = .80$, $p < .001$ (Skewness = 2.01, Kurtosis = 5.37). Therefore, the IFG effects were regressed onto a normalized distribution of depression scores (Skewness = .21, Kurtosis = -.64), yielding a more statistically robust model, $R^2 = .13$, $F(1, 89) = 12.91$, $p < .001$, of right IFG as a predictor variable, $t(89) = -3.59$, $p < .001$, 95% CI [-.07, -.02] (Figure 6.9).

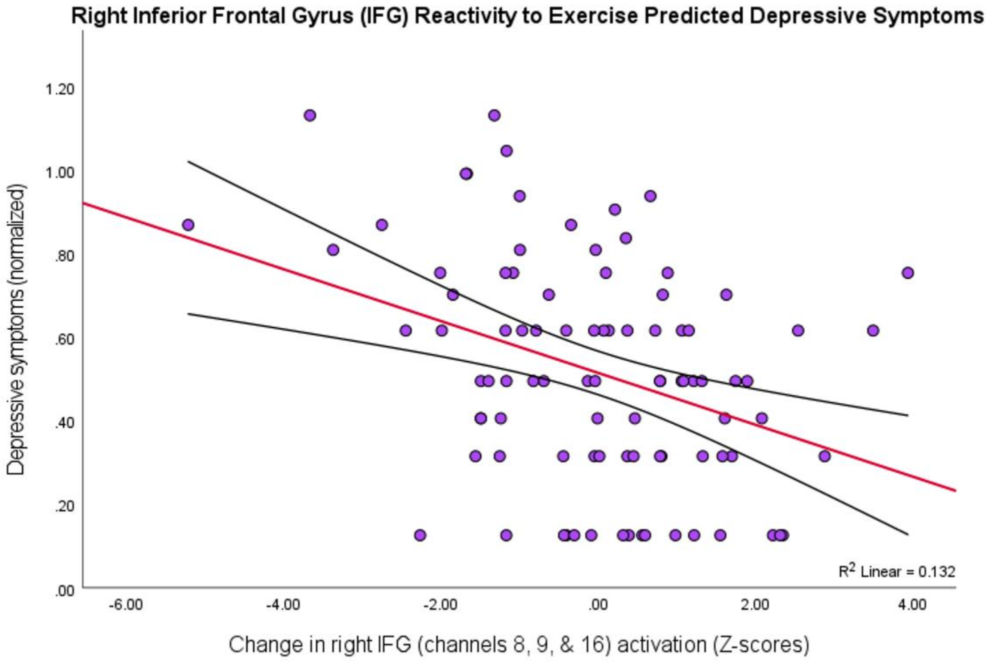


Figure 6.9. Higher depression scores on the MFQ (y-axis) predicted smaller changes in levels of activation in right IFG (BA44/45/47) (x-axis) as an effect of exercise ($r = .36$, $p < .001$, 95% CI [-.07, -.02]; 13% variance explained). The red line depicts the regression line, with black lines as confidence instervals.

Thus, there was a negative relationship between depression scores and the PFC activity that was due to exercise-elicited, processing-speed changes, particularly in right inferior frontal gyrus (BA44/45/47). That is, people with greater symptoms of depression showed lower levels of PFC activation across all tasks after exercise.

Following the same procedures for VO_2peak scores (*M* = 37.25, *SD* = .8.24) to investigate whether physical fitness predicted the PFC effects of exercise, since these data were also not normally distributed, *W* = .94, *p* < .001 (Skewness = -1.14, Kurtosis = 3.97), a one channel model, $R^2 = .09$, *F*(1, 89) = 8.81, *p* = .004, 95% CI [.79, 3.97], containing channel 10 (right rostral PFC; BA10) emerged as a significant predictor of a normalized distribution of VO_2peak scores (Figure 6.10). So, there was a positive relationship between VO_2peak and exercise-elicited changes in PFC activity in right rostral PFC (BA10), in that people with greater aerobic fitness showed greater levels of activation in this region after exercise. However, there was no association between VO_2peak and depressive scores, *r*(90) = -.05, *p* > .05.

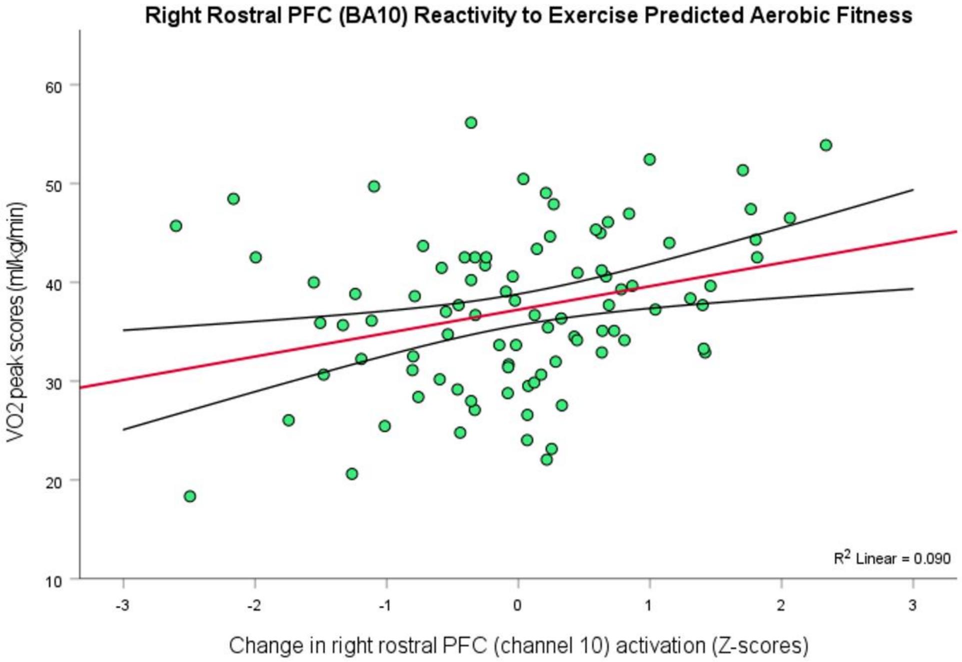


Figure 6.10. Higher levels of aerobic fitness (y-axis) predicted greater changes in the level of activation in right rostral PFC(BA10) as an effect of exercise (*r* = .30, *p* = .004, 95% CI [.79, 3.97]; 9% variance explained). The red line depicts the regression line, with black lines as confidence instervals.

6.4 Discussion

6.4.1 Effects of acute exercise on the PFC and its executive functions

Acute exercise had significant effects on the PFC and the cognitive operations it performs. For example, collapsing across all executive function tasks showed greater activation in bilateral dorsolateral (BA46/9) and ventrolateral (BA44/45) PFC, with the greatest changes in rostral PFC (BA10). Because this was across all experimental blocks, these effects might most closely represent broad changes in information-processing speed. Behavioural performance was improved by approximately 10% (i.e., faster RTs) for this factor of processing speed after accounting for learning in the no-exercise group. Attentional control, as a second factor (SIT and SOT blocks), showed greater activation in right rostral, dorsolateral (BA46), and ventrolateral (BA44) PFC. Examining the differences in contrast results between the subsample of the exercise group and no-exercise group showed spatially consistent trends in the PFC activation observed in the whole exercise group (n = 92), suggesting that these effects were largely unique to exercise. Importantly, the neural correlates of the cognitive factors of processing speed and attentional control evidenced broad recruitment of the PFC. This wider recruitment of PFC subregions is what would be expected of features that are shared across executive functions (e.g., implementation speed is relevant to all PFC subsystems involved in cognitive control). However, this global-like effect was not observed when assessing individual executive functions that the experimental tasks were developed to index. In other words, the observed upregulation to the PFC after exercise was largely specific to the subregions that are typically implicated in particular executive function tasks.

For example, one subsystem of interest was the ‘attentional gateway’ (Burgess et al., 2007). It is localized within rostral PFC (BA10) and operates in an executive capacity to modulate the selection of stimulus-oriented (e.g., perceptions) and stimulus-independent (e.g., mental arithmetic) representations. The tasks used to examine these aspects of the attentional gateway were comprised of blocks that either required participants to determine for each letter in the alphabet whether it contained at least one curved line. The letters were shown in the stimulus-oriented thought task but hidden in the stimulus-independent thought task, requiring participants to carry out the alphabet task in their minds. The only significant fNIRS channels for this condition that called for sustained biasing of endogenous attention were over right rostral PFC. These finding are in line with the literature on the neural basis of the attentional gateway subsystem (e.g., Burgess et al., 2007). In addition to attentional mode, a closely related executive function of interest was attentional monitoring. A go/no go task was used to assess this subsystem because this type of task requires a great deal of monitoring in addition to response inhibition. More specifically, the key cognitive demand placed on participants is the checking of stimuli to verify that a given stimulus is something to which one should *not* respond; in this case, participants were instructed to not respond if they saw a kitten. Peak activations in this post-exercise condition were found in right dorsolateral (BA46) and rostral (BA10) PFC. The upregulation of right BA46 is a common finding of response inhibition tasks that contain strong monitoring elements (Criaud & Boulinguez, 2013), so this finding is also consistent with the cognitive neuroscientific literature on executive functions and their neural localizations.

Therefore, exercise appears to have induced an upregulation of cerebral blood flow to the PFC (i.e., greater resource availability) that was global to the broad processing demands of all the cognitive tasks (e.g., processing speed), but the allocation and utilization of these resources (i.e., resource consumption) were to the demands of the specific executive functions in question (e.g., attentional mode and monitoring). The effects of acute exercise on these functions for which rostral and right dorsolateral PFC are specialized have not yet been investigated using fNIRS to our knowledge. In addition to extending this area of exercise neuroscience literature, the present findings support the idea of an optimal window of time (~30 minutes) in which cognitive functions might benefit from physical activity (Chang, Labban, et al., 2012; Lambourne & Tomporowski, 2010). More importantly, they counter predictions that the effects of vigorous exercise should be largely negative within the PFC (Dietrich, 2006), favouring instead the interpretation that exercise affects metabolic mechanisms such as local cerebral oxygenation, leading to greater availability and allocation of cognitive resources (Kahneman, 1973), including those required of higher-order cognitive operations. It is worth noting that although vigorous exercise can lead to global reductions in cerebral blood flow to protect the body during strenuous physical activity (i.e., central governor hypothesis; Noakes et al., 2005), this phenomenon—if it was present—did not appear to persist into the post-exercise haemoglobin signals.

6.4.2 PFC reactivity explained variability in levels of mood and fitness

Our results show some relationships between symptoms of depression and exercise-elicited changes in PFC activity, as well as between this activity and level of fitness. Specifically, there was a negative relationship between symptom severity and activity in right inferior frontal gyrus (BA44/45/47), in that greater activation changes in these subregions were associated with lower depression scores. Right inferior frontal gyrus (i.e., ventrolateral PFC) has been consistently implicated in the controlled downregulation of negative emotion (Zilverstand et al., 2017) and is an area that is relatively hypoactive during emotion regulation in depressed populations (Rive et al., 2013). So, the evidenced negative relationship is consistent with the idea that this area of the PFC is underactive during executive function tasks in people with depressive symptoms (see Wang et al., 2008). Although this relationship was not found in rostral PFC, it does not mean that there is no link between this subregion and mood in relation to exercise. A stronger relationship might be evidenced should alternative self-report measures be used that index not only mood and negative affect but also the dysfunctional cognitions that underpin them (e.g., the shorter Attitudes and Belief Scale 2; DiGiuseppe et al., 2021), as well as people's tendency to downregulate negative affect and mood from a 'top-down' approach (i.e., reappraisal), such as with the Emotion Regulation Questionnaire (Gross & John, 2003). Such measure might mediate the relationship between PFC reactivity and depressive symptoms.

In addition, there was a positive relationship between aerobic fitness (VO_2peak) and a different area of right PFC (BA10), in that greater fitness was predicted greater activation changes in right rostral PFC. While decreased activation of the PFC appears to be the rule in depression (see Hariri, 2014), there are some exceptions: For example, one study recently showed that pessimistic future-thinking in people with major depressive disorder exhibited greater activity in right rostral PFC compared to healthy individuals (Katayama et al., 2019). Given the cognitive operations for which this brain region is largely functionally specialized (i.e., regulating thought that is dependent or independent of the external world; Burgess et al., 2007), it makes sense that dysfunctional, prospective appraisals would be supported by the biasing of stimulus-independent thought—that, here, there would be hyperactivity in depressed individuals. Equally supported by this orientation of attention are the hypothesized cognitive operations of ‘recogitation’ (Crum, 2021): executive functions in which depressed people appear to have deficits and, therefore, hypo-activity in BA10 might be present during their implementation. Thus, rostral PFC is potentially as associated with dysfunctional cognitions and psychopathological symptoms as it is with the facilitation the cognitive mechanisms that ameliorate them. So, it is plausible that the relative hypo- or hyper-activation of this brain region might depend on the particular type of executive function task in which depressed individuals are take part. For example, collapsing across different executive function tasks might result in BA10 activation that explains little variability in depression, as was the case in the present study, but that the exercise effect in this PFC subregion was sensitive to how aerobically fit people were might suggest an important role of fitness in treating depression. More specifically, it is plausible that the frequency of physical activity is a factor that works to correct issues of abnormal activity in the PFC (e.g., hypo- and hyper-activation). Future investigations might further elucidate this possibility, but the present findings represent a starting point for assessing the potential interrelations between the PFC, physical activity, physical fitness, and mental health.

6.4.3 Conclusions

In sum, evidence is converging from behavioral neuroscience, exercise psychology, and neuroimaging suggesting that acute bouts of exercise have positive effects on well-being. Although research using approaches in exercise psychology and neurobiology are together yielding findings that are seen as beneficial to physiological well-being, the nature of the precise neurocognitive and metabolic mechanisms into which these benefits translate remains unclear. Cognitive neuroscientific studies have been attempting to address this by investigating exercise-related changes and interrelationships between cerebral oxygenation, hemodynamic upregulation, and cognitive performance. The PFC is a region of the brain that has long been shown to be critical to the cognitive functions supporting complex tasks in everyday life (Knight & Stuss, 2013; Shallice & Cooper, 2011), and both chronic and acute physical activity appear to affect its functional and structural aspects. However, whether the nature of these functional effects on the PFC consists of global changes in oxyhemoglobin across its subregions, or of specific upregulations to the executive subsystems required of task demands, remains ambiguous in the fNIRS literature, in part because of issues relating to insufficient spatial coverage.

The present study therefore sought to address this question and several other methodological issues, finding that task performance across all tasks improved in speed after an acute bout of vigorous exercise. In addition to this change in general processing speed, the upregulation of PFC hemodynamics was also found across many PFC subregions. These findings are consistent with the idea that an increase in global cerebral oxygenation might translate into a greater availability of cognitive resources. However, in information-processing terms, neuroimaging does not measure that which is globally available, but rather reflects the *consumption* of resources that are available during cognitive tasks. So, more precisely, the present findings suggested that the greater hemodynamic response across all tasks represented greater use of resources. Assessing the effects of exercise on specific executive function tasks allowed us to examine the allocation of these upregulated hemodynamics, finding that they are spatially sensitive to the operations responsible for meeting task demands. That much of the PFC would not be upregulated for individual executive functions makes more sense from an efficiency perspective: Resources—however available—are probably more efficiently utilized if they are allocated to those subregions that most require it during a given cognitive task. However, this might only be the case for the lateral surfaces of the PFC, which has highly specialized, domain-general functions. It is also plausible that the degree of improvement observed in information processing depends on how close people are to ceiling prior to exercise.

It is plausible that much of the medial surfaces of the prefrontal cortices, particularly their superior and caudal aspects, could be providing the global exercise-induced energization of executive functions (see Shallice & Cooper, 2011; Stuss & Knight, 2002, 2013, for review of energization). But this remains to be tested. Unfortunately, the penetration depth of fNIRS limited the investigation of medial PFC subregions. Another limitation of the present work was the size of the control group; ideally, almost one hundred participants should have been recruited for this group to match the experimental one. In addition, because long-term changes in cognition, behavior, brain, and fitness were not measured, inferences about the effects of repeated sessions of vigorous exercise were not warranted. Future research should investigate the chronic effects of vigorous exercise on PFC systems such as the rostral attentional gateway and attentional monitoring. Interestingly, there might be important ergonomic implications of this research. For example, law enforcement comprised the present sample, which is a vocation in which people are required to engage in many complex cognitive tasks, such as needing to make decisions quickly, direct attention appropriately, and recall memories accurately. There are real-world situations in which it is crucial for these mental processes to be carried out as successfully, and if not better, under stress and fatigue as when not under such conditions. So, whether different professions might benefit from different types and intensities of physical activity should be assessed.

A similar limitation of the present work was that long-term changes in mood were not measured. This constrains the type of inferences that can be made about interrelations with cognition and fitness, so future research investigating the chronic effects of exercise on the brain, particularly the PFC, might examine how functional changes in ventrolateral and rostral PFC related to executive function tasks vary with changes in psychopathological symptoms. Another possibility for future research is to examine how much and what kind of physical activity is sufficient to facilitate marked mental health changes. For example, are a few acute bouts of exercise enough to cultivate these changes or do overall fitness levels need to be increased, which is achieved through more repeated, habitual activity? Another limitation was that post-test measures in mood were not taken, so it was not possible to assess the acute effects of exercise on mood. However, this is not a significant limitation given the current theoretical presuppositions about how exercise improves mood over time. Namely, although physical activity tends to indeed improve positive affect due to low-level neurobiological changes (e.g., runners' high), such effects are typically transient (Dishman & O'Connor, 2009) and do not constitute mood. Therefore, it is perhaps to the potential effects of exercise on top-down cognitive strategies within the PFC to which researchers ought to look for explaining lasting improvements to mood and the ability to downregulate negative emotion.

Such mediating effects of the PFC might explain the lack of a negative relationship between physical fitness and depressive symptoms and, more broadly, why there are many people who are depressed despite being physically fit. Indeed, the relationship between increases in aerobic fitness and decreases in depressive symptoms is relatively weak (Martinsen, Hoffart, & Solberg, 1989). One possibility is that frequency of exercise, which is a driving force in promoting fitness, is less distal in its relation to changes in mood. In addition, it is perhaps not enough to exercise or be fit: The benefits of exercising on cerebral oxygenation in the brain might need to be taken advantage of to augment the facilitation of regulation strategies that cause long-term changes in mood; that is, the mind also needs to play an active role in cultivating mental health. Interestingly, this is in line with the idea that improvements to executive functions during and after exercise are optimized to the extent that these functions are a part of the task demands of a physical activity (e.g., hunting was a cognitively demanding exercise task for early humans; see Raichlen & Alexander, 2018). Therefore, it could be the case that the influence of exercise on decreasing psychopathological symptoms is optimized to the extent that an exercise includes the individual executive functions that are integral to the cognitive change strategies which drive future efforts to downregulate the onset of negative affect. This raises the interesting question of whether the physical activities of extremely fit, yet depressed individuals are not sufficiently enriched, cognitively. At this stage, however, these must remain speculations, but the results presented here are consistent with the possibility that there may be a unifying neural mechanism that links the effects of physical activity upon the brain and changes in cognitive performance. The potential clinical implications for the role of physical activity and fitness in treatment seem clear, so it would be highly valuable to investigate these results in a clinical population.

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Chapter 7: A Brain-First Approach to Recovering Stimulus Designs

7.1 Introduction

Although carrying out neuroimaging experiments using real-world tasks in naturalistic settings markedly improves the ecological validity of a paradigm, it raises some challenges that a laboratory needs to be prepared to address. Chief among these is what might be termed the ‘stimulus design problem’. A stimulus design holds information about the onsets and durations of stimuli. It is critical to the estimation of hemoglobin signals to build single-subject design matrices during data analysis (i.e., convolving the onsets and durations with the selected hemodynamic response function, HRF; Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). This information is largely determined *a priori* on the part of the researcher prior to data collection or, in self-paced paradigms, the observed timings of the onsets and durations are collected via direct computer mediation. Ecological validity is lost in both approaches: The former might not require direct interactions with a computer on the part of participants, but it is not self-paced—despite the fact that most tasks in everyday life are self-initiated—and the latter requires interactions with a computer despite being self-paced. The stimulus design problem, then, is largely a computer problem. This issue needs to be addressed before experiments attempt to conduct neuroimaging in settings in which computers, screens, cameras, and so forth would detract from the naturalism of behavior (e.g., clinical situations). But how can the data constituting a stimulus design be acquired in the absence of computer-based tasks? If there is no computer to collect response times and log stimuli presentations, then a multi-modal approach becomes necessary to achieve this. For example, one way around this issue is to record video and audio data of the experimental tasks of interest whilst they are completed and subsequently timestamping each task-related action and stimulus event. However, this is incredibly taxing work since it is carried out manually, and there are some theoretical shortcomings.

For example, Burgess and colleagues (2022) investigated the contributions of the prefrontal cortex (PFC) to prospective memory (PM; McDaniel & Einstein, 2000) tasks involving both interpersonal interactions and navigation of a real-world environment using a wireless, wearable functional near-infrared spectroscopy (fNIRS) system (Figure 7.1).

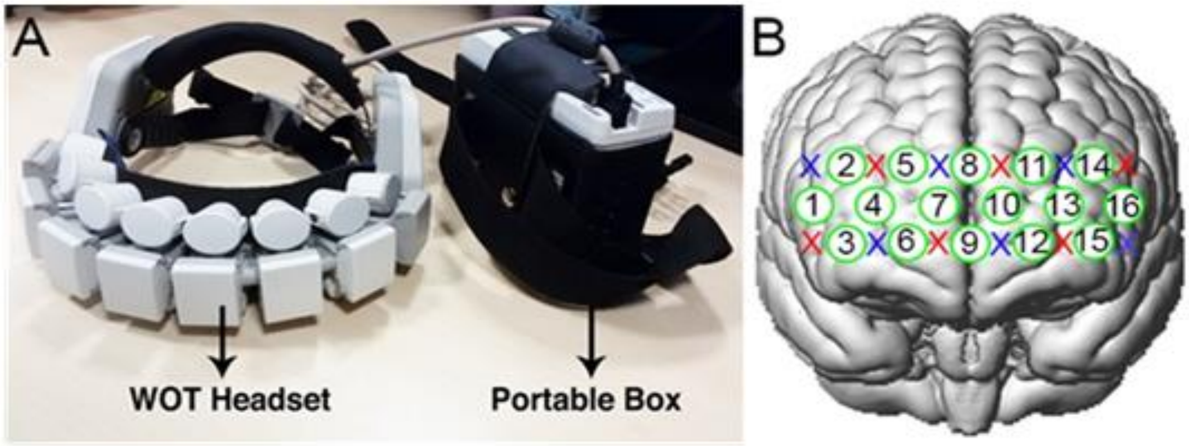

Figure 7.1. The Hitachi Wearable Optical Topography (WOT) fNIRS system (A). The channel positions, where green circles represent the 16 measurement channels and the red and blue crosses indicate the sources and detectors, respectively (B).

In this paradigm, twenty-five participants were required to walk counter-clockwise around Queen Square, London, and complete an ‘ongoing task’ (OG) such as determining the number of signs on buildings that contained the word “Queen” or the number of unobstructed stairways, but in some blocks, if participants saw a particular experimenter in the environment, they needed to interrupt their OG task and approach the individual and give them a ‘fist-bump’ (Figure 7.2). This constituted the social PM condition. The non-social PM condition required participants to instead execute this action on a parking meter each time they identified one.

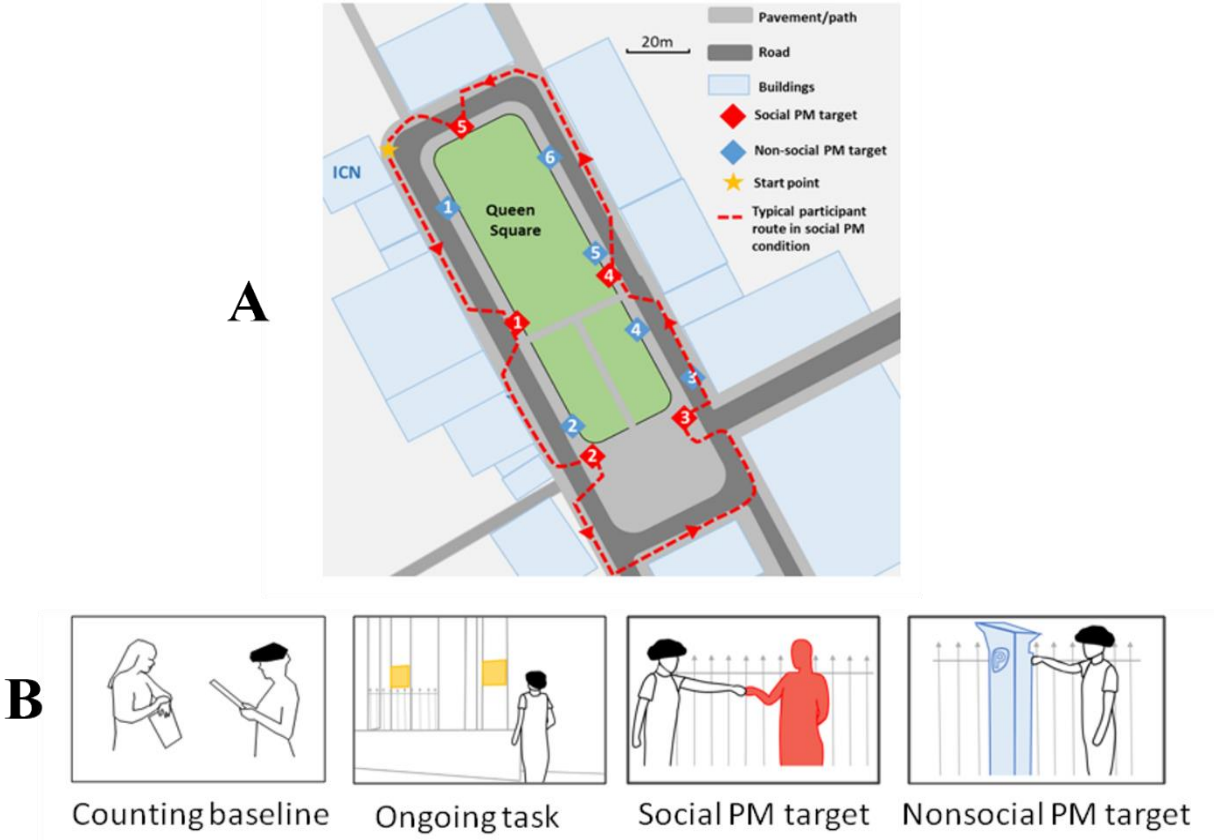

Figure 7.2. (A) A map of Queen square showing a typical participant trajectory and the locations of PM events, which are shown as colored diamonds. (B). Sample events including the baseline task, the ongoing task, the social PM task, and the non-social PM task.

The data were analyzed in accordance with the recommendations of Pinti and colleagues (2019); for instance, heart and breathing rates were collected and included in the single-subject design matrices to remove noise associated with systemic confounds. Typically, subtracting ongoing conditions from PM ones yields greater activation in rostral PFC (BA10; see Burgess, Gonen-Yaacovi, & Volle, 2011, for review), which was indeed the case in this study. Moreover, when group differences were examined between the social and non-social PM conditions, there were significant changes in the PFC (Figure 7.3). Specifically, subtracting the non-social from social PM blocks showed greater activation in an area covering right middle and inferior frontal gyri (BA46/45, respectively). Previous findings in the PM literature have suggested that future intentions within a social context tend to be ascribed greater importance (Meacham, 1988), resulting in improved PM performance in social situations compared to non-social ones (e.g., Brandimonte, Ferrante, Bianco, & Villani, 2010; Cicogna & Nigro, 1998; D’Angelo, Bosco, Bianco, & Brandimonte, 2012; Kvavilashvili, 1987; Marsh Hicks, Landau,1998; Meacham & Kushner, 1980; Penningroth, Scott, & Freuen, 2011). So, one explanation for this effect in the PFC is that the social and non-social intentions differed in importance—an ascription of subjective value which is itself perhaps an appraisal operation—leading to greater upregulation of the subsystems involved in monitoring for PM cues to act (i.e., right dorsolateral PFC). In sum, this work was successful in continuously and robustly measuring PFC activation with fNIRS in a real-world environment.

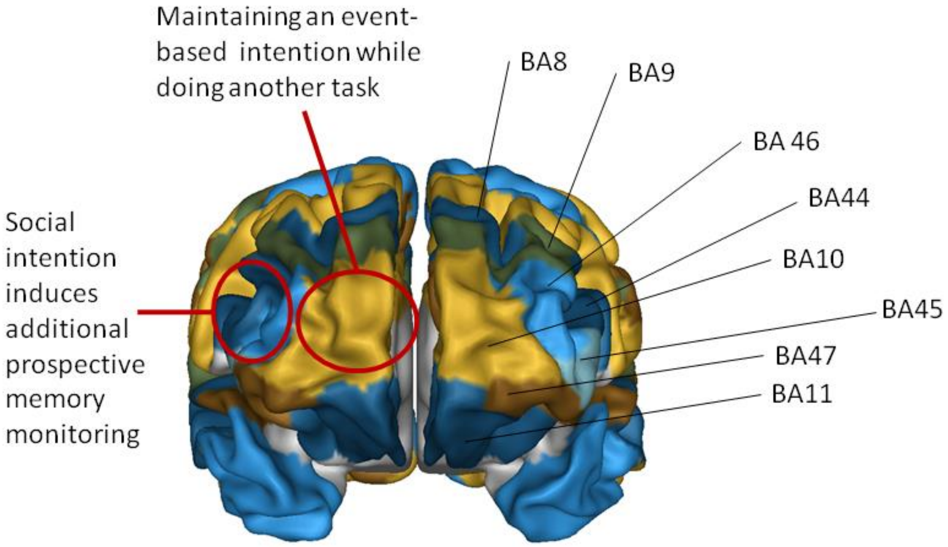

Figure 7.3. A simple hypothetical information processing explanation of the results.

However, with greater ecological validity comes greater situational complexity: No two participants will experience the same pattern of ‘stimulus presentation’ such environments despite great efforts on the part of researchers to control for what might occur during naturalistic task performance. Rather than endeavoring to account for all the complexities of the world in an ecological experimental design, a more advantageous approach might be to recover the experimental design from the real world by adopting *a posteriori* approaches (i.e., techniques based on observations). So, because the above study could not use computer mediation, the stimulus designs needed to be meticulously identified using the data from multiple cameras; perhaps at some point machine-learning methods will take over such work. For example, three video streams for each participant were synchronized (in ELAN; Brugman & Russel, 2004) and coded to identify the timings of key events and block transitions within each run. Event timings and blocks generated from the video analysis were then synchronized with the fNIRS timeline and modeled as boxcar functions for convolution with a standard hemodynamic response function. This approach to acquiring the stimulus designs of participants raises a number of issues in addition to its laboriousness. For example, experimenters following around participants with video cameras is not only impractical in certain paradigms but also confounding in its likely influence on the participants, namely there are probably observer/audience effects on performance which recruit subsystems that are not of interest in a given condition (e.g., mentalizing; Hamilton & Lind, 2016). Critically, this approach to building real-world stimulus design fails to account for the possibility that the functional activation events in the brain mediating the relationship between environmental events and self-initiated behavior might not always correspond to observable behavior or exogenous stimuli. That is, some of the cognitive demands of a task on the functional resources of the brain can be of a stimulus-independent nature and, therefore, it is impossible to log the onsets of *endogenous* events from video data, leaving a rather marked explanatory gap in the growing enterprise of ‘real-world’ neuroimaging.

Rather than relying solely on video data, could the fNIRS data also be useful in indexing the onsets and durations of events constituting stimulus designs? For example, a ‘brain-first’ *a posteriori* approach to recovering stimulus designs is the Automatic IDentification of functional Events (AIDE) method (Pinti et al., 2017). AIDE was developed to detect from cleaned HbO_2 or HbR signals the onsets and durations of functional events related to an experimental task to estimate activation models. Pinti and colleagues (2017) applied this technique to synthetic data as well as to the single case reported in Pinti and colleagues (2015) and found that, with respect to the real data, AIDE not only supported the block-level results of the antecedent study but also provided additional information regarding the spatial location of the participant when significant functional events were detected. That is, a temporal pattern of activation in the brain was revealed in an analogous way to single-cell recordings from rats in a maze, a domain of research that has been quite successful in elucidating the functions of other brain areas such as the hippocampus (e.g., O’Keefe, 1976). However, the object of this investigation was proof-of-principle and, therefore, additional demonstrations of the effectiveness of AIDE is needed to mount support against potential objections (e.g., overfitting). Importantly, the validity of AIDE-derived activation models depends in large part on whether or not the detected functional events that yield them correspond to *task-relevant* information processing in the brain. Therefore, the present work applied the AIDE to data at the group level and investigated the extent to which recovered functional events were indicative of the patterns of activation that would be expected from the resource requirements of subsystems supporting stimulus-oriented and -independent attending on PM tasks (Burgess, Dumontheil, & Gilbert, 2007).

7.2 Method

7.2.1 Participants

AIDE was applied to nineteen data sets from the sample (n = 25; *M* = 26; *SD* = 6.65; 76% female) collected in Burgess and colleagues (2022): more specifically, to the cleaned signals of the channels that were found to have significant effects (e.g., social PM), covering rostral PFC (BA10), inferior frontal gyrus (BA45) and middle frontal gyrus (BA46). Written consent was gained, and the protocol was approved by the UCL local research ethics committee (approval number CEHP/2014/901).

7.2.2 Measures

AIDE is an algorithm that uses the GLM-based least-squares fit analysis to estimate functional events from all possible temporal combinations of event onsets and durations in the fNIRS time-series. For example, a box-car function is produced for all possible durations at the onset of 1 second, then again at the onset of 2 seconds, and so forth for each possible event onset in the observed signal(s) of each channel. These functions are subsequently convolved with an HRF, resulting in a multitude of GLMs (Figure 7.4).

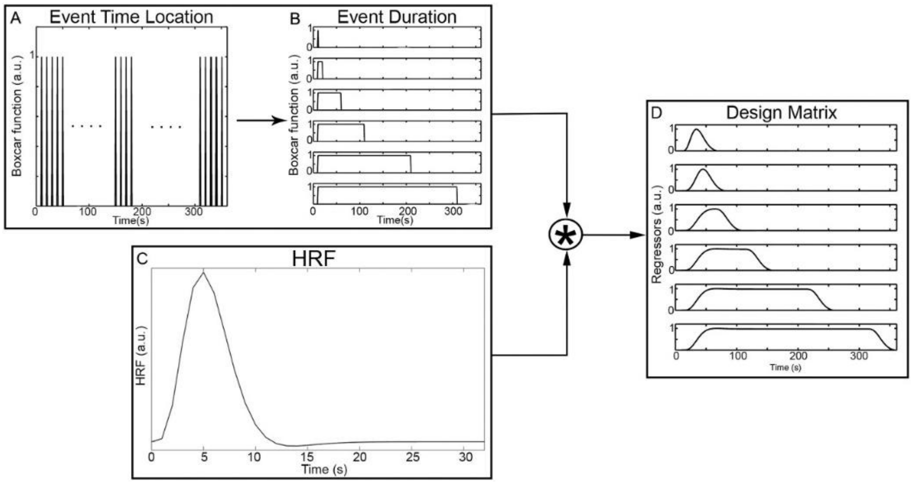

Figure 7.4. Boxcar function and design matrix computation. Boxcar functions are created by translating the event onset using 1-s steps throughout the experiment duration (A) while increasing the boxcar duration at 1-s steps (B). Each boxcar function is convolved with the HRF (C) to compute the design matrix (D). Adapted from “A novel GLM-based method for the Automatic Identification of functional Events (AIDE) in fNIRS data recorded in naturalistic environments,” by Pinti and colleagues, 2017, *NeuroImage*, p. 294, with permission from authors.

Next, AIDE determines which GLMs represent the best fit with the fNIRS data. More specifically, an iterative procedure retains the resultant β- and t-values corresponding to these GLMs that are significant ($p < 0.05$) and combines the t-values into a 't-signal' of onsets across the time-series. Peak-values are then extracted from this signal using the 'peakfinder' function (Yoder, 2016) in Matlab, which finds the local maxima (Figure 7.5).

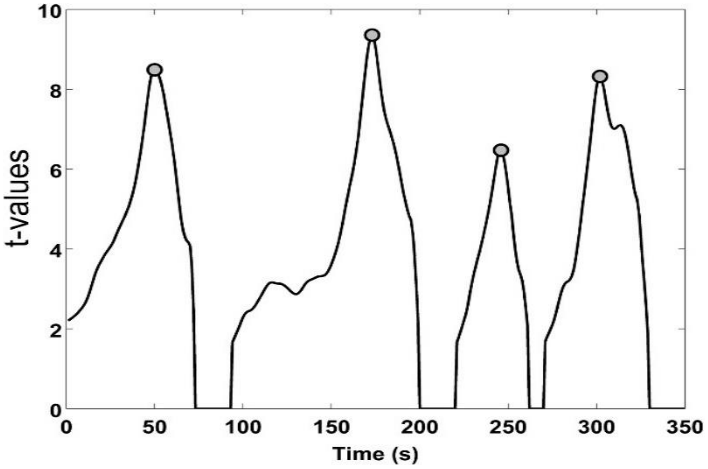

Figure 7.5. Events onset identification. An example of a t-value signal is represented by the black line while the peak-values representing functional events identified through the AIDE algorithm are shown as grey dots. Adapted from "A novel GLM-based method for the Automatic Identification of functional Events (AIDE) in fNIRS data recorded in naturalistic environments," by Pinti and colleagues, 2017, *NeuroImage,* p. 294, with permission from authors.

The identified 'functional events' and their respective onsets and durations are rejected if they fail to meet a certain significance threshold (p_{thresh}) that is set by the user of AIDE; the optimal value is $p < 0.0001$ (Pinti et al., 2017). The results are also corrected using the false-discovery rate (FDR; Benjamini & Hochberg, 1995). Again, this procedure is applied to each fNIRS channel; so, it produces an activation model for each channel of each participant for each task (Figure 7.6). These activation models represent the typical parameters of estimated HRFs in the single-subject design matrices of first-level analysis. Second-level analysis can subsequently be carried out as normal.

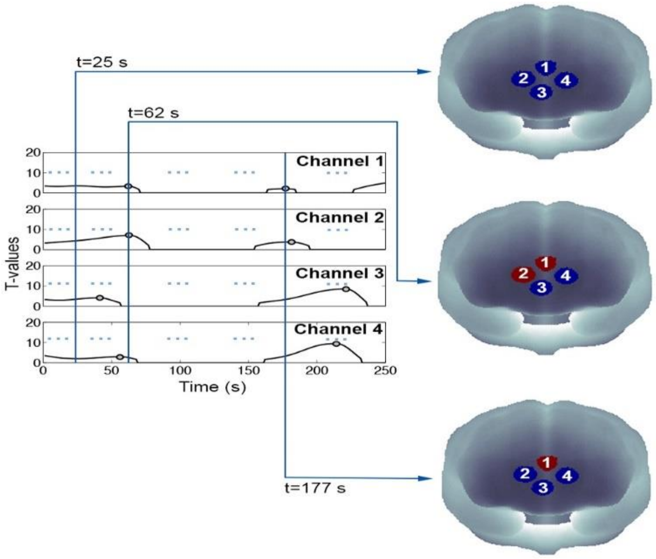

Figure 7.6. Example of binary maps development process using synthetic data. Binary maps are created for each signal time point and show the activated channels (red circles) and non-active channels (blue channels) as predicted by AIDE. t-values signals are represented by black lines while functional events are identified by grey dots. Adapted from “A novel GLM-based method for the Automatic Identification of functional Events (AIDE) in fNIRS data recorded in naturalistic environments,” by Pinti and colleagues, 2017, *NeuroImage,* p. 295, with permission from authors.

7.2.3 Data analysis

To investigate the reliability of the functional events that AIDE detects—rather than the activation models it subsequently generates—three measures were operationalized: event distribution, event frequency, and event rate. *Event distribution* refers to where during a given experimental condition functional events occurred. The onsets of these events should be detected where participants are either engaged in task-related actions in the environment (e.g., interacting with another person) or in key information-processing steps relating to the task (e.g., spontaneously retrieving the intention to interact with another person via recognition). The distribution of these event onsets over time and conditions should sufficiently indicate this engagement (e.g., group-level aggregations of functional events in relevant spatial locations). *Event frequency* refers to the degree to which functional events are extracted from different brain subregions throughout the time-series. Whether the detected functional events between and within regions should exhibit greater or lesser frequencies depends on the hypotheses of individual paradigms, but for the present one, this measure of incidence should theoretically be greater in subregions of interest than those not of interest (i.e., BA10) and, more specifically, in those areas onto which a task places the most operational demands (i.e., PM condition). *Event rate* refers to the temporal change in functional events throughout the course of a given task. One means by which to evidence task-related variation in event rate is to show that some random process does not equally account for it, such as a Poisson random variable (see Gabbiani & Cox, 2010). That is, at least some events should not be independent from each other. To test whether event rates were not random, synthetic null distributions of Poisson arrays were produced using the standard Matlab function ‘poissrnd’ from the Statistics and Machine Learning Toolbox. This approach uses the real data vectors of event onsets and the means of their rates as input to simulate random event rates. Differences between the real and synthetic data were then tested.

7.3 Results

The functional events detected from the fNIRS channels were synchronized to the video recordings of each participant (n = 19) performing the PM and OG tasks. Specifically, the onset timings of each testing session in the video recordings were used as reference points in the fNIRS time series to correct the onset timings of the detected functional events so that the spatial locations of these onsets could be plotted over a map of Queen Square. The distribution of detected functional events from the PM conditions were plotted over this map (Figure 7.7). Interestingly, condition-specific events tended to aggregate around task-related moments: The detected events in the social PM condition largely occurred where the intention to interact with a confederate (i.e., the fist-bump) was executed, but especially just before this behavior (e.g., when participants might have spontaneously retrieved this intention upon seeing the confederate). Similarly, events detected in the non-social PM condition largely occurred where the intention to 'fist-bump' a parking meter was executed, but especially just before this behavior (e.g., when participants might have spontaneously retrieved this intention upon seeing the parking meter).

Figure 7.7. A map of Queen Square showing the spatial locations of rostral PFC functional events. Large blue and red stars indicate the location of the social and non-social PM cues, respectively, and the blue and red asterisks represent the locations of participants when social and non-social functional hemodynamic events occurred, respectively. The peaks in activity in rostral prefrontal cortex tend to occur when the participants were close to the prospective memory cues (either the confederate or a parking meter), especially a few seconds before the intention was executed.

As regards event frequency, functional events were more frequent in rostral PFC compared to lateral PFC during both the PM and OG tasks (Table 8.1) and, importantly, the average number of functional events in the sample were more frequent within rostral PFC during the PM conditions than during the OG ones, $t(18) = 3.84$, $p = .001$, $d_s = .94$, 95% CI [1.0, 3.42] (Figure 7.8).

Table 7.1

Descriptive Statistics of Event Frequency

Measure	*n*	*M*	*SD*	∑
Rostral PFC (PM)	19	10.37	2.95	182
Rostral PFC (OG)	19	8.16	1.74	153
Lateral PFC (PM)	19	7.89	1.52	139
Lateral PFC (OG)	19	6.26	.81	117

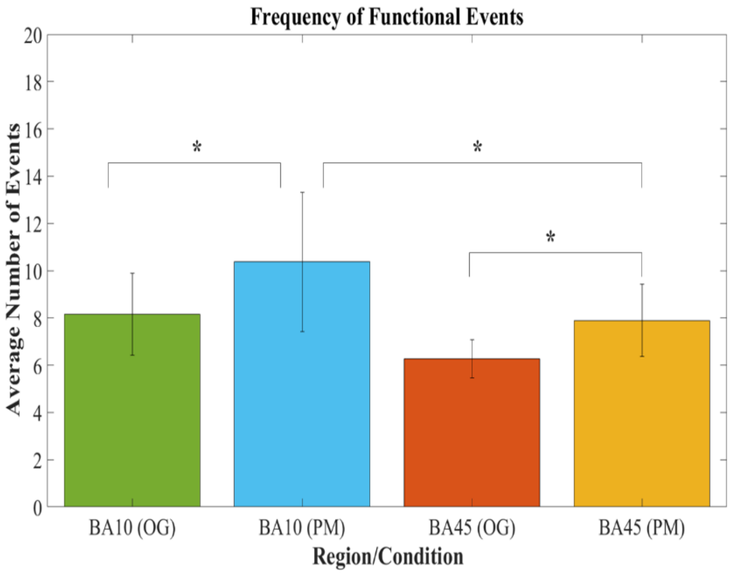

Figure 7.8. Comparisons of the average group frequencies of functional events detected in rostral PFC during the OG (*green*) and PM (*blue*) tasks, and in lateral PFC during the OG (*orange*) and PM (*yellow*) tasks. The frequency of functional events was greatest in rostral PFC during the PM tasks. An asterisk indicates a p-value ≤ .01.

Representing the distribution of functional events arising from the PFC in 2D yields figures analogous to neural-spike trains (Figure 7.9).

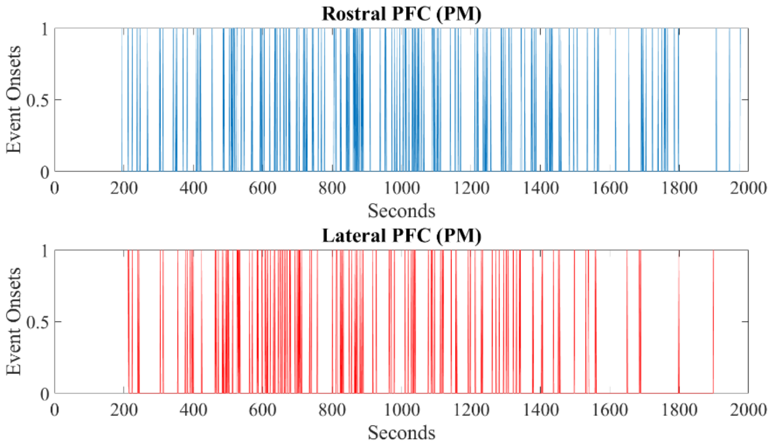

Figure 7.9. Functional event onsets detected in rostral (blue) and lateral (red) PFC during the PM conditions. Significant events have an amplitude of 1 (y-axis) in the fNIRS time-series (x-axis).

The temporal variation between each functional event needed to be computed to determine the event rates of these vectors, which was carried out using the Matlab function ‘diff’ [X(2)-X(1) X(3)-X(2) ... X(n)-X(n-1)].

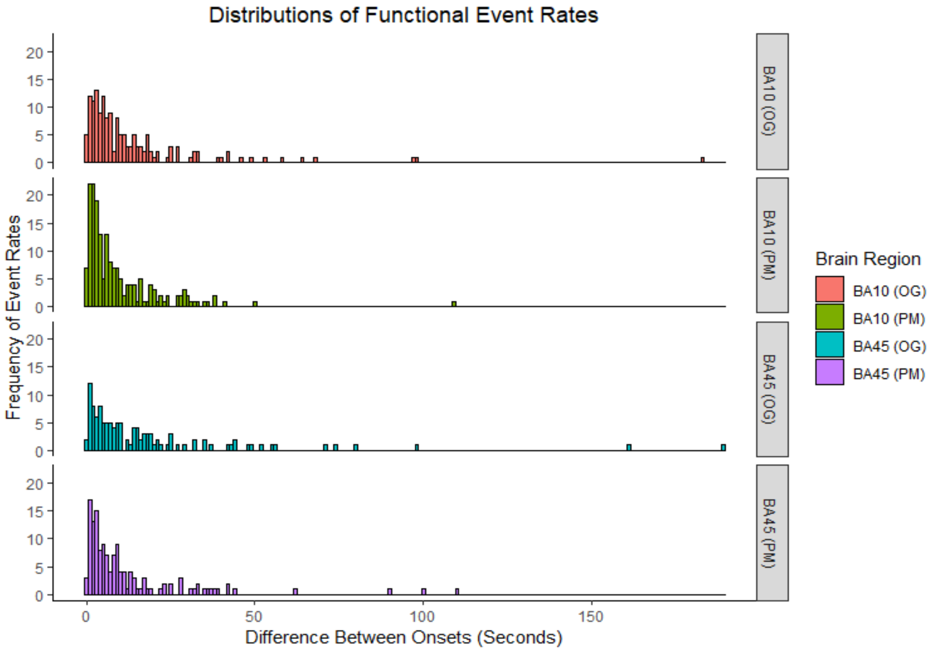

Figure 7.10. Distributions of event rates in rostral and lateral PFC during the PM and OG tasks.

Next, the null hypothesis that these rates are explicable by a random process was tested. Poisson random variables are phenomena that are comprised of a number of events which occur independently of each other and at a constant rate over time if they are homogenous, and at an inconstant rate if they are inhomogeneous (e.g., meteors that hit the earth annually; Gabbiani & Cox, 2010). If the stimulus designs that AIDE recovers from fNIRS data are not task-related, then there should be no significant difference in the timings between detected onsets (i.e. temporal variation) and their synthetic Poisson distributions. However, there was such a difference between the real and synthetic data, $U = 114004$, $p < .001$, $d = 0.64$ ($Z = 10.57$) (Figure 7.11).

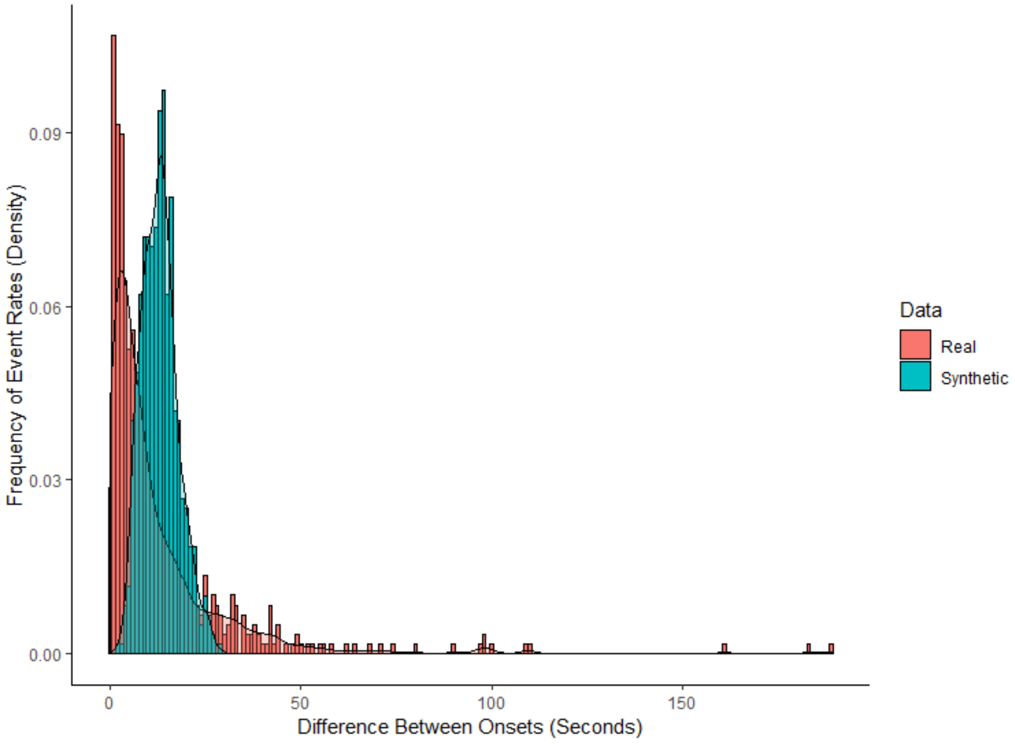

Figure 7.11. Group comparison of the real (*red*) and synthetic, Poisson (*blue*) distributions of the variation in functional event onset timings collapsed across tasks and subregions (rostral and lateral PFC). The real data significantly differed from the synthetic distribution: The real functional event onsets were too variable to be described by a random process, in that the nature of the task sometimes elicited a fast burst of functional events and sometimes slower, more periodic ones.

Interestingly, a marked decrease in event rate (i.e., longer time periods between functional events) was observed across every condition and ROI near the end of each task (Figure 7.12). This growing drop in the incidence of functional events is consistent with the idea that the cognitive resource requirements across rostral and lateral PFC should decline near the end of carrying out the demands of a given task; indeed, there is a moment shared by each participant where they will realize that there are no more retrieval cues (i.e., parking meters or confederates) between where one is currently located and the end location of the test (i.e., Institute of Cognitive Neuroscience, UCL).

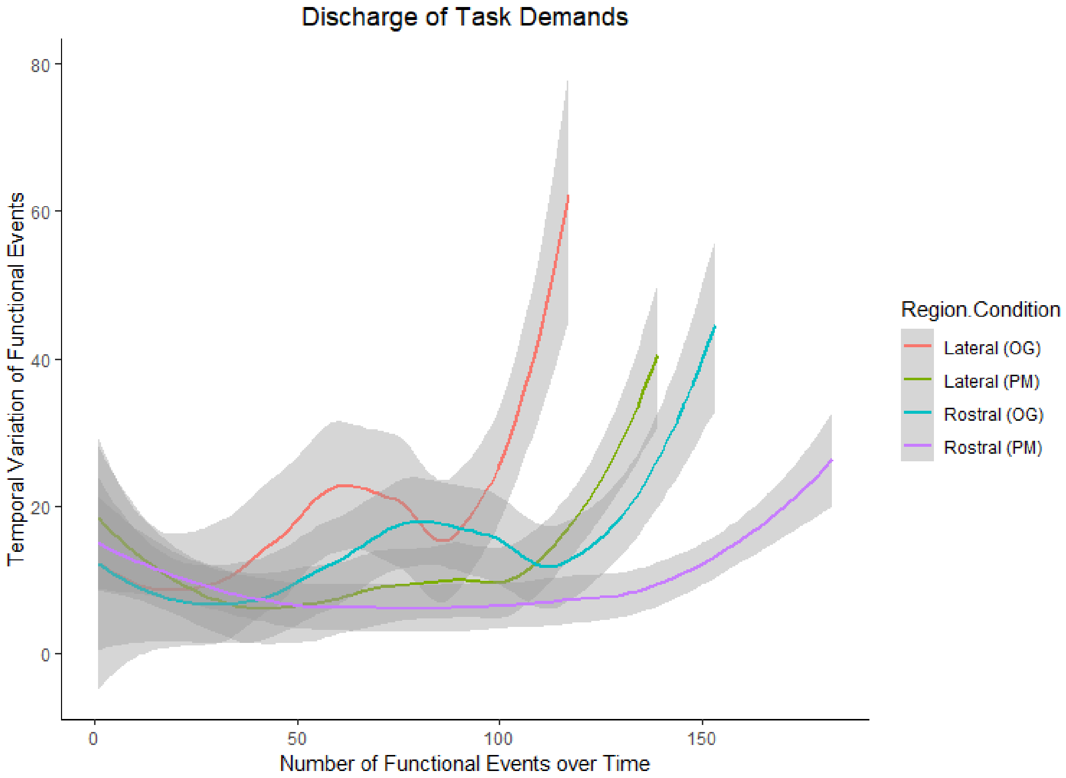

Figure 7.12. Group variations in functional event onset timings. Event rates for rostral PFC during the OG (*blue*) and PM (*magenta*) tasks, and lateral PFC during the OG (*orange*) and PM (green) tasks, fluctuated throughout their respective blocks, but each task showed a slowing in event rate as the task neared completion, with rostral PFC in the PM condition showing the least sharp drop in functional events. This is what would be expected of a subregion that is critical to a task (i.e., consistently and dynamically engaged throughout it), of a subregion that shows a high event frequency (Figure 7.8).

7.4 Discussion

There are a few notable conclusions from Burgess and colleagues (2022) and the present work. The first is methodological: It is possible to use fNIRS to measure PFC activity in freely moving adult participants while they behave in a ‘real-world’ environment, and to link this activity to complex mental operations (i.e., those relating to prospective memory). Participants were free to choose where (within certain geographical parameters) and when to go. No special preparation of the environment was undertaken: This was a busy London street, with all the usual happenings occurring around the participants that are common to inner-city centers; and, while the participants were instructed about the task just beforehand, they were not specially trained in any way. The second main conclusion is a cognitive neuroscience one. Medial and lateral rostral PFC (BA10) subregions showed greater activation during both the social and non-social PM conditions compared to the ongoing-only conditions, and activation differences during the social prospective memory condition relative to the non-social one were also evidenced, but these differences resided in right lateral PFC subregions (middle and inferior frontal gyri; BA46/46, respectively). One interpretation of this pattern of activation might be that it is a neural signature related to a ‘social intention superiority effect’, as discussed above.

A complementary analysis method (i.e., AIDE) was used to take advantage of the temporal resolution of fNIRS to reveal when and where PFC functional events occurred in the environment, providing not only a novel approach to recovering stimulus designs from data collected in ecological settings but also an improved spatial understanding of the data. This showed that functional events from the social and non-social PM conditions tended to cluster around non-random locations, namely where participants appeared to discern, approach, and interact with a target that was specific to the current condition. Other functional events occurring further away from targets might relate to periodic monitoring for intentional cues. Future research should attempt to classify qualitative differences between functional events (e.g., intention retrieval vs. execution) using machine-learning techniques (e.g., k-means clustering). Moreover, the greatest frequency of functional events was detected in rostral PFC (BA 10) in the PM conditions compared to other conditions and PFC subregions: The PM conditions elicited a higher frequency of functional events in both rostral and lateral PFC compared to the ongoing ones, and event frequency across PM conditions was greatest in rostral PFC compared to lateral PFC. These findings are consistent with what should be expected of an attentional subsystem localized in rostral PFC that is required to switch frequently and dynamically between attentional modes during an event-based PM task. Interestingly, comparing the functional event rates (i.e., temporal variation between events) across the PFC regions of interest to synthetic event rate distributions showed that these rates were too variable to be random (i.e., there were periods of time across the group where the incidence of these events would speed up and then slow down, and then speed up again, and so forth). So, it can be deduced that at least some functional events depended on antecedent ones; perhaps this is because they were part of the implementation of the same cognitive operation being carried out in a particular subregion. In addition, a chance finding was that there were marked and sustained drops in the incidence of these neural events near the end of each task. The notion of a discharge of intention-related processing towards the completion of a task has a long history going back to Kurt Lewin, with his characterization of a release of 'goal tension' as intentions are completed, with the Zeigarnik Effect (the tendency to remember unfinished or interrupted tasks better than completed tasks) as a behavioral consequence (Lewin, 1935). This finding and potential explanation clearly requires further investigation, but it is an intriguing possibility raised by the use of the AIDE method.

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PART IV

CONCLUSIONS

Chapter 8: Extensions and Implications

8.1 On the recogitation of thought

Normativity refers to what should be the case rather than what is the case. Facts provide the normative force for thinking and acting in certain ways that realize what people have most reason to do, such as to cultivate their psychological and physiological well-being (Parfit, 2011). For example, the positive effects of aerobic activity on the body constitute reasons for desiring them and guiding one's conduct accordingly. However, people have a propensity to subjectively impose normativity onto their descriptions of experiences that are inconsistent with personal goals (Ellis, 1994), namely through the propositional attitudes (e.g., beliefs, desires, appraisals) they form or assimilate about the world, self, and others (Churchland & Churchland, 2013). Propositional representations such as appraisals are inextricably tied to the production of emotion (Scherer, Schorr, & Johnstone, 2001) and, left unchecked, these types of thought can create distress and dysfunction in people's lives (David, Lynn, & Ellis, 2010). Unfortunately, this seems to be the rule rather than the exception, because human beings are innately fallible: It is all too easy to raise a preference for an outcome in proportion to its personal significance—that is, to place an absolutistic, inflexible demand on the world, self, and others. Such conceptual, affective valuations are dysfunctional when they consist of inferences that are ungrounded in logic, empiricism, and pragmatism, result in unhealthy negative emotions, and future goal-obstruction (David et al., 2010). Therefore, irrational thoughts pose a serious risk factor for the degradation of mental health. These 'cognitive-vulnerability' factors (Barlow, Durand, Lalumiere, & Hofmann, 2021) are deviations from regular dimensions of human functioning and are not inherently etiopathogenic (Johnstone & Walter, 2014; Ochsner & Gross, 2014).

Interventions aiming to cultivate the mental health from which dysfunctional cognitions instrumentally distract typically consist of cognitive-behavioral therapy (CBT)-based forms of psychotherapy. These interventions are highly efficacious in treating a wide range of psychopathological symptoms (Hofmann, 2014), but psychologists have little idea why this is the case beyond their commonsense-psychological explanations. For example, much cognitive neuroscientific research has amassed in the last decade observing changes in affect, mood, behavior, and brain, as well as other physiology, as a function of mental health interventions, but these findings represent outcome measures rather than the neurocognitive mechanisms underpinning these changes (Crum 2021a).

The interpersonal interactions between clinicians and clients during clinical practice are probably central to understanding the nature of these mechanisms (Crum 2021b). Of most notable importance is the verbal communication that facilitates these interactions; it is dialectical in nature. Clinicals employ verbal intervention strategies to modify dysfunctional cognitions into functional ones (Beal, Kopec, & DiGiuseppe, 1996). As discussed in Chapter 1, this disputation process of cognitive restructuring—this strategic verbal behavior—is necessarily predicated on the principle of cognitive mediation (see Crum, 2019) and, therefore, must depend on a set of information-processing systems that work together to achieve this clinical goal. More specifically, it was hypothesized that a metacognitive ‘thought’ procedure likely precedes verbal elaboration in these clinical situations, namely recogitation. Because this mental task can be carried out endogenously in the absence of observable behavior, the cognitive operations potentially forming this mental task are largely independent of those which operate on perceptions (stimulus-independent thought; SIT). Moreover, this mental task is not only metacognitive (its objects are thoughts) but also non-routine and open-ended. This suggests that recogitation is possibly an ill-structured reasoning problem. Such problems require active, or controlled, thinking that biases attention in favor of the endogenous, self-generated information that might solve them (Shallice & Cipolotti, 2018).

8.2 Principles of frontal lobe function

Chapter 2 examined the information-processing systems into which this sense of cognitive control fractionates, namely executive functions and their neural bases in the prefrontal cortex (PFC). Information-processing systems that modulate other systems are implemented during an active goal state to realize some outcome in a novel situation for which there is no appropriate automatic procedure (Norman & Shallice, 1986). Neurobiologically, this modulation consists of activation biasing in favor of the cognitive operations which generate and implement the thought and action sequences that are appropriate to these situations. These operations are separately modifiable subsystems and, therefore, localizable in the brain (Shallice, 1988). This localizability means that the material substrate of executive functions can be damaged in isolation, making them amenable to empirical investigation. Neuropsychological research over the past few decades has shown that these isolable, executive subsystems are predominantly situated in the frontal lobes of the brain, particularly the PFC (see Shallice & Cooper, 2011; Stuss & Knight, 2002). Critically, the subregions comprising the PFC (bilateral Brodmann areas 8, 9, 10, 11, 12, 44, 45, 46, and 47) are functionally organized according to their computational operations rather than by the information-processing domains of what they can process (Petrides 1989); that is, their executive functions are domain-general. Importantly, although the functional specializations within the PFC are operationally distinct, they work together within the overarching role of the PFC to generate and select strategies that run the cognitive operations appropriate for satisfying goal states in novel situations (Shallice & Burgess, 1996).

8.3 A model of recogitation and the ecological challenges to its investigation

Some of these executive functions are highly relevant to the mental task of recogitating human belief systems (Chapter 3). Because recogitation is an open-ended problem and used in novel situations, it represents a reasoning problem whose solving probably lies in the processes of active thought (i.e., the Supervisory System). Specifically, it was hypothesized that this task should place marked demands on the PFC subsystems that support generating, testing, and rejecting reasons (i.e., hypotheses) in ill-structured problems. So, the most important subsystems are perhaps the rostral attentional gateway of BA10 (Burgess, Dumontheil, & Gilbert, 2007), the strategy generation procedure of left BA46 (Shallice & Cooper, 2011), and the monitoring and checking functions of right BA46 (e.g., Sharp, Scott, & Wise, 2004). In addition to these executive functions, the temporo-parietal semantic network (e.g., BA39 & BA40) was also postulated as an integral part of recogitation (see Messina, Bianco, Sambin, & Viviani, 2015). Other brain regions might also be involved, such as the language and inhibitory functions of left inferior frontal gyri and the mentalizing and energization functions of medial PFC. Theoretically, the role of lateral BA10 in supporting endogenous thought processes should evidence itself in pronounced resource consumption during clinical interpersonal interactions, particularly on the part of clinicians between periods of listening and speaking (i.e., hearing others' utterances and verbally articulating their irrationalities).

However, investigating recogitation as a mental-health strategy at the level of the brain raises some theoretical, methodological, and practical challenges. Namely, experimental design and ecological validity are the major limitations to clinical cognitive neuroscientific research studying the mechanisms mediating the relationship between treatments and outcomes (Chapter 3). Collecting data periodically, such as before and after a given treatment, is useful in examining its effects on outcome measures, but it preludes inferences from observed changes between these periods to the mechanisms driving them (Figure 3.2). In addition, the paradigms in which neuroimaging data are collected poorly represent the clinical environments in which these changes are brought about and use tasks that fail to reflect treatment strategies for restructuring dysfunctional appraisals. Although it follows that neuroimaging techniques should therefore be used in clinical environments to examine the interpersonal interactions driving cognitive restructuring, a practical prerequisite for this is to demonstrate in terms of experimental design and task development a paradigm that better represents these situations and places the appropriate tasks demands on the information-processing systems of interest. More specifically, the interactions during verbal intervention might be experimentally fractionated into constituents, namely epochs of speaking and listening on the parts of both the clinician and client, as well as an epoch representing the period between the clinician's speech comprehension and production that is the 'thinking' component of recogitation. This would provide a proof-of-principle for such an ecological experimental design and, therefore, a way forward for research interested in linking mechanisms of change at a neurobiological level of scientific explanation with that of cognitive theorizing. But what is the appropriate method(s) for carrying out an experimental design tailored to capture such clinically relevant phenomena?

8.4 Functional near-infrared spectroscopy as a neuroimaging method

A neuroimaging method that is well-suited for investigating these aspects of mental health interventions is functional near-infrared spectroscopy (fNIRS), an optical technique that has long been used to study brain function and metabolism (Villringer & Dirnagl, 1997). As discussed in Chapter 4, fNIRS is unique among optical techniques in its ability to safely, non-invasively assess human brain tissue within living organisms. The localization of neural activity during task engagement is inferred from local changes in hemodynamics (Yücel et al., 2021). Systemic, extracerebral, and non-evoked sources of noise represent challenging confounds to signals which are intracerebral and task-evoked, but there are a multitude of signal processing methods to address these physiological artifacts and improve the signal-to-noise ratio (Tachtsidis & Scholkmann, 2016). Multi-modal neuroimaging studies in humans have reliably correlated measures of hemodynamic changes and their spatial localizations to cross-validate fNIRS as an effective, complimentary tool for investigating human brain function (e.g., Noah et al., 2015). Portable systems make possible the investigation of brain function in more diverse situations, posing a distinct ecological advantage over similar neuroimaging methods because participants can complete tasks that represent and generalize to real-world behavior (Pinti et al., 2018). fNIRS systems with hyperscanning capabilities can assess authentic human-to-human interactions within naturalistic settings (Redcay & Schilbach, 2019). Future studies in this area stand to potentially contribute unique insights into the governing dynamics of social interaction. Although these advancements in neuroimaging raise some technical, methodological, and logistical challenges (e.g., how long one can wear an fNIRS), it is unclear how neuroscientific theories involving emergent, enactive systems (e.g., the ‘interactive brain hypothesis’; Di Paolo & De Jaegher, 2012) might be falsified without the application of hyperscanning. Researchers adhering to the accepted practices that have recently emerged (Yücel et al., 2021; e.g., data cleaning) will be critical to replicability going forward. Building in the option to examine aspects of test-retest reliability in a study and pre-registration are also important.

8.5 Neuroimaging interpersonal interactions in mental health interventions

The option to use a multi-person neuroscience approach and to create experimental designs using naturalistic tasks that would otherwise not be possible within the confines of conventional laboratories are reasons that fNIRS might be well-suited for investigating the neurocognitive mechanisms driving psychotherapeutic change. Importantly, contriving ecologically valid situations and using methods that continuously collect data from the interpersonal interactions within these situations address the explanatory gap of clinical cognitive neuroscience (Figure 3.2). That is, with the appropriate paradigm, researchers should be able to assess the *in situ* neural dynamics engendering treatment outcomes. Therefore, the experimental design suggested in Chapter 3 that fractionates a prototypical clinical situation (Chapter 1) into epochs of speaking, listening, and 'thinking' (Figure 6.4) was used in combination with fNIRS-based hyperscanning (Chapter 4) to investigate the role of the PFC and its executive functions (Chapter 2) in interpersonal interactions involving the modification of dysfunctional cognitions (Chapter 5).

The most theoretically significant finding of this study, with respect to the cognitive model of recogitation, was that greater activation was observed in rostral PFC (BA10), particularly its lateral aspects (Figure 5.7), when participants whose role it was to be the 'clinician' were tasked with mentally generating at least two hypotheses that challenged the tenability of each appraisal. That is, participants performed this task between hearing linguistic propositions from 'clients' (i.e., listening to appraisals) and elaborating their reasonings (verbal articulation). This finding is consistent with the rostral attentional gateway hypothesis (Burgess et al., 2007), but does not suggest that a function of rostral PFC is to perform recogitation. Rather, it only suggests that this subregion might provide critical support (i.e., endogenous attentional biasing) to the cognitive operations into which recogitation fractionates. The practical applications of the ecological design, tasks, and methods used in this study to investigate clinically relevant phenomena are numerous, and the findings set a precedent for the real-world neuroimaging of inter- and intra-brain systems supporting the interpersonal interactions that have long been integral to psychotherapeutic treatment. For example, understanding recogitation at the levels of the brain and information processing could be crucial to explaining treatment outcomes, such as improvements in emotion regulation, adaptive behavior, and functional connectivity. Differential recruitment of its neural systems might predict the ability of clinical populations to identify, dispute, and modify their dysfunctional appraisals and, therefore, predict their ability to successfully downregulate negative emotions.

Future research in this area would benefit from using a hybrid experimental design that takes advantage of the periodic measurement framework of existing designs and the continuous, *in situ* approach of this study to investigate the neurocognitive mechanisms by which psychotherapeutic change is facilitated in evidence-based treatments for the pathogenesis of psychopathological symptoms. Future research might also use different control conditions depending on the cognitive functions of interest and, in the case of purely endogenous functions, create explicit checks of participants' engagement. Control conditions involving verbal communication might also use dialog that is more natural than simply repeating propositions. It is also worth noting that the blocked design used in the present work consisted of 8 trials per block, which lies somewhere between the many trials that are common of computer-based tasks and the single trial that a clinician might get in an encounter with a patient. Additional trials should be used for studies that aim to replicate the neural contributions of recogitation and to study the subfunctions of this mental ability. On the other hand, investigating a live clinical interaction between two people might benefit from the ability to extract trials from the observed data—rather than contriving them in the situation (Chapter 7).

8.6 Interrelations of executive functions, physical activity, and mental health

Recall from Chapter 1 that most people (non-clinicians) are not as trained as practitioners in the executive exercise of recogitating thoughts deriving from the self or others. They lack the mental ‘task instructions’ that describe what recogitation is, the nature of its objects, and when to actuate it. So, they have not a learned procedure and intention for carrying out recogitation in certain situations. Again, in everyday life, self-initiated recogitation as a mental health exercise has a strong prospective memory component: It is implemented in an *online* sense once a hypothetical condition unfolds, particularly the occurrence of a goal-incongruent event. To address this issue, clinicians often spend much time working patiently with clients to help them become more independent in their ability to identify, challenge, reject, and revise their propositional attitudes; however, these efforts are typically met resistance and, therefore, can take a long time (Ellis, 2002; Ellis & Dryden, 2007). From a cognitive neuroscience perspective, this is perhaps less of a question of ‘resistance’ as it is a potential issue with the ability of the brain to implement recogitation as a cognitive task. People experiencing psychopathological symptoms might genuinely find it more difficult. One reason is that the presence of cognitive deficits detracts from the effectiveness of cognitive strategies used in mental health interventions (Roiser & Sahakian, 2013). Indeed, there is a growing body of research directed towards this possibility, showing relationships between psychopathological symptoms and executive deficits (Joormann & Vanderlind, 2014; Rock, Roiser, Riedel, & Blackwell, 2014).

These deficits seem to be rooted in an insufficiency of resources rather than in some innate or acquired impairment that is structural in nature. For example, there might be fewer executive resources available for emotion regulation strategies due to the overuse of maladaptive ones, such as rumination (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), needlessly taxing functions that could otherwise be used for more adaptive mental tasks. Because recogitation heavily depends on the executive functions of the PFC, particularly rostral PFC (BA10), it is worth considering how these functions might be manipulated or augmented (Chapter 6). Increasing the availability of metabolic resources for the executive functions involved in mental health strategies might influence the efficiency with which they are carried out in clinical populations that tend to exhibit executive deficits. Although cognitive training paradigms potentially hold an important role in improving performance on executive function tasks, a more practical approach to influencing the availability of metabolic resources in the PFC is from the ‘bottom-up’ through physical activity (Kahneman, 1973). An amassing literature on the effects of exercise on cognition has tended to show that, unsurprisingly, exercise is beneficial to cognitive functions (Pontifex et al., 2019). A general effect of exercise on cognition is processing speed: People can process information more quickly, but only for a limited period of time (~30 minutes). These effects are thought to relate to the metabolic effects of exercise on the brain, such as the upregulation of oxygenated hemoglobin. However, it is unclear whether these increases in concentration are specific to the subregions on which a given cognitive task places resource demands or global in the sense that there is a general change in signal across all subregions. Therefore, for the first time, the acute effects of exercise on the PFC were investigated using a portable fNIRS system and executive function tasks that were specifically designed to measure the rostral attentional gateway system of BA10.

As demonstrated in Chapter 6, over one hundred participants were tested on executive function tasks that measured response inhibition and attentional monitoring, as well as stimulus-independent and oriented-thought, after completing a VO_2max test. All experimental conditions comprised the factor ‘Speed’, representing the speed of information processing that all executive functions share, and the attentional mode conditions constituted an ‘Attention’ factor. As regards the individual executive functions comprising these variables, they showed activation patters that were specific to the subregions in which they are typically implicated. For example, the stimulus-independent thought condition recruited only lateral rostral PFC (BA10). However, the broader constructs of Speed and Attention showed a much larger number of channels spread across multiple PFC subregions. These patterns of activation were also found when comparing these contrasts to a control group (Figure 6.8). So, the utilization of elevated resources was spatially specific when tasks placed demands on individual executive functions, and a more global use of metabolic resources in the PFC was found when examining features that are shared across executive functions (i.e., broader functions formed from a network of areas). Therefore, exercise might affect the global supply of metabolic resources in the PFC as well as have specific effects on their consumption depending on the tasks used in an exercise neuroscience paradigm; that much of the PFC would not be upregulated for individual executive functions makes sense in terms of an efficiency perspective at the level of information processing. Behaviorally, it is plausible that the shift towards speed might come at the cost of accuracy, but this was not the case for the tasks used in the present work; however, accuracy for the SIT condition might not be as precise as the other accuracy computations, since there was know way of knowing which trial people were on in their minds. If there is a trade-off, its size might depend on the type of cognitive functions in play.

Although most people showed a positive change in PFC activation after acute exercise, those with more depressive symptoms showed a relatively decreased effect across all tasks. More specifically, smaller activation changes in right inferior frontal gyrus (BA44/45/47) predicted greater levels of depression. This might be an indication of what is already known about the tendency of people with mood disorders to have hypoactivity in the PFC during cognitive control tasks (Rive et al., 2013), but what it does not suggest is that such people will fail to benefit from physical activity as a means of ameliorating psychopathological symptoms and executive deficits. After all, acute exercise improved processing speed in the PFC by ~10% for all participants, and it could be that *repeated* exercise—rather than a single bout—is what is requisite to close the gap in terms in differential activation. Interestingly, increases in fitness (e.g., aerobic) are the expected outcome of repeated or habitual exercise and, in this study, participants with greater levels of aerobic fitness showed greater activation in right rostral PFC. That is, the positive change in PFC activation across all tasks was greater in this subregion for those with higher VO_2max scores. Thus, physical fitness resulting from chronic exercise is potentially an impactful factor with respect to the availability and utilization of cognitive resources in the PFC, such that repeated exercise plausibly works to correct issues of hyper- and hypo-activation in the brains of individuals with diminished mental health.

Interestingly, physical activity could be an important behavioural component in mental health interventions, and not in the sense that has already been under empirical investigation (McArdle, McGale, & Gaffney, 2011, 2012). Namely, exercise might not best consist as a complementary element of treatment. Repeated, vigorous physical activity outside clinical environments is beneficial to people across several dimensions of well-being, but interventions strategies—which are now understood to tap executive functions—do not get to benefit from the acute effects of such activity within clinical environments. This means that, therefore, most mental health interventions are probably too physically stagnant. Getting the body moving and 'blood flowing' whilst clients are tasked with learning and carrying out mental health strategies is probably better than sitting for approximately an hour. So, it could be the case that the influence of exercise on decreasing psychopathological symptoms is optimized to the extent that an exercise also requires of an individual the executive functions that are integral to the cognitive change strategies that drive future efforts to downregulate negative affect. This is strangely consistent with the evolutionary perspective that exercise is most beneficial to the mind when it is combined with cognitive demands that exceed those required to sustain it (Raichlen & Alexander, 2018). The practical corollaries of this are that clinician-prescribed exercise, as a complementary component of treatment, should involve mental health exercises that are carried out in parallel, and that clinics would need to be equipped with machines such as stationary bikes, stair climbers, and so forth. Thus, using exercise as a ‘bottom -up’ approach to improving executive functions that are relevant to cultivating mental health is a distinct possibility, but this clearly warrant further investigation.

8.7 A brain-first approach to recovering stimulus designs

Future cognitive neuroscientific research on clinical interpersonal interactions in real treatment settings, and the integration of exercise and its effects on these interactions and outcome measures, will need to be prepared to address the stimulus design problem (Chapter 7). The need to interact with a computer (e.g., keyboard, mouse, joystick, etc.) likely represents a needless distraction from the social tasks of interest, and this requirement for participants places demands on the cognitive system which are not of interest (e.g., maintaining the intention to press a button at particular moments during interactivity). It was argued that using a ‘brain-first’ approach to experimental design replaces the need for computer mediation: Rather than contriving an ecological situation for an *a priori* stimulus design, this approach—the Automatic IDentification of functional Events (AIDE) method (Pinti et al., 2017)—recovers stimulus designs from authentic, real-world situations. Specifically, it detects functional events in regions of interest from observed changes in local concentrations of oxygenated and deoxygenated haemoglobin. The validity of applying this analysis method to recover functional onsets from real-world data across multiple individuals (reliability) was investigated using a portable, wearable fNIRS system.

The adopted paradigm was one that tested the executive functions involved in prospective memory (PM) tasks (McDaniel & Einstein, 2000), so rostral PFC (BA10) was the region of most interest. It also required participants to complete these tasks in a real-world environment (i.e., without computer mediation), namely around the streets comprising Queen Square in downtown London, England. It was found that maintaining future intentions generally recruited rostral PFC, particularly the lateral aspects of BA10 (Burgess et al., 2022), which is what would be expected of this area in this type of paradigm (Burgess, Scott, & Frith, 2003). But when the nature of these future intentions was inherently social, greater resource consumption was found in not only BA10 but also dorsolateral PFC, specifically right BA46. This potentially reflects its functional specialization for strategic monitoring, because social intentions are likely ascribed greater semantic importance than non-social ones, which is consistent with evidence for a ‘social superiority’ effect (Penningroth, Scott, & Freuen, 2011). When the individual onsets of functional events in these PFC subregions were detected using AIDE on the observed fNIRS data, the general aggregation of condition-specific events across the physical space in which participants completed the PM tasks (i.e., event distribution) suggested that these functional events indexed task-related processing. The frequency and rate of these activations further validated the brain-first method, because event frequency was greatest in BA10 compared to BA46 and event rate was faster or slower in different environmental locations, respectively. Thus, the executive events recovered from the rostral and dorsolateral PFC data were non-random.

These novel PFC findings showing spatial-temporal dynamics of functional activation in a real-world setting would not have been possible without this *a posteriori* approach to ecological neuroscience, together with the wireless neuroimaging technique. This approach therefore represents a promising future direction towards developing experiments that better account for the environmental and social complexities inherent to naturalistic paradigms in cognitive neuroscience. Although it seems to address the stimulus design problem, some computer mediation might be required in future research to further validate AIDE. For example, future research not involving aspects of navigation—and, therefore, spatial distributions of events—might test AIDE by assessing event frequency between subregions of interest during tasks derived from traditional experimental psychology. New works could also focus on determining if brain-first approaches can be improved to involve the classification of detected functional events into particular operations of information-processing systems (e.g., intention creation, maintenance, retrieval, & execution). That is, distinguishing between event types would potentially improve the specificity of brain-first approaches. With respect to future research exploring the potential applications of this approach, the application of AIDE in clinical paradigms involving interpersonal interactions might be useful in its ability to recover the onsets of complex social behavior—behavior that ought not be interrupted with a human-computer interaction.

8.8 Conclusions

This thesis examines the role of the PFC in human higher cognition using the relatively new method of fNIRS. More specifically, it proposed that the verbal communication that forms the crux of non-pharmacological treatments for mental illness (Crum, 2019) depends on a mental ability that consciously works out whether evaluations about the self, others, and world ought to be epistemically rejected: recogitation (Crum, 2021a,b). From a cognitive neuroscience perspective, this weighing of the tenability of beliefs and appraisals about goal-related things constitutes a form of open-ended human problem-solving that uses metacognitive and reasoning faculties. Because these faculties share similar executive resources, the proposed model of this cognitive procedure hypothesizes that, neurobiologically, the modulatory functions of PFC subsystems, such as those that bias activation in favor of stimulus-independent attention (BA10) and that check or test hypotheses (right BA46), should therefore support recogitation. A significant role of the PFC during verbal interventions strategies was demonstrated using fNIRS-based hyperscanning. Specifically, rostral PFC (BA10) showed a marked degree of activation when participants needed to silently generate reasons for why appraisals were irrational, with right dorsolateral PFC (BA46) being recruited to a lesser degree (Crum et al., 2022a). This was consistent with predictions and suggested that the recogitation subtask placed significant demands on the cognitive operations for which these subregions are functional specialized; however, future research will need to assess whether this remains the case when using clinical populations.

It was then shown that some of these cognitive operations into which recogitation potentially fractionates can be perturbed in a positive way. Namely, an acute bout of exercise in over one hundred participants showed relative increases in activation in the PFC during executive function tasks, particularly those requiring attentional monitoring, response inhibition, and attentional biasing. The general effects that were observed across all executive function tasks were bilateral activation changes in dorsolateral (BA46/9), ventrolateral (BA44/45), and rostral (BA10) PFC, with the greatest changes occurring in right BA10 and BA46. In addition, there was a general increase in processing speed (~10%) across all experimental conditions. These findings highlight the positive link between exercise and cognitive functioning. Interestingly, it was also found that people with more depressive symptoms showed a smaller effect of acute exercise on these PFC subregions, but those who were more aerobically fit showed the opposite relationship (Crum et al., 2022b). Therefore, exercise could be a ‘bottom-up’ approach to upregulating the availability of executive resources that are tapped in mental health interventions. Although exercise could help to counteract executive deficits and hypoactivation in clinical populations, the effects of acute and chronic exercise on the specific ability to reason about propositional attitudes relating to the self, others, and world remain unclear.

So, a new vein of research at the crossroads of clinical psychology and exercise neuroscience is empirically feasible. However, if future paradigms are to be ecologically valid, researchers will need to develop or adopt experimental designs and methods that make it possible to study interpersonal interactions in real-world settings. This is because the stimulus designs that are typically used in cognitive neuroscience are determined *a priori* whereas the onsets and durations of behavior in genuine clinical interactions are not. Rather than endeavoring to account for all the complexities of the real world in an experimental design, a more advantageous approach might be to recover the experimental design from the real world—that is, to use an *a posteriori* approach based on observations. To address this ‘stimulus design problem’, the present work investigated the validity of such an approach using group data that were collected during a real-world executive function task (prospective memory). Functional events were detected from areas of the PFC that are commonly recruited during this type of task and, what is more, the frequency and rate of these PFC events were not random (Burgess et al., 2022). For example, they aggregated around task-related stimuli within the spatial environment (Figure 7.7).

These findings represent a promising direction towards neuroimaging research that is not conducted through computer mediation.

All in all, the theoretical, methodological, and empirical contributions of this thesis have brought new scientific insights to long-standing questions in philosophy and psychology, such as the neurocognitive mechanisms driving the ‘transvaluation’ of human belief systems (Nietzsche, 1883/1995). Understanding these mechanisms and how they work together to cultivate psychological well-being at the levels of information processing and the brain will bring clinical cognitive neuroscience closer to one that explains how people participating in mental health interventions not only get better as a function of treatment but also *stay* better in everyday life.

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