THE EFFICIENT BRAIN
ON HOW CONNECTIVITY MODULATIONS UNDERPIN COGNITIVE TASKS

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INTRODUCTION

This thesis is about the functional organization of the brain during cognitive performance and addresses the efficiency of this organization by looking at variations within an individual throughout human development. As such, I present a new viewpoint on how brain function supports and integrates knowledge across cognition. To this aim, this thesis introduces a novel method for the examination of changes in communication between brain areas. I further validate the utility of this new perspective and method in understanding abnormal development and investigate how alterations in this functional organization can be linked to multiple current theories. In order to understand the construction and advantages of developing this new method, this introduction will review the knowledge and methods that are used to study brain networks underlying cognitive processing and how they relate to maturation mechanisms during human development. We will end by outlining the aims of this thesis and the content of the subsequent chapters.

INVESTIGATING INFORMATION PROCESSING IN THE HUMAN BRAIN

Cognitive functions interact by exchanging information across complex and distributed networks of brain areas (1,2). Early neuroanatomy studies aimed to determine the general organization of the brain and the role of each brain area (3). By examining post-mortem brains, these studies tried to disentangle brain areas in terms of differences in their cellular composition, or cytoarchitecture. Resultant structural definitions of brain boundaries and histology-based atlases contributed to the identification of neuroanatomic locations across studies of patients with brain injuries, thus linking loss of cognitive functions to certain damaged areas. The arrival of multiple non-invasive tools to measure brain activity, such as functional magnetic resonance imaging (fMRI) (see fMRI box), provided the opportunity to study in-vivo brain functioning during task performance. In an effort to assess if brain areas have specific cognitive functions, researchers began to observe activity changes in brain areas of
study participants while performing various cognitive tasks in an fMRI scanner. Brain research was therefore no longer limited to searching for patients with specific cognitive impairments.

**fMRI**

Magnetic Resonance Imaging (MRI) capitalizes on magnetic properties of hydrogens atoms and aims at capturing variation of magnetic field. Oxygen, when bonded with two hydrogen atoms, is of particularly interest and can be selected from a specific frequency of the magnetic signal captured by MRI. Indeed, oxygen navigates the body via the vascular system and is consumed by cells to produce energy. Functional MRI (fMRI) captures changes in blood vessel oxygenation, hypothesised to be associated with oxygen consumption by brain cells and used as a proxy to study neuronal activity. This signal, the Blood Oxygen Level Dependent (BOLD) response, is an indirect trace of neural activation and is delayed from the actual neural activity. This response curve, the haemodynamic response function (HRF) (4), starts with a decrease in oxygen levels due to neural consumption, quickly followed by blood vessel dilatation from the action of other brain cells, i.e. glial cells, which act as a support for neurons. The most important glial cells of this response are astrocytes. Their action increases blood flow and changes the electric and chemical balance of the blood vessel environment, enabling oxygen to flow across cell membranes along an electrochemical gradient and thus replenishing intracellular oxygen. The HRF is used as a model to detect neuronal activity following an event that participants experience in the MRI, e.g. presentation of an image during a task. The brain’s BOLD response is modelled and compared to the BOLD signal and corrected for the observed baseline signal. Such analyses aim to define areas by following a significant response to the task event (5,6). The most common resolution for fMRI is 3mm³ in space and 2.4s in time for a 3T research scanner.

After years of task-based fMRI studies, researchers began to realize that only few areas seemed to have a specific function, whereas groups of areas showed greater specificity for certain cognitive functions (7,8). They started to move away from localizing function in the brain, i.e. segregation, towards the study of networks and how regions coordinate
and exchange information, i.e. integration (9). One way to study the activity of and interaction between functional networks is to examine the structural connectivity as the biological substrate of information processing in the brain. Neurons exchange information through synapses between protoplasmic extensions: axons send and dendrites integrate signals. Axons compose the white matter of the brain and connect neurons across the brain by grouping into bundles, forming white matter tracts. They can be studied by looking at diffusion properties of brain tissues using other MRI-based techniques, such as diffusion-weighted imaging. Aside from structure, one can also look at the coactivation of brain areas to estimate their functional connectivity (FC) (10). Though temporal resolution is low, as in fMRI, it is assumed that two areas coactivating in time are most likely involved in the same network. We can therefore study the information exchange between areas, evaluate which networks respond to tasks events, and investigate the numerous intricate subprocesses that occur during a task event--from perception to response (2,11). A number of networks have been characterized as a result of task studies. An exploration of co-occurring activation across studies has also been performed to validate these networks (12). Co-activation of areas can also be studied without tasks. By simply asking participants to rest without requesting them to engage in specific cognitive activity, we now know that the brain is never at rest and that functional networks are always active (12–16). In fact, almost all functional networks that are well-known from task-based studies have also been observed through the analysis of resting-state MRI data (12). From resting-state activity, i.e. baseline activity free from task performance, we can disentangle which brain activity orchestrates information exchanges within and between networks, specifically during cognitive processing, also known as functional connectivity modulation. Once this modulation layer is defined, we can compare brain responses across cognitive tasks and experimental conditions, thus dividing typical brain activity from that which is specific to a certain cognitive process and validate the existence of sub-networks.

In this thesis, I focus on using FC acquired through fMRI to describe cognitive networks and I define how to ascertain their interactions in response to task performance. I aim to develop a framework that establishes task-related FC modulation relative to a common baseline of processing that is assumed to be represented in the brain at rest. The so-called “task potency” resulting from this framework is computed as the
amplitude and localization of connectivity modulation in response to the task. By standardizing FC to a normalized baseline, we can then compare tasks and clarify task relatedness through unique and shared modulation. Defining these modulations will shed light on which elements impact multiple cognitive domains, as well as how one deviant mechanism can cascade into complex and multiple divergent behavioural responses that result in clinical symptomatology.

Patients with psychiatric disorders present with complex clinical symptomatology and multiple cognitive impairments. By comparing healthy participants to clinical populations, we want to gain new insights into whether impairments result from the alteration of either a core brain mechanism or a set of independent mechanisms. While only a larger and task-specific dysfunction might be revealed when evaluating cognitive tasks independently, the task potency framework described here provides a new angle for studying complex disorders and integrates results across tasks that target different cognitive impairments. In this thesis, I use this newly developed framework to estimate the task FC of healthy participants and compare it to those of two populations with neurodevelopmental disorders: Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) (see ADHD and ASD boxes). Using multiple tasks where clinical subjects exhibit underperformance, we establish and compare the shared and distinct connectivity patterns across tasks with the aim of discovering a core pattern of connectivity present in the healthy population that is altered in the clinical population.

An important aspect of studying FC in neurodevelopmental disorders such as ADHD and ASD is determining whether or not functional connectivity varies across development and how maturational mechanisms interact with the outcome of developmental disorders (17–24). Recent theories about normal development such as interactive specialization and neoconstructivism propose that cognitive functions mature and specialize by interacting with each other (25,26). The maturation of one cognitive function is then partly related to the maturation of other cognitive functions. In such cases, one can imagine that the neural pathway shared by two cognitive functions can be key to this interdependent maturation effect. In this thesis, I investigate the common neural correlates of cognitive function and their relative maturation in healthy subjects. Validating these theories unlocks new hypotheses on how deviant pathways shared by multiple cognitive
functions can progressively impact the maturation of multiple cognitive domains, resulting in multidimensional disorders.

**ADHD**

Attention-deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with an onset that mostly occurs early in life, followed by a strong persistence throughout development into adult age (27,28). The key defining symptoms are a pattern of inattentive and/or hyperactive-impulsive behaviour that can be represented as predominantly inattentive or predominantly hyperactive, or combined inattentive and hyperactive. Symptoms lead to impairment of functioning in important domains of daily social, academic or/and working life. The prevalence is high with 5 to 7% of children and adolescents diagnosed and 3% of adults diagnosed (27). Symptoms can fluctuate across the life-time and cases of remittance, persistence and late onset/diagnosis can be observed in the population (29). The disorder often co-occurs with other developmental disorder such as ASD (30 to 50%) (30–36).

Along with symptoms, ADHD is also characterized by multiple cognitive impairments, most notably reward processing and executive functioning (37) and motor difficulties (38,39). Within the umbrella of executive functioning, we’ve found that the three basic cognitive functions--inhibition, cognitive flexibility and working memory (40)--are all impaired in ADHD (41–45).

**ASD**

Autism Spectrum Disorder is a lifetime persistent neurodevelopmental disorder with symptoms that are frequently detectable as early as 3-4 years old, and with a prevalence of 1-2% in the population (46). It is characterised by problems in three dimensions of impairment: reciprocal social interaction (verbal and non-verbal communication), restricted and rigid patterns of behaviour and interests, and abnormal sensory processing. Across the spectrum, individuals can demonstrate a low or high IQ and be verbal or non-verbal.
In terms of cognitive impairment, there are several core axes of dysfunction. Prominent theories include the empathizing-systemizing hypothesis – related to a tendency in autistic patients to interpret events based on few observations and create over-generalized rules (47). Because of low executive processing performance, ASD has also been linked to an executive dysfunction hypothesis (48). Additionally, both lower empathy and executive functioning skills have been tied together in the mind dysfunction theory, which posits that patients with autism lack cognitive flexibility and project their own emotions and perceptions on others in order to interpret someone else's behaviour (49). Alternatively, according to the weak central coherence hypothesis, autistic patients integrate only the nearest information available to interpret their environment (50).

Comorbidity with other disorders is highly present in the ASD population, with as high as 81% co-occurrence for psychiatric disorder (51,52), mainly ADHD, anxiety disorder, depression and epilepsy.

FUNCTIONAL CONNECTIVITY UNDERLYING COGNITIVE PROCESSES: A CLOSER LOOK AT TASK-POTENCY

FUNCTIONAL CONNECTIVITY VERSUS ACTIVATION
In fMRI, we measure the local changes in oxygenation level called Blood Oxygen Level Dependent (BOLD) signal, representing the changes in blood flow supplying active neurons in the brain with fresh oxygen (4,53) (see fMRI box). Depending on the resolution of the scanner, the BOLD signal is measured in 1, 2, or 3mm³ voxels of the brain. As the BOLD response is assumed to reflect the average consumption of oxygen by cells, it is regarded as a proxy for neuronal activity which requires a supply of oxygen. Because neurons fire regularly to process information or simply to maintain their functional networks, the BOLD signal is very noisy (54,55). Neuroscientists have designed experiments using cognitive tasks which contain specific events that a participant performs inside the scanner in order to average BOLD response across task trials and isolate robust neuronal activity-related BOLD changes. These so-called
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“activation studies” compute the average activity of a subject’s brain during that event against the baseline activity of his/her brain (56).

In comparison to activation analysis, studies investigating FC aim to capture coactivation of brain areas—when two areas exhibit similar changes in BOLD signal (57). Since neurons are connected to each other and exchange information through electrochemical signalling across the brain within a short timescale, the coactivation of brain areas is assumed to reflect this exchange of information, thereby yielding networks of brain areas involved in processing information.

**RESTING STATE ACTIVITY AND FUNCTIONAL ARCHITECTURE**

FC is readily available information extracted from the BOLD signal and can be analysed without a cognitive task by acquiring resting state scans where participants lie awake in the scanner with eyes fixated on a cross, or with eyes closed for a minimum of 10 min. Resting state analyses show that brain areas coactivate in networks at all times (12,58–60). The brain is spontaneously active and processes internal signals that comprise uncontrolled silent thinking, mental imagery, monitoring of body posture, fluctuation of vigilance, arousal or attention; even during sleep, at no point is the brain not performing a cognitive operation, for example, the brain continuously processes information and memories (61–63).

From resting state analyses, statistical methods can extract maps of the brain that show coactivating voxels. Some of these maps are clearly related to noise resulting from head motion, movement of cerebrospinal fluid around the brain and in ventricles, or cardiac rhythm or respiration (64–69). Other maps correspond to biologically and functionally relevant networks which can be confirmed through comparison with previous brain meta-analyses (70–72). These maps describe well-known networks such as attention, motor, or visual networks (12). This suggests that the brain’s main cognitive networks are active at all times, thus shaping brain activity into a functional network architecture that we now further consider as the functional baseline activity of the brain.

**USING TASK TO STUDY THE ONTOLOGY OF NETWORKS ACTIVITY**

Because resting state data reveals ordinary functional organization of the brain, we can test how task activity builds upon this baseline architecture.
While engaged in a task, the brain’s activity does not simply flow from a fixed functional organization. Previous studies of changes in FC from resting state have demonstrated that these alterations are meaningful and can be used to predict tasks or differentiate between mental states (73–77).

To study FC during a task, researchers use the same methods as those in resting state studies: seed connectivity or element-wise correlation (57,78). Because task-fMRI acquisition and participant behaviour are constrained by task design, methods are adapted to analyse FC in relation to cognitive events by using differences between task conditions to parse specific cognitive processes. For example, the BOLD response can be modelled for each event resulting in a beta map and the co-activation of areas for a specific task event can be estimated using beta time-series across events of a certain condition (79). Unfortunately, tasks often do not include enough trials to satisfy FC power analysis requirements. A correlation needs to be estimated with a minimum of three points per pair of nodes in order to give enough independence between each value in a connectivity matrix. The length of the time series must be adjusted according to the number of parcels included in the correlational analysis. A regularization method can be used to approximate correlation or covariance matrices, enabling the reduction of the number of time points; even when considering the full time series, the size of the matrix rightly estimated would be low (57).

However, the aforementioned method only accounts for modulation of connectivity following standard BOLD activation response. The expected connectivity modulation is not yet fully known as exploring FC during task acquisition involves other caveats and considerations. For example, recent methodology studies have investigated whether task design can induce spurious time-constrained correlation between areas (80–82). Following the discussion of our proposed framework and results in Chapter 1, these factors will be revisited throughout this manuscript in an effort to bring new insight into the understanding of task-related FC modulation.

In our framework, we consider the resting state as the baseline of functional architecture (12) and use it to increase our sensitivity for task-
induced changes of FC. Therefore, modulation from resting state can be defined at the individual subject level, enabling control for individual differences in baseline FC and comparison of task modulation in a standard space. We can then start to disentangle multiple processes in the brain during a task by assessing if some neural pathways are activated in either multiple tasks or a unique task. For example, we might observe similar degrees of modulation during motor response, visual processing, or attention that are not task-specific but are present across all tasks. Task general connectivity was also proposed in several investigations (77, 83). This further supports the idea that we can find not only common subprocesses across tasks but also task-specific modulations of connectivity.

In this thesis, I investigate the sensitivity of these modulations for task designs, as well as their potential for informing us about cognition. I focus on the full acquisition time series to create a task connectivity profile, referred to as the ‘task fingerprint’, and to gain understanding about the information exchange between networks while solving a task. The global effects of a task must first be characterized before delving further into subtle alterations that arise from task design.

MOVING FROM A BEHAVIOURAL TO A NEURAL DEFINITION OF COGNITIVE UNITS
To relate FC modulation to cognition, a proper definition of the relationship between cognitive processes, the task protocol, and behavioural observation is required. Indeed, investigating the neural correlates of behaviour (e.g. individual subject task performance or questionnaire response) is constrained by what we are able to observe (84–86). However, several brain mechanisms are active during behavioural observation. For example, it is possible to predict a plateau in memory performance from whole-brain connectivity, where only half of the information used for the prediction comes from the connectivity between areas activated during the memory task, such as the left fronto-parietal network (87). In this regard, behavioural measures would erratically correlate with neural activity, yielding the specificity of these brain mechanisms as inaccessible.
Neuroscientists design and compare cognitive tasks with multiple trial conditions to access neural correlates of a specific cognitive process (9). While this method approximates neural specificity, it remains dependent on the definition of cognitive states from a behavioural perspective. Definitions of neural mechanisms can be very different from those of actual observable behaviour. This approach for investigating a one-to-one mapping of behavioural-to-neural processes is therefore limited. Furthermore, this relationship might not be linear, which adds a level of complexity when researchers want to model effects of task parameters. For example, the number of visual inputs is not linearly related to the amplitude of neural activity (56).

Although a task may be designed to study a cognitive function, it may still not be specific to that function. For example, in an n-back task, participants see a series of stimuli. When a stimulus appears twice with precisely N stimuli in between the two presentations, the participant is expected to answer (88). While this task is categorized as a “working memory” task, the stimulus presentation is fast enough to require high, sustained attention at each moment of the task. The participant must stay focused on the series and constantly update his/her memory span (89). Additionally, the N-back task is a test for inhibition as it requires subjects to not respond when presented with the same stimulus twice, but only when the presentations of a stimulus are separated by the correct number of intervening stimuli. One project described tasks as a function of all known cognitive components that the task elicits: The Cognitive Atlas (84). Using the framework proposed in this thesis, we can compare tasks to highlight common and task-specific processes in order to disentangle brain mechanisms from behavioural correlates.

FROM NEURAL CORRELATE TO BEHAVIOUR: SENSITIVITY, SPECIFICITY AND REVERSE INFERENCE

By moving away from investigating a single task and its behavioural correlates, we take on another viewpoint of brain mechanisms while avoiding the limitation of the number of behavioural outputs available. These behavioural outputs depend on what we are able to create within a task design and still do not fully describe the cognitive mechanisms involved in a task. For example, in a working memory task, control trials
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in which the participant receives the same visual stimuli without memorization only controls for the visual system, but not for the participant’s level of attention in comparison to the working memory condition (90,91). The attention network is sensitive to the working memory task; it is detected in many tasks and is therefore not specific to the working memory task. At a more conceptual level, any neural correlate observed in a task is only sensitive to that task; forward inference analyses only describe neural responses following a stimulation (56). The same local activation can be evoked through multiple cognitive processes that are common to different tasks. For instance, the frontal area has a well-known link with the working memory network, but was also found to be activated by other neural processes and is thus not specific to working memory (92). When we analyse variation in BOLD response to a task design, we are dependent on many factors such as the task-design itself and variability between subjects or scanners. These dependencies limit our ability to directly compare activation differences across tasks (56).

To generalize results, we must access neural activation specificity through reverse inference analysis and define cognitive processes evoked by a task on the basis of the observed neural correlate. Such an inference cannot be solely based on results from a forward inference analysis of a given task, but must also describe the specificity of results (56). Studies have tried different methods to investigate specificity of neural correlates to enable reverse inference (8,93). Attempts to link neural activity with a specific cognitive state are not based on entirely erroneous assumptions and do, in fact, originate from the first studies of neuroscience and the injured brain. The observation that damage to an area results in the disappearance of a very specific cognitive function is certain proof that an area is essential for this function. Nonetheless, this observation does not demonstrate unique specificity of function (56). To obtain the necessary evidence of specificity between neural correlates and cognitive function, researchers are particularly interested in patients who present “dissociation”, where a unique injury impairs a specific cognitive function, but not another. However, this method is limited as it is dependent on available patients (94). Nowadays, reverse inference analyses are used in an effort to look back at a range of neural correlates
induced by tasks and to quantify common localization. For example, this quantification can be done by data mining of literature. Nevertheless, due to literature biases induced by article imprecision or p-hacking, these methods remain imperfect (8). Two examples of coordinate-based meta-analyses of fMRI activation studies are BrainMap (71,95,96) and NeuroSynth (97). To quantify the specificity of a signal, literature revision can be combined with probabilistic methods such as Bayesian analysis (Poldrack, 2011). We can therefore better account for some literature bias, such as the number of publications with hypotheses based on region of interest (ROI) analyses. Specificity can also be estimated by testing its predictive power in independent data using machine learning algorithms, including the prediction or decoding of mental states using large scale pattern analysis, or classifier training at the individual level to predict naturalistic stimuli within and between subjects (8,72,93,98). While the results of prediction algorithms in a naturalistic signal are impressive, the procedure is burdening for participants as it requires a lot of acquisition time to train the algorithm and therefore can’t be easily generalized.

Comparing tasks and defining the building blocks of the brain could provide a representation of cognitive mechanisms and states to use as models in studying dynamic change within a naturalistic signal. Some specificities, such as age-related variation, can be characterized; these representations should be accounted for in individual specificities.

NETWORK MATURATION AND INDIVIDUAL DEVELOPMENTAL TRAJECTORIES:

FUNCTIONAL CONNECTIVITY MATURATION

Brain structure and activity are shaped by genetic, developmental and environmental mechanisms. For example, genetic expression in the womb is regulated in time and drives subsequent cortical folding (99) in a series of key biological events (100). After birth, several behavioural developmental stages (101) are associated with important changes in the brain (102). Age-related brain changes are diverse, such as thinning of
grey mater, white matter maturation or functional maturation (18). This vast range of brain maturation results in a network organization that involves neurons from distant brain areas exchanging and integrating information. Through network activity, I aim to investigate how network architecture develops, matures, and performs in different cognitive states.

Age-related variations are an essential part of the understanding of brain mechanisms and brain organization. Indeed, FC is one of the features of the brain that needs to mature during human development. Some studies have observed maturation at the third trimester of pregnancy (103,104) in preterm babies and, after complex 4D movement correction (105), others have visualized the existence of a Default Mode Network (DMN) in the human fetus in-utero (106,107). Later networks develop by segregating activity between local areas and integrating activity from distant areas of a network, displaying stronger connections between these areas (19,108–112). These changes in connectivity have been used to construct a developmental curve of brain maturation, (113) showing that the brain’s FC matures through young adulthood. Studies have found rapid changes between 4 and 13 years old, followed by slower maturation in the prefrontal cortex closer to adulthood, particularly involving densely connected areas called ‘hubs’ (19,111,114,115).

These findings suggest that important processes in brain development involve pattern organization of inter-regional interactions. More precisely, there are changes in structural connectivity and FC that have been integrated into several principles as summarized by Menon (116): A small-world organization emerges with local strong connectivity hierarchically connected to a backbone of hubs, increasing long-range connectivity at the cortical level, enhancing the efficiency of functional networks, and shaping cortical-subcortical communication (18,19,102,103,106,108,112,114,115,117–123).

The aforementioned connectivity changes match the specific time-windows of maturation of cognitive skills and higher cognitive functions. For example, reward processing and inhibition change during adolescence in parallel with the maturation of frontal activity (124–129). To investigate age-related neural changes, one must first validate that
these changes are related to cognitive and behavioural maturation; investigating changes in the functional organization of the brain using resting state is not sufficient. Although functional architecture supports activation during a task, changes in baseline structure affect brain response during cognitive performance (74,130,131); therefore we cannot yet capture the underlying mechanism and establish a direct link to cognitive performance. Instead, we must study cognitive performance during tasks with which we can establish that task-relevant networks display developmental changes. For example, in a working memory task (121,132), children recruit a broader network compared to adults, demonstrating a network maturation toward a more defined and specialized organization (126,133). Such a refined network might be more efficient as it matures together with an improvement in working memory span with age (134). This efficiency can be linked to less energy consuming pathways and/or a better, quicker integration of information. Additionally, these tasks might be more challenging for children because they require the use of such a broad network (135).

Thus, I will use the framework described in this thesis to disentangle age-related changes in functional architecture from task-related age effects in order to better understand the link between baseline and cognitive modulation across development.

**THEORIES OF HUMAN DEVELOPMENT**

The understanding of human cognition is invariably linked to understanding cognitive maturation and brain development. Multiple theories updated the principal work of Piaget (101) to explain the maturation of cognition and cognitive abilities (25). One recent developmental theory is the Interactive Specialization Theory, in which maturation of cognitive function is a slow and progressive process, challenging the idea that skills suddenly come “on-line” according to timed mechanisms (26,136,137). An update of that theory, the Neuro-Constructivism Theory, proposes that this progressive maturation is based on learning processes (138,139). These theories were used to create models of development and explain behaviour. For example, Schultz et al. successfully simulated Piaget’s stages of development (140).
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The establishment of neurobiological evidence for these developmental theories requires bridging the gap between theoretical concepts and neural features.

The Interactive Specialization Theory states that cognitive functions interact throughout maturation. For instance, the development of working memory and speed processing skills are predictive of language maturation (141). In practice, if we assume these interactions to be an exchange of information between cognitive networks, we can then link the theory to changes in FC during development. To verify this hypothesis, we must investigate changes in network interaction during task performance as a function of age.

As a second concept, the Interactive Specialization Theory proposes that maturation is a combination of planned biological, experience-induced, and learning-induced changes—a statement supported by training experiments (142,143). For instance, during memory maturation, knowledge emergence can be modelled as building upon prior knowledge (144). To understand brain maturation, we need to look for underlying common neural correlates of cognitive skill development, thus uncovering how multiple skills interact with each other. In Chapter 3, I explore the use of our framework to detect common maturational effects across multiple tasks.

Abnormal Development

In patients with neurodevelopmental disorders, the growth trajectory of brain connectivity deviates from normal (20,145–148). Developmental mechanisms can be altered or pushed to adapt to strong individual differences that can be intrinsic to the individual, such as a genetic mutation, or can be external and interact with key developmental processes. For instance, exposure to Zika virus during pregnancy is considered an external cause, highly correlated with altered development of the foetus and results in microcephaly (149). Alteration of brain maturation might result in changes in the perception and integration of, or reaction to, the environment - manifestations of which are observable in patients from an early age.
Because key developmental events arise in specific time-windows, the onset of a deviation from normality can be observed at particular ages, thus enabling the observation of early symptoms. A child can be clinically diagnosed with autism or ADHD as early as 2-2.5 years old or 4-5 years old, respectively (150,151). One of the theories on the aetiology of ASD is that the ratio of inhibitory to excitatory neurons in patients is different from that of the general population, resulting in altered information processing (23,152–155). As the brain continues to mature and children learn from life experiences, either specific compensatory strategies develop, or other abilities worsen, moving the individual farther away from the normal developmental curve. This chain reaction can partly explain the heterogeneity of ADHD and ASD (145,156). An additional theory of ASD is that individuals perceive the world differently due to altered activity of sensory networks, hence, the whole brain learns and matures by experiencing the world in a different way (157–160). Consequently, this may shape functional networks that are still in maturation, wherein brain networks of ASD patients segregate and integrate information differently from those of their healthy peers.

The interpretation of differences between healthy and abnormal development requires integrating multiple developmental mechanisms and examining how they result in functional alteration. If the maturation of various cognitive functions is interrelated, as proposed by the Interactive Specialization Theory, then developmental alterations in one cognitive function will interact with the maturational processes of related cognitive functions in a chain reaction, resulting in a very complex deviant profile (20,156,161–164). Developmental disorders such as ADHD or ASD fit this hypothesis as they present a complex symptomatology, covering multiple cognitive domains. If a unique cause can explain each of these disorders, then it must be a primary mechanism that may branch into the disruption of the maturation of multiple cognitive functions. In this regard, understanding maturational relationships between cognitive functions is key to understanding developmental trajectories and how a deficient mechanism can longitudinally result in an overall abnormal trajectory.
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Because development is a long process which involves interactions with the environment, each individual develops slightly differently—these differences accumulate and progressively amplify a child’s divergence with age (164,165). In developmental disorders, failure in cognitive performance can be handled by each individual differently by using a unique strategy (24,45,166–169). The use and reinforcement of diverse, independent brain paths increases within-group heterogeneity. Even in a remittent population, individuals may use very efficient alternative strategies or undergo a restoration of normal cognitive processes. Over the last few years, studies characterized changes in network connectivity in typically and atypically developing populations (110,111,170–173). However, due to very similar general functional organization, small sample sizes, clinical heterogeneity, different analysis methods, different preprocessing pipelines, differences are very small and not adequate to investigate complex patterns in a very heterogeneous population (174). We aim to use the framework proposed in this thesis to control for variability in baseline FC across individuals and increase our sensitivity to group differences. In chapters 4 and 5, we explore two developmental disorders.

In chapter 4, we study ADHD cases and investigate whether their undiagnosed siblings present an endophenotype, showing similarities with a biological profile of ADHD traits. Using three tasks from the NeuroIMAGE database (175), we focus on investigating a missing subnetwork shared across tasks of different cognitive domains, but all of which involve executive functioning. Many patients with ADHD exhibit deficits in executive functions. Accordingly, the neural circuitry underlying executive functioning has been a prime target of both resting state fMRI (R-fMRI) and task-based fMRI studies to investigate whether this circuitry is disrupted in patients with ADHD. Task and resting state studies have demonstrated differences in connectivity involving the DMN, the frontal cortex, the striatum, the parietal cortex and the cerebellum (176). However, results are inconsistent between R-fMRI and task-based fMRI studies. Indeed, we can observe hypoconnectivity in the Default Mode Network (DMN), in the cognitive control network or also in the striato-thalamo-cortical loop in the resting state (176). In tasks, for example in an inhibition task, the DMN seems hyperconnected (45),
showing the complexity of the task-rest relationship. We aim to focus on task-specific connectivity to remove differences in baseline when interpreting task performance differences. Another theory proposes that ADHD involves a developmental delay (177) and there is evidence that neural features are almost indistinguishable when comparing ADHD-remitted adults to healthy controls (24). A lack of energy required to reach a cognitive state is also a hypothesis (178), though it remains difficult to investigate with current available tools. In chapter 4, we test if our results support these theories from the viewpoint of FC.

In chapter 5, we examine the ASD population and if the same viewpoint can further inform us about the mechanisms of human development. ASD has also been linked to disrupted FC with a lack of long-range connections (179–181) and a mixture of under- and hyper-connectivity, depending on the network. Patients had less FC at rest, except for in sensory and motor networks, than did controls, showing that differences in connectivity profiles involve the whole brain and that interaction during cognitive maturation may become more complex (162,179,180,182–184). Again, because this population exhibits much heterogeneity, understanding the disease is a challenge. To limit the variability between individuals, task potency promises to control for differences in baseline connectivity at the individual level. We use different cognitive domains in which ASD patients exhibit impaired performance and investigate the lack of a common core mechanism across these domains using the EU-AIMS LEAP dataset (185,186), which includes five tasks of emotion processing, theory of mind, executive functioning, and reward processing (social and monetary). We integrate theories related to autism, wherein there is a possible enhanced sensitivity to the environment and an imbalance in the basal functioning of the brain. The use of task potency in two different developmental disorders allows for a more integrated view of development and newly defined hypotheses for developmental mechanisms.
# Introduction

**NeuroIMAGE dataset**

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder with a strong genetic background. NeuroIMAGE is an integrated DNA-cognition-MRI-phenotype project with the aim to identify cognitive, neural and genetic underpinnings of ADHD. The project includes research groups at three sites in the Netherlands: Nijmegen, Amsterdam and Groningen.

Between 2004-2006, a cohort of 350 ADHD families (probands with ADHD combined type and one or more siblings) and 150 control families (control probands with one or more siblings) was gathered as part of the Dutch side of the International Multisite ADHD Genetics (IMAGE) project. Data collection included detailed information on ADHD status, and extensive phenotypic, neuropsychological and genetic data. From 2009-2011, this cohort was invited for a follow-up investigation as part of the NeuroIMAGE project, and the sample was enlarged with 100 new children. ADHD status, phenotypic and neuropsychological data were again collected, furthermore magnetic resonance imaging (MRI) brain scans were acquired and additional genome-wide genotyping completed.

Source: www.neuroimage.nl

**EU-AIM LEAP dataset**

The EU-AIMS Longitudinal European Autism Project (LEAP) is the largest multi-centre, multi-disciplinary observational study worldwide that aims to identify and validate stratification biomarkers for ASD.

LEAP includes 437 children and adults with ASD and 300 individuals with typical development or mild intellectual disability. Using an accelerated longitudinal design, each participant is comprehensively characterised in terms of clinical symptoms, comorbidities, functional outcomes, neurocognitive profile, brain structure and function, biochemical markers and genomics. In addition, 51 twin-pairs are included to identify genetic and environmental factors in phenotypic variability.

Source: www.eu-aims.eu
OUTLINE AND AIMS OF THIS THESIS

The overall aim of this thesis is to determine cognitive specific modulations of FC above and beyond the functional baseline architecture of the brain. I propose to use the resting state as a proxy for ongoing neural activity and continuous cognitive processing to investigate task-specific modulations of FC. In particular, I aim to define these specific modulations across multiple tasks to compare them, disentangle their shared modulation, and understand the subnetworks involved across cognitive domains. To this aim, I developed a framework to define the “task potency” that is described in Chapter 1. I then apply this task potency framework to a longitudinal database called “MyConnectome” (187), composed of only one subject scanned more than 100 times over a year. This longitudinal database enables us to study baseline stability and test the intra-subject variability of task potency. The analyses presented in Chapter 2 investigate how a different State-of-Mind (SoM) could impact the rest-task relationship and might explain how some of the subject’s performances are linked to the ability to engage brain networks at a specific moment.

In chapters 3 and 4, I apply the task potency framework to a developmental database of individuals aged 8 to 28 years (NeuroIMAGE project). In chapter 3, I first use healthy participants only and investigate changes in task potency with age to define how the relationship between task and rest evolves with age. I test the Interactive Specialization Theory by looking at how the maturation of cognitive functions is interrelated using three different cognitive tasks: An inhibition task, a reward processing task, and a working memory task. Chapter 4 presents the first clinical application, where ADHD participants and their siblings are compared to healthy participants by studying the relationship between the three above cited tasks in which ADHD participants display impairments. I aim to provide a new angle on the disorder and identify a core failing mechanism. Lastly, in chapter 5, I apply the same reasoning from chapter 4, but on the EU-AIMS LEAP (Longitudinal European Autism Project) database to investigate task potency in ASD across 5 tasks: Two
Introduction

reward processing tasks, an emotion recognition task, a theory of mind task, and an inhibition task.

I end this thesis with a discussion of my interpretation of the task potency metric as an index of brain efficiency, possible future applications, and alternative frameworks to enhance the detection of specific cognitive mechanisms. I propose ideas for future investigations of the building blocks of cognitive function and their implications in studying human development. Finally, I explore how these insights can potentially contribute to educational processes and applications in primary schools.
CHAPTER 1

DISENTANGLING COMMON FROM SPECIFIC PROCESSING ACROSS TASKS USING TASK POTENCY

This chapter is based on: Chauvin RJ, Mennes M, Llera A, Buitelaar JK, Beckmann CF. Disentangling common from specific processing across tasks using task potency. NeuroImage. 2019 Jan 1;184:632–45.
ABSTRACT
When an individual engages in a task, the associated evoked activities build upon already ongoing activity, shaped by an underlying functional connectivity baseline (12,77,188). Building on the idea that rest represents the brain’s full functional repertoire, we here incorporate the idea that task-induced functional connectivity modulations ought to be task-specific with respect to their underlying resting state functional connectivity. Various metrics such as clustering coefficient or average path length have been proposed to index processing efficiency, typically from single fMRI session data. We introduce a framework incorporating task potency, which provides direct access to task-specificity by enabling direct comparison between task paradigms. In particular, to study functional connectivity modulations related to cognitive involvement in a task we define task potency as the amplitude of a connectivity modulation away from its baseline functional connectivity architecture as observed during a resting state acquisition. We demonstrate the use of our framework by comparing three tasks (visuo-spatial working memory, reward processing, and stop signal task) available within a large cohort. Using task potency, we demonstrate that cognitive operations are supported by a set of common within-network interactions, supplemented by connections between large-scale networks in order to solve a specific task.
Disentangling common from specific processing across tasks using task potency

INTRODUCTION
Advances in functional brain imaging have provided tremendous insight into the neural correlates of cognition by relating behavioural descriptions to local changes in brain activity via oxygen metabolism using functional Magnetic Resonance Imaging (fMRI). Typical experimental studies probe specific cognitive functions (189,190), and thereby inform about the sensitivity of brain areas to the experimental manipulation of interest (56,191). Yet, single neuroimaging studies do not allow making inferences about whether an observed area exclusively responds to cognitive function A or whether it is also sensitive to manipulation of function B. As such, single studies cannot inform about the specificity of a brain area for the tested cognitive function.

To be informative about specificity rather than mere sensitivity and thus allow for reverse inference (8,56), study participants would need to be probed for various cognitive functions across a broad repertoire of domains. Such multi-paradigm investigations are technically and logistically challenging and therefore remain rare. Accordingly, in order to indirectly infer specific behavioural relevance for the neural responses they observed, authors typically resort to previously reported results via literature meta-analysis or alternative initiatives that validate study results (72,93,98,192). Yet, such literature-based techniques are troubled by typical biases associated with the publication process including article imprecision, ‘File Drawer’ issues, and potential p-value tweaking (8,193).

In all of these approaches, the collection of alternative tasks directly measured or inferred upon through meta-analysis provides a functional baseline that allows defining specificity in light of estimates relative to this baseline state. Moving from a focus on localised brain activity towards covariation patterns across distributed areas (by means of functional connectivity) various metrics have been proposed that index processing efficiency in the brain. Quantities like clustering coefficient or average path length (194,195) are thought to reflect inter-individual differences in the degree to which processing in the brain builds upon differences in the baseline infrastructure for information integration. Typically, however, such quantities are being derived from individual
scans and do not integrate information across different cognitive tasks and/or resting sessions.

Corroborating the idea of such a functional baseline, we here propose to take advantage of the fact that resting state functional MRI (rFMRI) data exhibits dynamics that correspond to major functional activation patterns that can be observed across a vast repertoire of tasks (12). The existence of the brain’s ‘functional repertoire’ during rest supports the idea that specific cognitive states are produced by specific modulation upon a baseline of common, ongoing network activity (196–199), rather than being orchestrated by independent activity in single regions. An important corollary is that cognitive function emerges through embedding unique regional activity within the context of larger network processes, as described in the ‘massive redeployment hypothesis’ (200,201). This hypothesis is further supported by research showing that functional connectivity can successfully differentiate between mental states (76), corroborating the idea that mental states can be defined based on specific connectivity profiles, similar to a “brain fingerprint” (130,202). In accordance with these ideas, we propose to utilise rFMRI-derived connectomes as a functional baseline, effectively representing a standard space to compare task modulation requirement against. Using this independent functional baseline, we formulate an innovative framework to assess the sensitivity and specificity of cognitive processes and their relative change in connectivity score across tasks using task potency, a measure that indexes task-related connectivity modulations away from this functional baseline.

Our framework fits in the context of emerging large cohort functional imaging studies that involve multiple experimental fMRI designs along with rFMRI measures, allowing for within-subject comparisons between cognitive paradigms relative to the resting condition. One prominent example is the Human Connectome Project (203,204) aimed at deciphering the complex relationship between brain functions, cognition, and the functional and structural human connectome within a normal cohort. Similar projects are translating these efforts to the clinical domain (e.g., NeuroIMAGE (175), PNC (205), ABCD (206)).
Disentangling common from specific processing across tasks using task potency

We aim to capitalize on the increased statistical sensitivity to standardized modulation differences that such within-subject designs offer. In this context, the task potency metric can be used to characterize effect-size differences in light of experimental manipulation against a baseline that represents that participant’s full functional spectrum. Importantly, we utilise this concept to disentangle *general from task-specific* connectivity modulations by indexing the presence or absence of significant functional connectivity under different tasks and posit that general neural modulations occur across multiple tasks yielding limited differences in potency between tasks. In contrast, specific neural modulations that might be attributed to a single cognitive process, will yield large differences in potency between tasks or sets of tasks. We demonstrate the application of task potency to multi-subject fMRI data involving – along with a resting-state fMRI session – three different experimental tasks probing different aspects of cognition. Using population distributions of task potency, we assess task-specificity of edges in the connectome and compare the similarity of the ensuing task fingerprint across different cognitive domains.

METHODS

PARTICIPANTS

We use MRI data from the NeuroIMAGE sample (N total > 800 participants; see von Rhein et al., 2014). In the current analyses we included data from healthy control participants only (initial N=385) who each performed at least one of the following tasks during fMRI scanning: response inhibition (Stop Signal Task (STOP)) (see (45,175,207)), reward processing (REWARD) (see (175,208–210)), spatial working memory (WM) (see (133,175,211,212)) (see supplementary table 1). In addition, to the task-based MRI scans each participant completed a task-free resting state fMRI scan (10 min, eyes open). All participants also completed an T1-weighted anatomical scan for registration purposes. MRI acquisition parameters are shown in table 1.
Functional scans exhibiting limited brain coverage or excessive head motion were excluded from further processing. Limited brain coverage was defined as having less than 97% overlap with the MNI152 standard brain after image registration. Applying this criterion excluded 47 subjects (details in table 1). In addition, we excluded from each task those participants who were among top 5% in terms of head motion as quantified by RMS-FD, the root mean square of the frame-wise displacement computed using MCFLIRT (213). After applying these criteria, we selected only participants that completed at least a task and a resting state scan resulting in the inclusion of data from 218 healthy controls, comprising 218 resting state acquisitions, 111 STOP acquisitions, 123 REWARD acquisitions, and 147 WM acquisitions. Participants ranged in age between 8.6 and 30.5; mean=17.0; sd=3.5; 45.9% were male.

Table 1: MRI Acquisition Parameters and Participant Characteristics (Demographic Information is Presented in Supplementary Figure 1)

<table>
<thead>
<tr>
<th>T1-weighted structural MRI parameters</th>
<th>T1-weighted MPRAGE, TR=2730 ms, TE=2.95 ms, T1=1000ms, flip angle=7, matrix size=256x256, FOV=256mm, 176 slices with 1mm isotropic voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMRI image acquisition parameters</td>
<td>rFMRI</td>
</tr>
<tr>
<td></td>
<td>STOP</td>
</tr>
<tr>
<td></td>
<td>REWARD</td>
</tr>
<tr>
<td></td>
<td>WM</td>
</tr>
<tr>
<td>General parameters</td>
<td>TE=40 ms, FOV=224mm, 37 axial slices, flip angle=80, matrix size=64x64, in-plane resolution=3.5mm, slice thickness=6.0mm/0.5mm</td>
</tr>
<tr>
<td>N volumes</td>
<td>&gt;260</td>
</tr>
<tr>
<td>TR in ms²</td>
<td>1960</td>
</tr>
<tr>
<td>N volumes rejected²</td>
<td>5</td>
</tr>
<tr>
<td>N initial</td>
<td>302</td>
</tr>
<tr>
<td>N rejected for limited brain coverage</td>
<td>73</td>
</tr>
<tr>
<td>N rejected for head motion</td>
<td>11</td>
</tr>
<tr>
<td>N who also completed a resting state scan and that were used in final analyses</td>
<td>218</td>
</tr>
<tr>
<td>RMS-FD min-max</td>
<td>0.026 - 1.930</td>
</tr>
<tr>
<td>RMS-FD mean (std)</td>
<td>0.171 (0.224)</td>
</tr>
<tr>
<td>Age min - max</td>
<td>8.6 - 30.5</td>
</tr>
<tr>
<td>Age mean (std)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>% male</td>
<td>45.8%</td>
</tr>
<tr>
<td>IQ mean (std)</td>
<td>104.1 (14)</td>
</tr>
</tbody>
</table>

1 Except 1 scan which was done at 1860ms in rFMRI, 1 at 2150ms in STOP, and 1 at 2280ms in REWARD

2 The number of initial volumes removed from further analyses varied to ensure comparability with earlier studies that used these data. This variation will have very limited impact on the current analyses.
Disentangling common from specific processing across tasks using task potency

FMRI PREPROCESSING
All fMRI acquisitions were processed using tools from FSL 5.0.6. (FSL; http://www.fmrib.ox.ac.uk/fsl; (214–216)). We employed the following pipeline: removal of the first volumes to allow magnetization equilibration (see table 1), head movement correction by volume-realignment to the middle volume using MCFLIRT, global 4D mean intensity normalization, spatial filtering with a 6mm FWHM Gaussian kernel. We then denoised all preprocessed data for motion-related artefacts. We used ICA-AROMA to detect motion-related artefacts in single-subject data through classification of ICA components extracted by MELODIC. We subsequently regressed components identified as motion-related artefacts out of the data (using fsl_regfilt, see Beckmann, 2012; Pruim et al., 2015a, 2015b). Subsequently, we regressed out mean signals from CSF and white matter extracted using participant-level masks obtained by multiplying – in the participant native space – participant-level CSF and white matter segmentations with the MNI152-based CSF and white matter masks provided as part of FSL. Finally, we applied a 0.01Hz temporal high-pass filter (Gaussian-weighted least square straight line fit to the data). For each participant, all acquisitions were registered to its high-resolution T1 image using Boundary-Based Registration (BBR) available in FSL FLIRT (213,218). All high-resolution T1 images were registered to MNI152 space using 12-dof linear registration available in FLIRT and further refined using non-linear registration available in FSL FNIRT (219). Transformations were not applied. Instead we used the inverse of the obtained transformations to bring a hierarchical atlas of brain regions to the participant’s native space (see below).

CONNECTOME ATLAS
For each functional imaging scan we defined connectivity matrices using regions defined in a hierarchical whole-brain functional atlas (220). This atlas contains 185 non-overlapping regions and was defined through Instantaneous Connectivity Parcelation (ICP, (220)) as applied to resting state fMRI data of 100 participants of the Human Connectome Project (HCP; (203,204)). In short, ICP aims to parcel larger regions into subregions based on signal homogeneity, where the optimal number of subregions is determined based on split-half reproducibility at the cohort level.
Chapter 1

Figure 1 illustrates the hierarchical brain atlas, where areas were grouped in 11 higher-level networks: 9 resting state networks (visual1, visual2, motor, right attention, left attention, auditory, default mode network (DMN), fronto-temporal and cingulum), and 2 networks based on anatomical structures, i.e., the subcortical areas, and the cerebellum. These higher-level networks respectively contained 19, 12, 22, 22, 18, 8, 18, 13, 7, 23, and 23 subregions, resulting in a total of 185 initial parcels.

Connectivity matrices were calculated in each participant’s native space for each of the functional scans. To this end we transformed the atlas to each participant’s native space using the inverse of the anatomical to MNI152 non-linear warp, and the inverse of the linear transformation of the functional image to the participant’s high resolution anatomical image. Atlas areas that were on average across our population > 50% outside of the brain were rejected from further analyses. As a result, we used 179 areas, shown in figure 1 colour coded by their associated top-level network, to compute connectivity matrices.

To assess dependence of our results on the network grouping within our ICP atlas, we replicated our analyses using the 7 networks as described in Yeo et al (202) as top-level networks. We included all areas overlapping at least 50% with one of the Yeo networks. This selection resulted in a total of 77 areas across the 7 networks and divided as follows: 13 (visual), 10 (somatomotor), 9 (dorsal attention), 9 (ventral attention), 9 (frontotemporal), 18 (default), 9 (limbic). Areas in the ICP atlas that did not sufficiently overlap with the Yeo networks were removed from the replication analysis. Results of these analyses are included in the supplement.

**Figure 1.** ICP atlas with 179 areas represented in their corresponding top-level networks. R_attention: right attention network; L_attention: left attention network; DMN: default mode network; sub cort: subcortical regions; cereb: cerebellum. Supplementary figure 2 shows the higher-level networks projected to the brain surface.
Disentangling common from specific processing across tasks using task potency
**CONNECTIVITY CALCULATION**

For each participant and each task (rFMRI, WM, REWARD, STOP) we calculated 179x179 connectivity matrices, by cross-correlating the time series of all regions in the atlas. We obtained each region’s time series through multivariate spatial regression, using all 179 regions as regressors and each task’s preprocessed time series as dependent variable. The resulting regional time series were demeaned. Using these time series, we calculated 179x179 partial correlation matrices through inverting covariance matrices estimated by the Ledoit-Wolf normalization algorithm (221,222) as implemented in nilearn (http://nilearn.github.io/). Ledoit-Wolf normalization algorithm is a shrinkage algorithm that optimises estimation of the covariance matrix and ensures sparseness. We opted for partial correlations in order to avoid redundancy in the functional connectivity estimation, thereby allowing making inferences about direct connections without the influence of indirect connections in the fingerprint. Results obtained using full Pearson correlation are presented in the supplement. Finally, all pair-wise correlations were Fisher r-to-Z transformed.

To allow comparing connectivity values between acquisitions and to account for the potential differences in temporal degrees-of freedom due to scan length differences, we normalized the distribution of connectivity values within each connectivity matrix using a mixture-modelling approach (223–225). Note, that this approach allows to correct for differences in task-specific parameters including the number of volumes or differences in TR. In this mixture modelling approach, we fit three parameterised distributions to the histogram of connectivity values: a central Gaussian distribution representing the noise and two gamma distributions on each side of the central Gaussian that represent the signal as the tails of the data distribution. We fit this mixture of distributions under the assumption that evidence for a non-zero connection is unrelated to the spatial location of the nodes and that non-zero connections are sparse. Further, we assume that there is a sufficient total number of nodes so that the distribution of values for non-significant edges (i.e., noise) in the network can be used to estimate the within-subject null distribution of non-existing connections. In practice, we modelled the obtained connectivity values per task using a Gaussian-
Disentangling common from specific processing across tasks using task potency

gamma mixture model and used the main Gaussian, i.e., the one fitting the body of the distribution, to normalize our connectivity values. Note that this overcomes any issue in deciding on the appropriate degrees-of-freedom for the Fisher r-to-Z conversion of partial connectivity values. We applied mixture modelling to each connectivity matrix and subsequently normalized the connectivity values by subtracting the mean and dividing by the standard deviation of the obtained Gaussian model. As a result, and despite differential loss in temporal degrees-of-freedom due to the partial correlation calculation, the values within the normalized, Z-transformed partial correlation matrices are readily comparable across participants and tasks.

Finally, to allow interpretation of the task-based connectivity matrices in terms of their deviation from a functional baseline defined as connectivity during the resting state, we further standardized each participant’s task-based connectivity matrix. Specifically, we standardized each individual-level pair-wise correlation obtained during task by subtracting the corresponding individual pair-wise correlation obtained during rest for the same participant. As such, each task-based pair-wise correlation or edge quantifies how connectivity for that edge differed from that edge’s connectivity during the resting state. As a result, after standardization, we obtain for each participant an individual connectivity matrix for each of their task acquisitions. We refer to these matrices as task potency matrices, which quantify for each edge how strongly the task-based connectivity was modulated away from its resting state baseline (i.e., the amplitude of the task-based modulation). For each task, we finally create group-level task potency matrices by averaging across participant matrices and multiplying by the root mean square of the number of participants to avoid bias in between-task comparisons related to the number of observations in each task. All scripts needed to compute task potency and ensuing analyses are available via [https://github.com/roscha/task_potency](https://github.com/roscha/task_potency).

**Task-based Fingerprints**

To compare those connections that characterize a task’s functional fingerprint across different tasks we selected, for each task, those edges that showed significant task potency. Similar to the normalization
procedure described above we used the mixture modelling approach to determine a significance threshold (224). After applying the mixture modelling to the task potency distribution, we use the main Gaussian to estimate the false discovery rate according to the density of the Gaussian distribution and the ratio of connections above a certain threshold (226). We use an overall FDR of 0.05 to detect significant connections. To be able to estimate the corresponding task potency threshold for each side of the distribution, instead of applying an FDR of 0.025 to each side, we weighted the unilateral FDR by the size of the gamma distributions estimated by the mixture model (see formula in supplement). This weighted FDR allows us to account for asymmetry of the signal and avoids over- or underestimation of positively or negatively potentiated connections. We refer to edges with significant task potency as task-based fingerprints. The task-based fingerprints are subsequently used to define the task sensitivity and task specificity of each edge in the fingerprint.

To enable statistical testing on our analyses, we estimated the task fingerprint 10000 times using 80 percent of the population randomly selected. This bootstrap procedure allows estimating the variance of the task fingerprints for significance testing.
Disentangling common from specific processing across tasks using task potency

Figure 2. Analysis framework to obtain connectivity-based task fingerprints. The framework starts at the participant-level with obtaining a partial correlation matrix (Fisher-Z transformed), which is normalized, and subsequently standardized by that participant’s resting state connectivity (subtraction of baseline), resulting in individualized task potency matrices. A group task fingerprint can be obtained by averaging the individual task potency matrices and thresholding based on the Z-score of the group potency.
Figure 3 illustrates how we can characterize each edge within a task potency matrix in terms of its sensitivity and specificity to the different tasks included in the study. An edge was regarded *sensitive* to task modulation when the strength of connectivity was above the statistical threshold in at least one of the tasks. An edge can be sensitive to
Disentangling common from specific processing across tasks using task potency

modulation by several tasks, yet with a different level of potency in one task compared to another. This differential potency is not considered when assessing sensitivity.

Task **specific** edges were those edges that were selected for one task only. Common edges of our three tasks were defined as edges selected in all three tasks. Note that specificity and commonality are determined by the collection of available tasks, accordingly conclusions regarding the specificity of edges in the current manuscript need to be interpreted in light of the tasks we included. Also note that design choices made for the included tasks, e.g. shorter task duration and/or fewer trials within a task, will influence the signal-to-noise (SNR) properties of a given task and thereby influence the degree to which edges in the connectome become up- or down-regulated relative to the resting-state scan. While our approach to connectome-wide task fingerprinting is not aimed at adjudicating between experimental design choices, we note that it is effectively possible to assess the connectome-wide impact of such choices using our potency approach.

To differentiate which task most strongly modulated which connection, we differentiated tasks based on their **potency** in connections regardless of a sensitivity threshold. To this end, we assessed for each edge whether we could differentiate the tasks based on the average potency across the population using a measure of anisotropy across the three tasks, calculated as: (highest potency – second highest potency) / sum of potency across the three tasks. Note that this comparison relies on the normalization of all matrices prior to standardization by the resting state connectivity (see supplementary figure 3). We displayed the anisotropy measure using colour gradients where values close to 0 are light, i.e., tasks could not be differentiated based on differences in their potency. In contrast, highest anisotropy values will appear darker, and in the colour associated with the task that exhibited the highest potency. We used the same approach to label maximum task-related up- or down regulation in connectivity in the 11-network framework. Here we used the sum of potency across selected edges for each network. Finally, we investigated maximum task potency at the level of areas (i.e., columns in
our connectivity matrices). To this end, we summed potency for group-level edges across each area’s 179 connections.

NETWORK-BASED SUMMARY METRICS
The hierarchical ICP atlas defines 179 areas as subdivisions of 11 large-scale networks. Accordingly, next to reporting at the level of individual areas, we can average across edges within each network to summarize potency, sensitivity, and specificity at the network level. We can differentiate edges that link areas within a network (within-network edges) from edges that link areas between two different networks (between-network edges). In order to compare between networks, we corrected for the number of edges averaged over the different 11x11 interactions by multiplying each average by the root mean square of the number of edges within or between two networks. By comparing the within- and between-network connections we assessed whether a task was associated with specific networks or resulted in an overall, diffuse modulation of connectivity. In practice, to derive network-level scores, we calculated the percentage of selected edges included in each network. This was done for each entry in the 11x11 network connectivity matrix, and allowed quantifying the selection of edges at the within- (diagonal matrix entries) and between-network (off-diagonal matrix entries) level.

REPRODUCIBILITY OF THE EDGE SELECTION PROCEDURE
Every single participant has associated within-subject differences relative to the cohort-derived group potency fingerprint. In order to assess reproducibility of our group-level fingerprint pattern, we defined individual task fingerprints, applying the same selection procedure as above, but applied to the individual task potency matrices (i.e., select those edges with a pFDR<=0.05 in the individual task fingerprints). This enables us to quantify subject-specific variations in the edge selection and thereby permits quantification of reproducibility across participants. We indexed the number of times an edge was selected across participants. This proportion is interpreted as the reproducibility of an edge’s potency.
Disentangling common from specific processing across tasks using task potency

RESULTS

TASK-BASED FINGERPRINTS

**Figure 4. Illustration of connectivity matrix calculation for the reward task.** A: Normalized resting state Z partial correlation averaged across the population; B: Normalized Z partial correlation for the reward task averaged across the population; C: Average reward task potency across the population. Upper triangle displays the 179x179 connectivity fingerprints; lower triangle displays the average summary per network. R_attention: right attention network; L_attention: left attention network; DMN: default mode network; sub_cort: subcortical regions; cereb: cerebellum. The normalized Z partial correlation and task potency matrices for the two other tasks are display in supplementary figure 4.

To evaluate connectivity sensitivity to each task we created task-based fingerprints by standardizing the task connectivity by the resting state connectivity, resulting in a matrix quantifying each edge’s functional potency, as illustrated in figure 4C for the reward task (see supplementary figure 4 for the other tasks). This task-based fingerprint...
served as the basis to identify sensitive edges and assess their task specificity.

**Task Sensitivity**

Significance of task sensitivity was determined using mixture-modelling thresholding applied to each task’s functional fingerprint. We applied the mixture-modelling thresholding on the average potency across participants. From these we calculated both the relative proportion of selected edges (above the mixture-modelling threshold) as well as the normalised proportion of edges per individual task. Further, grouping the parcel-wise estimates into the 11 large-scale networks we quantified the percentage of sensitive connections within and between the large-scale networks (Figure 5).

Across tasks and networks, 5.37% of all edges exhibited significant sensitivity to task modulation (Figure 5, top row). When comparing the percentage of sensitive edges across tasks we observed that WM potentiated significantly more connections compared to REWARD (4.2% (sd=0.66) vs. 1.9% (sd=0.54); p<0.05). In turn, REWARD significantly potentiated more connections than STOP (1.9% (sd 0.54) vs. 1.1% (sd=0.19); p<0.05).

When further differentiating between edges that connect regions within networks versus edges that connect between regions in two networks, we observed a higher prevalence of sensitive edges for within-network connections compared to between-network connections. In particular, the visual1 and motor networks showed a high percentage of within-network sensitive edges, both networks include the primary sensory areas needed to process the task information (Figure 5, middle row). In contrast, the number of sensitive between-network connections was considerably lower, with on average only 1.55% of edges selected across the 11 networks versus 25.44% of within-network connections. At the between-network level, sensitive edges were relatively equally distributed across the 11 networks (Figure 5, bottom row). We highlight the result for the cingulum network which exhibited the highest percentage of between-network sensitivity and the lowest within-network sensitivity.
Disentangling common from specific processing across tasks using task potency

Across networks, the relative distribution of sensitive edges per task (task proportion) showed little variations, with the exception of the within-network DMN connections, where STOP did not yield any sensitive within-network edges (see stacked bars in figure 5).

At the network level, we observed that compared to the other networks, the motor, visual and cerebellum networks exhibited significantly stronger within-network potentiation, while the cingulum network exhibited lower within-network potentiation and stronger between-network potentiation compared to the other networks in our analysis (Bonferroni corrected p-values across each pair of networks are reported in supplementary figure 6). The higher level of significant within-compared to between-network connectivity supports the hypothesis that the brain strongly segregates information at the level of individual networks, while more weakly integrating information between networks, in line with theoretical predictions using integration and segregation to model the dynamic of brain networks (227,228).

**Task Specificity**

To disentangle overlapping connectivity modulations in light of the included tasks, we defined the task specificity of edges by splitting the collection of sensitive edges into those that were modulated by one task only (i.e. are specific to a particular task), those that were sensitive to modulation by several (but not all) tasks, and those that were significantly modulated by all tasks (see also figure 2). Figure 6 illustrates the percentage of sensitive edges modulated by one task only and those modulated by all tasks. We observed that overall 68.85% of the sensitive edges were specific to a particular task, compared to 12.8% that were modulated by all tasks (we refer to these as ‘common’ edges). Note that this also means that 18.35% of sensitive edges was modulated by more than one, yet not all, tasks.
FIGURE 5. RADAR PLOTS OF THE PERCENTAGE OF EDGES SHOWING SIGNIFICANT TASK POTENCY (I.E., SENSITIVITY) SUMMARIZED ACROSS 11 BRAIN NETWORKS. WHEN SPLITTING THE PERCENTAGE OF SENSITIVE CONNECTIONS (TOP ROW) INTO WITHIN- (MIDDLE ROW) AND BETWEEN (BOTTOM ROW) CONNECTIONS, WE OBSERVED A LARGER PERCENTAGE OF SENSITIVITY FOR WITHIN-NETWORK CONNECTIONS, COMPARED TO BETWEEN-NETWORK CONNECTIONS. AS AN EXAMPLE, 58.7% PERCENTAGE OF EDGES WITHIN THE MOTOR NETWORK EXHIBITED SENSITIVITY, COMPARED TO ONLY 1.76% OF ITS BETWEEN-NETWORK CONNECTIONS. TO ALLOW DIRECT COMPARISON BETWEEN BOTH RADAR PLOTS, WE ALSO SHOW THE BETWEEN-NETWORK PERCENTAGES ON TOP OF THE WITHIN-NETWORK PERCENTAGES IN THE MIDDLE LEFT PLOT. BAR PLOTS ON THE RIGHT ILLUSTRATE EDGE SENSITIVITY FOR EACH TASK. FOR FURTHER DETAILS REGARDING THE PERCENTAGE CALCULATION WE REFER TO SUPPLEMENTARY FIGURE 5. R_ATTENTION: RIGHT ATTENTION NETWORK; L_ATTENTION: LEFT ATTENTION NETWORK; DMN: DEFAULT MODE NETWORK; SUB CORT: SUBCORTICAL REGIONS; CEREB: CEREBELLUM.

We observed a difference in the level of specificity for within- vs between-network connections. Comparing the dark versus light coloured areas in the top row of Figure 6 it is evident that the ratio of specific
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versus common connections was smaller ($t=-3.82; \ p<0.05$) for the sensitive within-network connections (mean ratio across networks = 3.21 ± 1.96) compared to the ratio of specific versus common connections for the sensitive between-network connections (mean ratio across networks = 11.74 ± 9.59). This result shows that between-network connections are almost exclusively modulated in a specific fashion, where different tasks modulate different edges connecting networks to the rest of the brain.

We further characterised the nature of the task-specific connections to assess how specificity is distributed across tasks and networks (figure 6 bottom). While the between-network connections were more homogeneously distributed between tasks and across all networks, we observed greater variation in the specificity of the within-network connections, with some networks showing notable task specificity. We observed that REWARD showed more specifically potentiated connections involving subcortical regions, while STOP showed a limited amount of between-network specificity, yet strongly potentiated connections among subcortical regions. In contrast, edges specific to WM were equally distributed across networks, suggesting an extensive involvement of different networks, corroborating the observation that WM overall potentiated more connections. Indeed, in supplementary figure 10 we demonstrate that placing more stringent thresholds to determine sensitivity enables to capture network specificity in WM, showing that the edges exhibiting strongest potency are within the motor network and the DMN. Importantly, the relation of specificity to the amplitude of potentiation further supports the idea that potency should be considered as a continuum instead of defining a threshold of significance (see results).
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**Figure 6.** Percentage of sensitive edges for each task that end up to be specific to this task, e.g., percentage of edges selected in the group potency of a task that are not present in another task group potency selection. The percentage corresponding to the within- vs between-network connectivity is listed per network. Top row: overall results; bottom row: inflation of the edges modulated by one task only further differentiated per task. As an example: ~38% of the sensitive edges within the visual1 network were modulated by one task only. Of those 38% sensitive edges, about 78% was modulated only during WM performance, ~20% only during REWARD, and ~2% during STOP only. In contrast, ~7% of the sensitive edges within the visual1 network were modulated during performance of all tasks. Supplementary figure 5 illustrates the reference edges in the percentage calculations. R_attention: right attention network; L_attention: left attention network; DMN: default mode network; sub cort: subcortical regions; cereb: cerebellum.

In contrast to task-specific edges, about 13% of all task-sensitive edges were modulated by all three tasks (union across all tasks in figure 2; dark line in figure 6, top row). Brain regions that yielded the highest number of common edges are represented in figure 7. Apart from visual and motor regions where we expected shared modulation, as all three tasks were using visual stimuli and requested motor response, all tasks
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modulated edges involving regions that were part of the fronto-temporal and attention networks in our atlas. This modulation included anterior cingulate cortex, left inferior frontal gyrus, areas from inferior parietal lobe, bilateral frontal orbital cortex extending into Broca’s area, the temporal pole, amygdala, and enthorinal cortex. Interestingly, no DMN or subcortical regions were represented in the top selection of areas that potentiated edges across all tasks. Brain regions that showed the highest number of edges modulated by each task specifically are shown in supplementary figure 7 (STOP), 8 (REWARD) and 9 (WM).

REPRODUCIBILITY OF THE SELECTION ACROSS INDIVIDUAL FINGERPRINTS

The result in figure 6 shows that different tasks exhibit a specific pattern of network potentiation, which can be accessed by comparing a set of different tasks. Nevertheless, a large proportion edges are sensitive to all tasks. In order to establish the utility of evaluating individual task fingerprints in a reproducible manner, we studied the detection rate of edges sensitive to one or all tasks across task fingerprints obtained for individual participants. Specifically, we investigated whether the group selection was reproducible at the individual level and in particular how well the task-specific connections where represented at the level of individual participants. We defined the individual fingerprint by selecting edges that showed a pFDR below 0.05 using the mixture modelling thresholding on the individual-level task fingerprints. We computed the sum of selected edges across the population for each task. As shown in figure 8, we observed a set of edges with high selectivity across participants for each task: 2.3% of edges within the union of individual masks were selected by minimum 13.7% of the population and in each of the three tasks. These edges mainly linked homotopic areas of each hemisphere, including bilateral motor areas, cerebellum, attention networks, visual1 areas, and bilateral putamen (See figure 9).

In contrast to the set of highly selected edges at the individual level, we note that the edge selection at the individual level showed substantial variability: 80% of sensitive edges were selected in less than 12.6% of subjects (figure 8 dashed line). As indicated above, the most consistently selected edges between participants involved connections sensitive to all
tasks. In contrast, highest inter-individual selection variability was found for task-specific edges as edges selected in only one task at the group level showed a lower individual selection reproducibility than edges selected in all tasks at the group level (figure 9).

**Figure 7.** Brain regions with the highest number of edges commonly modulated by all three tasks. Here, we displayed the 10% brain regions with the largest sum of edges sensitive to all three tasks.
Figure 8. Distribution of selectivity of edges showing any sensitivity at the individual level. Distributions are shown for the selectivity of the corresponding edges at the group level for sensitivity to a task, sensitivity to one task only, and sensitivity to all tasks. The dashed line illustrates that 80% of the edges that were selected as sensitive to a task at the group level, were selected in about 12.6% of the individual task potency matrices. Through comparing the three distributions it is clear that overall edges modulated by all tasks were more consistently selected at the individual level.
Figure 9. Edges selected for more than 40% of participants at the individual level (corresponding to 40% in figure 8). The circle displays significant connections that are being formed. The brain areas that these edges correspond to are represented in the axial slices. R_attention: right attention network; L_attention: left attention network; DMN: default mode network; sub_cort: subcortical regions; cereb: cerebellum.
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**DIFFERENTIATING TASKS BASED ON POTENCY**

Even if each task’s set of specific connectivity modulations reflects network enlistment by a specific experiment, this information is only accessible in comparison to other tasks. Additionally, to define edges as being task-specific brings limitations as soon as the number of tasks increases or when tasks share cognitive processes that are differentially involved in the experimental design. Therefore, we propose to move from the binary concept of specificity and sensitivity to a continuous measure of connectivity potency that quantifies the amplitude of the connectivity modulation required to enlist a connection, a network, or an area under certain task processes.

Using potency as a quantitative measure of the strength of enlistment of connections in a task, we can characterise which task potentiated an edge, a region, or a network most strongly. To this end, we assessed whether modulation of each edge could be attributed to one of the three tasks in our comparison by computing a measure of anisotropy between them. We investigated this potency anisotropy of each edge separately (figure 10, upper triangle of the matrix) and observed that only few connections were modulated most strongly by one task compared to both other tasks. Across all edges, the anisotropy was on average 0.25 (sd=0.2) suggesting a relatively equal representation of tasks. At the brain region (figure 10 brain slices) and network-level (figure 8, lower triangle of the matrix), each task displayed a specific pattern of strongest potentiation across the brain (figure 10B). REWARD principally potentiated the fronto-temporal network as well as areas from the reward circuit (anterior cingulate cortex, prefrontal areas, thalamus). Whereas STOP most strongly potentiated connections with the visual 1 network and with areas in motor cortex. Finally, WM potentiated regions included in the DMN as shown in figure 10B.
Figure 10. The most potent task illustrated for edges (A, upper triangle), networks (A, lower triangle), and brain regions (B) by means of an anisotropy measure comparing potency across the three tasks: (highest − second highest)/sum of potency across tasks. The brain slices in B illustrate for each brain region which task on average most strongly potentiates edges involving this region. The same is shown for individual edges and at the network-level in the matrix in A. R_attention: right attention network; L_attention: left attention network; DMN: default mode network; sub-cort: subcortical regions; cereb: cerebellum.
DISCUSSION

When an individual engages in a task, the associated evoked activities build upon the brain’s ongoing activity, itself shaped by an underlying functional connectivity baseline (12,77,188). Here, we show how this functional baseline architecture can be used to index task-dependent modulations, providing a means for quantitatively comparing evoked effects across tasks and cognitive domains. This model incorporates the idea that functional connectivity observed under cognitive manipulation is task-specific with respect to its underlying resting state functional connectivity (12,73,76,229). To facilitate understanding the building blocks of cognition, we demonstrate that differential levels of localised sensitivity to task manipulation inform about the relative potency of a specific task.

In this regard, task potency could be interpreted as indexing the resources required to modulate away from the brain’s functional baseline in order to perform a task. As such, task potency provides a novel index of efficiency. By comparing task modulation away from a common baseline acquired in the same individual, task potency bridges between a traditional seed- or ICA-based connectomic description and derived measures of efficiency provided by graph theory analysis. As such task potency provides a context to interpret brain fingerprint modulations across tasks at the whole brain level.

We calculated task potency for three tasks (working memory task, response inhibition task, and reward processing task) in a large healthy population and showed that all tasks predominantly potentiated edges at the within-network level, i.e. connecting areas within networks, particularly those including lower-order sensory-motor regions. Such larger connectivity changes in primary sensory networks may highlight a more straightforward and automatic response to incoming stimuli, accompanied by standardized motor activity. This fits with the idea that visual and motor areas adhere to a highly constrained organization that is strongly evolutionary conserved, resulting in lower inter-individual variability (230), but higher within-subject flexibility (231).

Comparing tasks across multiple distinct cognitive domains allowed us to distinguish connections that were specific to each task versus those
common to all manipulations. Figure 6 illustrates how the edges that were specific to each of our three tasks were distributed across the higher-level networks. The largely similar distribution of percentages shown for WM indicates that functional connectivity modulations induced by WM did not display strong network specificity when applying a nominal threshold, illustrating the overall strong potentiation required to perform WM. When applying more stringent thresholds (see supplementary figure 10) we observed that WM exhibited highest potency in DMN, in accordance with the idea that DMN areas are involved in working memory (232,233). To access the areas involved in modulation, we summarized the number of selected edges per area and describe the highest 10% of them in supplementary figures 7, 8 and 9. Supplementary figure 9 illustrates the high specificity of ventral and dorsal pathway connectivity in WM (90). By comparison, STOP showed specific modulations involving areas typically observed in the inhibition networks (see supplementary figure 7; van Rooij et al., 2015), while REWARD specifically modulated putamen connectivity (see supplementary figure 8). Next to task-specific modulations, motor, visual, and higher-order cognitive regions including temporo-frontal areas showed sensitive yet unspecific involvement across multiple tasks (figure 7). This result suggests that while our tasks probed different cognitive domains, they did tap into similar cognitive processes resulting in similar connections exhibiting significant task potency. This is not surprising however, given that the three tasks included in the current study all loaded relatively high in terms of the amount of cognitive control needed to solve them successfully. Figure 7 illustrates this by showing that the commonly modulated edges loaded primarily on areas implicated in the cognitive control network as described by Cole and Schneider (234).

While task potency can be used in a binary way, it effectively indexes the amplitude of task-induced connectivity modulations. Accordingly, task potency can be regarded as a continuum of potencies across different tasks per connection. Here, we investigated different cognitive loads by computing the “most potent task” per connection. In line with literature (235,236) WM proved to be the most requesting task in our set in terms of absolute potency. In contrast, STOP seemed to be the least potent task in our study as less connections were selected compared to both other
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tasks, yet supported by specific potentiation of connections linked to the visual 1 and subcortical networks (see figure 10). REWARD most potentiated brain regions and networks known to be part of typical reward circuitry (see figure 10 and supplementary figure 8). While we compared between tasks in the current study, a task potency continuum can also be obtained in relation to variation in cognitive load within a given task. Including such task designs would allow investigating the link between potentiation of connectivity and cognitive complexity.

Our task potency model is based on the idea that task activity builds on the brain’s inherent functional architecture as captured in large-scale resting state networks (12,58,74,223). Here, we showed preferential modulation of connections within those large-scale networks, while the limited number of modulated between-network connections exhibited greatest task specificity. This observation is consistent with the hypothesis that local processing is supported by out-of-network connections during task performance (237). The idea that the resting functional architecture provides a common baseline further supports the need for a full and independent resting state acquisition to allow capturing the baseline functional landscape across the frequency range, as using in-task-OFF-block-resting-state data will be constrained by the task mind-set and relaxation of task potentiation. To demonstrate this point, supplementary figure 15 displays the potency value and selectivity of connections when computing task potency using the full acquisition time series (as used in all main analyses) compared to the time series with the task design regressed out (i.e., residual time series). Across edges, task potency computed from the residual time series is strongly related to the full acquisition-based task potency. Furthermore, when investigating edge selectivity and its variability across bootstraps, we observed that the selectivity in the residual-based task potency is lower compared to the full acquisition-based time series. This shows that regressing out the design reduces the stability of the edge selectivity by removing (part of) the functional connectivity modulations induced by the task.
These observations suggest a need to further investigate task potency around task trials to better understand connectivity modulation mechanisms and to study specific cognitive process by assessing specificity within a task design using task contrasts as is done in activation analyses. This could be approached by using beta time series that correspond to a concatenation of regression coefficient for each of the trial of a specific event type in the task (see Mennes et al., 2013 for an application; Rissman et al., 2004). We did not perform this analysis due to the limited number of trials, which did not provide the required statistical power. Additionally, we note that, as it is the case for activation analysis, the task potency will depend on task design choices such as the number of trials, their interval, or the task length. Therefore, in this manuscript, we explicitly interpret the specificity across the three tasks available in the NeuroIMAGE database without extrapolation to other (not included) tasks and cognitive constructs. More investigation on the impact of such design choices on the observed modulations is required.

In this regard, using task potency to compare a task’s ability to probe cognitive domains is possible as presented in figure 10. Yet, using the potency framework to make design optimization choices is not particularly beneficial compared to other available tools such as NeuroDesign (238) or FILM (239) as the task potency framework requires sufficient statistical power to reliably compute functional connectivity modulations.

In the context of reverse inference investigation, the opportunity to compare tasks in a standardized space can also be a means to resolve and quantify how specific a given task-activation pattern is for a cognitive function. Current implementations typically rely on mining available literature (72,93,98,192) to compare a task modulation amplitude across a multitude of tasks in order to infer task specificity for a certain region. In contrast, our approach is to compare each task against a common resting baseline that can effectively be regarded as a superposition of the brain’s full functional repertoire (12) allow the implicitly comparing of tasks against each other. This allows assessing connectivity specificity while avoiding potential literature bias or strong a-priori models (study design, HRF response), albeit at the cost of being restricted to the
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typically smaller number of within-study cognitive domains being probed.

While offering a framework to study task fingerprints and connectivity specificity, we did observe variability in task potency across individuals. Task-related functional connectivity yields potential to understand individual variability in performance or task-related individual markers, as it has been successfully used to categorize tasks (76), to predict performance (130), or to predict task-induced activity (77). In our investigation, we were unable to find strong associations linking task potency to task performance. Yet, supplementary figures 11 (STOP), 12 (REWARD) and 13 (WM) illustrate that when correlating task potency and a corresponding task performance value that edges showing the strongest behaviour-potency correlations were in fact linked to task-relevant areas. Moreover, understanding task-related modulations might enable predicting functional connectivity in individuals that deviate from the norm, e.g., in a pathological response or using an alternative strategy to perform a task. Indeed, defining task potency relative to an individual resting state baseline is relevant for clinical applications where we cannot assume that individuals with pathologies have similar baseline architectures as healthy control participants. As such, task potency might prove an interesting feature for cohort stratification, e.g. within the framework of normative modelling (163), aimed at characterizing how individual participants differ from a large normative range in regard to multiple brain-behaviour relationships. As an initial example, we investigated the effect of age on the development of potency amplitude in a separate manuscript (240). A similarly large age range was included in the current study. Accordingly, in light of the developmental effects we described, we here verified that the current results, which focused on sensitivity and specificity, were not driven by age. To this end, we replicated our results including only participants age 16 and older. The strong reproducibility of our results in this restricted age group is evident in supplementary figure 14.

Finally, two methodological considerations in light of our potency approach ought to be discussed. First, we chose to calculate task potency using partial rather than Pearson (full) correlations between regional
time courses. Pearson correlation is often used to study functional connectivity. It has the drawback of potentially including redundant information across edges as shared variance is not excluded. Using partial correlation allowed indexing direct connectivity between areas within our atlas, thereby facilitating to detect specificity. For comparison, we also report the analyses using full Pearson correlation in the supplementary material. Results are presented in supplementary figure 14 and yield conclusions that are consistent with the main analysis. However, we did observe that the ensuing results exhibit decreased specificity, in light of an overall increase in sensitivity (i.e., more edges were found to be modulated by task), yet with common edges being mainly related to motor and primary visual areas. Second, any interpretation of connectivity findings is inherently dependent on the regions used to build the connectome. Here, we used 179 regions that were part of a hierarchically defined atlas. However, this atlas is not purely function-based, as the subcortical and cerebellum network masks were anatomically defined. To verify that our results were not driven by our network definition, we repeated the analyses using an alternative higher-level grouping of our areas into seven resting-state networks (202). The results are presented in supplementary figure 14 and show very similar results to our main analysis, thus demonstrating that our results did not depend on our definition of higher-level networks.

In conclusion, our task potency framework quantifies task-induced connectivity changes relative to the resting-state baseline in order to index task-specific modulations away from the brain’s functional baseline. Here, we showed that while general task performance relied mainly on within-network interactions, task specificity related to network interactions involved a close exchange between functional networks in both the cortex and subcortical structures. Using the potency framework, we can address how function emerges in response to a task, as well as how the brain’s baseline functional architecture influences cognitive operations. As such, the potency of our model lies in its ability to unfold the brain’s fluctuations in terms of the resources that are required while performing a task.
Disentangling common from specific processing across tasks using task potency

SUPPLEMENTARY MATERIAL

TASK SAMPLE CHARACTERISTICS

**rfMRI**

**STOP**

**REWARD**

**WM**
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**Supplementary Figure 1.** Demographic information of each task sample. Age distribution is displayed in yellow. The left chart represents the percentage of participants across 4 age bins and the right chart displays the percentage of male and female participants. Note that these plots do not represent independent samples, i.e., participants can appear in multiple plots. The union of these plots constitutes the full sample included in our study as described in the main text.

**Potency Calculation**

**Supplementary Figure 2.** Surface representation of the ICP atlas with 179 areas represented for the 9 top-level resting state networks. Note that the anatomically defined sub-cortical and cerebellum networks are not shown here.
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**Supplementary Figure 3. Illustration of representative values of the different steps in the potency pipeline.** Each plot illustrates the distribution of edge values for the average and standard deviation across the population (columns 1 and 2) and across edges (columns 3 and 4). Each row illustrates a step in the potency pipeline: the Z partial correlation (row 1); the normalized Z partial correlation (row 2); and the final task potency (row 3). The distribution of the mean and standard deviation of the Gaussian extracted for each matrix in the normalization step is displayed in the bottom graph.
**Supplementary Figure 4.** Population-level normalized Z partial correlation (A & B) and the task potency (C & D) for the stop signal task (STOP) and working memory task (WM). The population average is corrected for population sample size. Figure 4 in the main text shows these matrices for the reward task.

**Adjusted FDR threshold**

\[ pFDR_n \leq \frac{w_n}{w_n + w_p} \cdot pFDR \]

\[ pFDR_p \leq \frac{w_p}{w_n + w_p} \cdot pFDR \]

**Supplementary Formula 1.** Adjusted pseudo False Discovery Rate of the negative tail (N) and the positive tail (P) of the distribution. The weights, \( w_n \) and \( w_p \) correspond to the area under the gamma distributions estimated by the mixture model. This adjusted FDR enables to estimate connections significantly modulated on both sides of the Gaussian distribution while accounting for asymmetry of the signal. In the manuscript we used pFDR ≤ 0.05.
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**Edge Selection Details**

**Supplementary Figure 5.** Details on the edge selection used in Figures 5 and 6 in the main text. In each section the bold line represents those edges used as the denominator to calculate the percentages shown in Figures 5 and 6. The coloured sections represent those edges used as the nominator in those calculations. Selections were made separately for edges making connections within networks and edges connecting regions between the large-scale networks.
Supplementary Figure 6. Bonferroni corrected P-values for the pairwise comparisons between networks regarding the percentage of selected edges across all bootstraps. This figure provides the statistics for the top bar graphs shown in Figure 5 in the main manuscript. Networks are compared pairwise and independently for the within network and between networks percentage. Only significant differences are coloured. The diagonals are meaningless, upper and lower triangles of the matrices are identical.
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**Region-wise potency for each task**

Supplementary Figure 7. Region-wise mean potency for connections modulated by STOP only. The average is calculated as the average potency across STOP-specific edges for each region. Each region’s opacity is related to the relative average compared to all areas in the atlas; the less transparent the higher the region’s average potency. The colours correspond to network reference colours as displayed in Figure 1 in the main text. The bottom two rows display the top 10% areas with the highest average potency.
Supplementary Figure 8. Region-wise mean potency for connections modulated by reward only. The average is calculated as the average potency across reward-specific edges for each region. Each region’s opacity is related to the relative average compared to all areas in the atlas; the less transparent the higher the region’s average potency. The colours correspond to network reference colours as displayed in Figure 1 in the main text. The bottom two rows display the top 10% areas with the highest average potency.
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Supplementary Figure 9. Region-wise mean potency for connections modulated by WM only. The average is calculated as the average potency across WM-specific edges for each region. Each region’s opacity is related to the relative average compared to all areas in the atlas; the less transparent the higher the region’s average potency. The colours correspond to network reference colours as displayed in Figure 1 in the main text. The bottom two rows display the top 10% areas with the highest average potency.
Supplementary Figure 10. Percentage of sensitive edges that are specific to WM in light of the FDR threshold applied when determining sensitivity. In this figure, pFDR 0.05 is represented on the outer circle as 100%, and subsequent thresholds are displayed relative to 0.05, e.g., for the motor network all edges that were significant at 0.05 remained significant at pFDR 0.01. Figure 6 in the main manuscript shows that at the nominal pFDR of 0.05 WM potentiated a high number of edges across all networks. We illustrate here that step-wise increases in the threshold reveal that for connections that are specific to WM, the DMN, motor and visual networks exhibited strongest potency.
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**LINKING TASK POTENCY TO TASK PERFORMANCE MEASURES**

To evaluate the relationship between task potency and task performance, we computed the correlation across subjects between the main task performance value of each task and the potency of each selected edges. A Z-score of these correlations was computed and edges showing an absolute z-score above 2.3 were conserved.

Below we show for each task those regions that are linked to these edges showing a high task potency at the group level and a high correlation with the task potency.
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Supplementary Figure 13. Areas showing a strong correlation between the task potency edges selection in WM and the visuo-spatial working memory task is the ratio of success and failed trials. The task performance loads onto regions within the ventral and dorsal pathway with the precuneus, temporal, fronto-opercular and frontal pole areas.
POTENCY AS A FUNCTION OF AGE, PEARSON CORRELATION, AND ATLAS

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**Supplementary Figure 14. Comparison of analyses shown in the main manuscript using different input data:** “NORMAL” refers to the analyses of the main manuscript (see figures 5 to 9); “OVER 16 YEARS OLD” refers to a sub-selection of our sample with only participants over 16 years old to verify whether developmental effects are influencing our conclusions; “CORRELATION” refers to using Pearson correlation instead of the Z partial correlation as input data as it is a metric often used in functional connectivity analysis; “Yeo 7” refers to a sub-selection of our atlas and a grouping of this selection into 7 functional networks as described by Yeo et al. (202) to verify that our conclusions are not related to our atlas definition. As evident from the figure, our conclusions are robust to each change. Moreover, it is clear that partial correlation as used in our main analysis allows capturing more specific information compared to the results obtained when using Pearson correlations to calculate task potency. While the results for the Pearson correlation show an increase in sensitivity and thus the number of selected edges, this increase proved to be less informative, including redundant sensitivity and edges that were less specific to each task, e.g., and abundance of visual edges was selected using Pearson correlation. A full resolution file of this figure is available in Supplement 2.
Disentangling common from specific processing across tasks using task potency

**POTENCY CALCULATED ON RESIDUAL TIME SERIES**

**Supplementary Figure 15. Comparison between task potency computed from the full time series versus residual time series obtained after regressing the task design out.** Top row: Difference between the percentage of edge selectivity in half of the bootstrap for the full acquisition-based task potency versus the other half of the bootstrap from the full acquisition or versus the bootstrap for the potency calculated from the residual time series. Bottom row: Direct comparison of the average potency across participants for each connection obtained using the full task time series versus the residual time series. The bottom row illustrates that there is a strong linear relationship at the edge level between potency from the full acquisition time series and task potency calculated using the times series with the task design regressed out. This result illustrates that the relative relationship between edges remains similar regardless of the time series that was used. However, we did observe a difference in edge selectivity (top row). We computed selectivity of each edge across the 10000 population bootstraps and observed that the difference in edge selectivity when comparing the task potency obtain using the full time series to task potency obtained using the residual time series shows an asymmetrical distribution that is shifted toward the negative, indicating a greater selectivity when using the full acquisition time series. This demonstrates that the full acquisition allows to more robustly assess task potency, suggesting that more relevant task information is captured when using full acquisition compared to only using the residual time series.
CHAPTER 2

DAILY STATE-OF-MIND AFFECTS TASK-REST CONNECTIVITY MODULATIONS: A MYCONNECTOME ANALYSIS

Chapter 2

ABSTRACT
It is thought that task activation in fMRI builds upon neural network architectures shaped through ongoing network activity. Accordingly, task performance can be influenced by the state of the ongoing activity, the state of the response network, and/or the interaction between these two. Here, we aim to disentangle how daily fluctuations in a participant’s state-of-mind (SoM) affect task-induced network connectivity modulations. To this end we use of the MyConnectome dataset, which provides numerous imaging and behavioural datapoints for a single participant.

We model the relationship between connectivity variations during resting state (RS) and during task performance using a novel task-potency approach and estimate associations with SoM measures available for all sessions of a N-Back task. To account for potential redundancy between SoM, we extracted five SoM clusters using Ward variance minimization on the correlation between SoM measures. Finally, we visualise the expression within the task of these SoM clusters to look at difference in mindset of the subject during hit and miss trials.

We observe that a higher task potency (i.e., a greater difference between rest and task) might be a marker of non-beneficial SoM, and that positivity-Attentiveness was generally linked to a reduced task potency, as opposed to Negativity-Fatigue-Anxiety. Within a task, during hit and miss trials, resources are allocated to different State-of-Mind, beneficial or not for the task performance. We can explain miss trials with a pattern of lack of attention during previous trials, and doubt at the response time.
INTRODUCTION

It is thought that in order to perform a task, brain activity builds upon existing neural network architectures, processing information through the modulation of network activity (12,77,188). The large-scale underlying networks appear to be active at all times and represent major functional activation patterns that can be observed across a vast repertoire of tasks (12). Yet, while providing a consistent functional baseline, it has been shown that network characteristics vary in time and can be influenced by variations within or around an individual, including mood-related variations (187,241,242). Similarly, an individual’s state-of-mind (SoM) is known to impact task performance (243,244). However, it remains unclear whether SoM variations impact task performance through effects on the underlying baseline activity, effects on task-induced activity, or an interaction between both. Here, we aim to disentangle how daily fluctuations in a participant’s SoM affect the brain’s functional baseline and task-induced network connectivity modulations.

Mood, motivation or stress have all been linked to changes in baseline functional architecture as measured through functional connectivity (245–247). For example, a sad mood has been shown to modify the strength of connectivity of the insula, cingulum and default mode network (245). Prolonged stress also impacts the connectivity strength at both the sensory processing level by altering the visual network, as well as at the higher processing level with changes in the Default Mode Network (DMN) and in attention networks (246). At the subcortical level, emotional and motivational processing are shown to alter striatum connectivity (247). These regions and networks are often also required in processing information when performing a task. Therefore, SoM-related changes in baseline architecture could impact a network’s ability to modulate connectivity under cognitive constraint. Studies support the idea of interactions between SoM, network state and network activation during tasks. Change in motivation assessed by modulation of reward in a task protocol is known to impact task performance. A change in reward does not only affect the response to the trial on which this reward applies, but also impacts consecutive trials via modulation of attention level (243,244). Due to the relationship between networks across the
brain, local changes can affect cognitive processing more globally (131). Studies support the hypothesis that changes in motivation modify the early processing of information by changing the perception of stimuli through the modulation of selective attention processing (248). Alternatively, motivation may also impact downstream information processing by altering higher cognitive processing (249).

Neural correlates of SoM are often investigated using cross-sectional research protocols where participants answer SoM-related questions at the moment of or directly after functional Magnetic Resonance Imaging (fMRI) acquisition. As an example, across the large sample of individuals from the Human Connectome Project, network activity has been linked to a general positive-negative axis extracted from a combination of lifestyle, demographic and psychometric assessments (250). This general effect successfully captures one aspect of an individual’s personality or cognitive abilities, describing the population using a single dimension like an IQ score for estimating intelligence (251). However, cross-sectional analysis might not be the most appropriate way to investigate neural correlates of a measurement with a time-varying component. The mindset of an individual varies longitudinally. Answers to questionnaires might be influenced by events taking place around the time of participation in the study or might depend on the more general mindset of the participant at that time. For example, the mood of a participant is shown to cycle over weeks or across the year (252–254).

In order to understand how daily changes in mindset might affect underlying neuronal activity and task performance, we need to investigate within-participant longitudinal data. In this study, we use the MyConnectome dataset, which provides numerous imaging and behavioural data points for a single participant (187), to investigate the neural correlates of daily changes within an individual. We apply a recently developed method to separate the task-related modulation of functional connectivity from the resting-state network architecture: task-potency (255). As functional connectivity is driven largely by group and individual variations (256), using a single subject longitudinal dataset enables the removal of group variation. By using the task-potency metric to relate rest and task from the same acquisition session, part of the
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

individual baseline architecture variation can be removed, therefore enhancing our sensitivity to SoM-related variation on the task performance. We previously observed that, during human cognitive development, the task potency, i.e. rest-to-task modulation, decreases with the increase of cognitive performance (255). We hypothesise that a more efficient network, built through learning or maturation, requests less modulation and so less energy to activate. In this line, we further hypothesise that a lower modulation toward the task state is an index of brain efficiency. We aim to investigate that hypothesis by using the participant’s SoM data and expect to observe a smaller difference between baseline and task-induced connectivity in SoM, beneficial for task performance (e.g. attentiveness).

METHOD

MyConnectome Dataset

We used daily measurements of one individual including resting fmri, task fMRI and behavioural questionnaires. These data come from the openly available “MyConnectome” dataset which provides data for one right-handed participant who performed two scan sessions per week with a fixed schedule for one year (187). The current analyses use data from 13 sessions where the participant performed both a resting state and an N-back task fMRI scan on the same day each week, while also recording multiple behavioural questionnaires.

The participant’s daily variations in SoM were captured using data from questionnaires that were completed on the morning and evening of the scan days. We selected a total of 31 measurements available for each of the 13 selected days. 13 mood-related scales were computed from the PANAS-X questionnaire (257): joviality, serenity, positive scale, negative scale, fear, self-assurance, attentiveness, surprise, fatigue, hostility, guilt, sadness, shyness. Further, three morning measures were self-reported: sleep quality, soreness, weight; and six behavioural measures were recorded on the previous evening and the evening of the scan: gut health, psoriasis severity, alcohol intake, time spend outdoors, stress. In addition to behavioural questionnaires, three text analysis measures were extracted from the participant’s response to emails using RIOT Scan word counting software (version 1.8.2, https://riot.ryanb.cc/) (258): the
Linguistic Inquiry and Word Count (LIWC; (259)) of positive and negative emotions, as well as a metric indexing abstract versus complex writing (categorical-dynamic index; CDI) (260). Finally, we also incorporated three measures from the scan session report: the use of a noise-cancelling headphone, the day of the week, and self-reported anxiety during the scan.

During the selected scanning sessions, the participant completed an anatomical scan, a resting state scan (eyes open), and an N-Back task fMRI scan. The N-back task is a working memory task in which items are presented sequentially and where the participant should detect whether the currently-presented item is the same item as that which was presented “n” items earlier in the sequence. The current tasks had a 1-back and a 2-back memory load condition, i.e. the participant had to respectively detect similar items following each other or with one item in between. Three types of items were used: Chinese characters, faces, or houses, resulting in six different block types during the acquisition. Both rest and task acquisitions used the same imaging sequence with an 8 min acquisition time. fMRI parameters can be found in table 1. N-Back task performance was defined as the difference between the hit trial rate and the false alarm trial rate (d prime) across all types of trials (261).

**Extracting SoM clusters**
To account for potential redundancy between the 31 measurements selected from the behavioural questionnaires and to aid in the interpretation of our results, we further clustered these measurements into 5 SoM clusters. To this end, we obtained the correlation matrix between these measurements and applied a hierarchical clustering algorithm incorporating Ward’s variance minimization to this correlation matrix. From the resulting dendrogram, we extracted five distinct clusters described in the Results section. All further interpretation of results was conducted using cluster-level SoM metrics.

**fMRI preprocessing**
We preprocessed all of our fMRI data in a similar way and used the preprocessed data to extract connectivity matrices for each dataset. All
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

fMRI acquisitions were processed using tools from FSL 5.0.6 (FSL; http://www.fmrib.ox.ac.uk/fsl) (213,216,262). We employed the following pipeline: removal of the first volumes to allow magnetization equilibration (Table 1), head movement correction by volume-realignment to the middle volume using MCFLIRT, global 4D mean intensity normalization, spatial filtering with a 6mm FWHM Gaussian kernel. Subsequently, we applied ICA-AROMA, an automated algorithm to detect head motion-related artefacts in single-subject fMRI data based on independent component analysis (ICA). ICA components identified as related to head motion were subtracted out of the data using fsl_regfilt (66,67). Finally, we regressed out mean signals from cerebrospinal fluid and white matter before applying a 0.01Hz temporal high-pass filter.

For each session, both rest and N-back acquisitions were registered to the high-resolution T1 image, closest acquired in time, using Boundary-Based Registration (BBR) available in FSL FLIRT (213,218). All high-resolution T1 images were registered to MNI152 space using 12-dof linear registration available in FLIRT and further refined using non-linear registration available in FSL FNIRT (200).

For further connectivity calculations, we used 158 regions defined in a hierarchical whole-brain functional atlas (220) derived from resting state fMRI data of 100 participants of the Human Connectome Project (HCP; (204,263)). We transformed the atlas to each participant’s functional space to compute connectivity matrices in the native space relative to the closest T1 of each session. The transformation was performed using the inverse of the anatomical-to-MNI152 non-linear warp, and the inverse of the linear transformation of the functional image to the participant’s high-resolution anatomical image of each respective session. Atlas areas that were, on average, across all included sessions, >50% outside of the brain were rejected from further analyses. As a result, we used 152 areas, shown in Figure 1, to compute connectivity matrices.
Figure 1 illustrates the hierarchical brain atlas, where areas were grouped in 11 higher-level networks: 9 resting state networks (Sensory-motor, Visual 1, Visual 2, Parieto-Frontal, Insulo-cingulum, Temporo-Frontal, Attention 1, Attention 2, Default Mode Networks (DMN)), and 2 networks based on anatomical structures, i.e., the subcortical areas, and the cerebellum. These higher-level networks respectively contained 10, 6, 19, 16, 17, 16, 17, 13, 17, 18 and 5 subregions, resulting in a total of 152 initial parcels.
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**STATIC FUNCTIONAL CONNECTIVITY**

**CONNECTIVITY CALCULATION**

To compute the functional connectivity between each pair of regions of the atlas for each resting state and N-back task fMRI acquisition, we obtained each region’s time series through multivariate spatial regression, using all 152 regions as regressors and each task’s preprocessed time series as a dependent variable. The resulting regional time series were demeaned. Using these time series, we calculated 152x152 partial correlation matrices through inverting covariance matrices estimated by the Ledoit-Wolf normalization algorithm (222) as implemented in nilearn (http://nilearn.github.io/). Finally, all pairwise correlations were Fisher r-to-Z transformed.

We normalized the rest and task connectivity matrices so they would be comparable between each other and between sessions in order to study longitudinal variations in resting state connectivity, task connectivity and rest-to-task connectivity interactions. The normalization was performed for each matrix according to the main Gaussian distribution extracted from a Gaussian-gamma mixture-model (225,264). This model fits three curves to represent the data: a central Gaussian distribution representing the noise and two gamma distributions on each side of the central Gaussian that represent the signal at the tails of the data distribution. As a result, the values within the normalized Z-transformed partial correlation matrices are readily comparable across rest and task sessions (225). Using the normalized matrices, we calculated task potency matrices which index the within-session difference between the resting and the N-BACK scan and characterise the rest-task interaction (255).

To index day-to-day variations in connectivity changes, we applied a second normalization. For each connectivity value in the daily rest and task connectivity matrices, we determined whether the value constituted a change towards or away from their alternative. To this end, we computed the difference between each edge’s daily connectivity value and the average connectivity value for that edge in its alternative (i.e. daily rest versus average task and daily task versus average rest). We then compared this distance with the difference in connectivity between the average rest and average task matrix. A smaller daily difference
compared to the average difference indicated that the daily connectivity value was closer to its alternative (e.g. for day 1, resting state connectivity was actually closer to task connectivity compared to the average difference; while for day 2, rest connectivity had moved away from that of task). We then applied the sign of this change (positive for moving closer, negative for moving away) to the daily connectivity matrices. For clarity: this procedure was not applied to the task potency matrices. Finally, all daily rest, task, and task potency matrices were demeaned with respect to their cross-session average.

STATE-OF-MIND (SOM) CONNECTIVITY MAP

In order to assess the relationship between these connectivity variations and daily changes in SoM, we related the 31 behavioural measurements to each matrix entry in the rest, task and task potency connectivity matrices. Specifically, for each of three connectivity matrices, we implemented a linear model for each behavioural measurement and extracted the beta-weight of each model into a measurement map. This resulted in 3 (connectivity metrics) x 31 (behavioural measurements) x [156x156] (connections) beta-weight matrices.

For the task and rest variations, we implemented the direct linear model between the measurement and the connectivity variation. For the task and rest interactions, the linear model incorporated the rest, task and task potency variation and the extracted beta-weights were taken from the task potency.

To summarize the relationship between the connectivity matrices and the behavioural measurements, we first grouped the beta-weight matrices based on the five SoM clusters. For each cluster and each connectivity metric, we then applied a principal component analysis (PCA) to extract the main mode of variation indexing the relationship between the SoM measurements and the respective connectivity metric. We tested the significance of this relationship for each connection (p<0.05) by comparing the obtained loading on the main mode of variation to a null distribution obtained by replicating the PCA across 10,000 beta-weight maps that we obtained via randomizing days within each behavioural measurement and rerunning the linear models.
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

**Dynamic Expression of the Task Functional Connectivity**

**Connectivity Time Series Calculation**

To assess whether SoM was related to within-session variation during performance, we computed a dynamic connectivity metric. We extracted the temporal derivative of each region’s time series and multiplied each time point in the derivative between regions, resulting in one connectivity matrix per time point (265). We filtered the dynamic connectivity matrices using the static connectivity in order to enhance the connectivity signal. To this aim, we used the inverse function derivative (formula in figure 2) creating a pseudo-dynamic partial correlation (p-dPC).

In order to assess patterns of dynamic connectivity (similar to what we implemented for analysing static connectivity) we calculated a dynamic task potency by subtracting the mean static rest from the p-dPC. In addition, the sign of the p-dPC was adjusted according to the mean static connectivity as previously done for static connectivity.

Both p-dPC and dynamic task potency were further demeaned by their relative static connectivity matrix to obtain the within-session variation.

**Time Course Analysis**

Using the p-dPC and dynamic task potency, we evaluated the expression of the static SoM-potency relationship within session. To this end, we regressed each SoM’s beta loading map onto each dynamic connectivity signal: the rest and task SoM maps into the p-dPC and the task potency SoM maps into the task potency dynamic connectivity. We summarized the resulting relationship across edges for each connectivity metric. This resulted in one timeseries for rest, task, and task potency which indexed how strong each time point within each session was related to each SoM.

To assess the relationship between SoM and task performance, we indexed the obtained SoM-dynamic connectivity relationship around hit and miss trials by averaging the SoM expression in the -5 to 2 seconds window around trials, for hit and miss trials independently (across all sessions). We again assessed the significance of the difference in expression between hit and miss trials using 10,000 permutation maps.
**Chapter 2**

**Figure 2**: Pipeline of the Connectivity Computation starting at the Z Partial Correlation, normalized according to the main Gaussian of the mixture modeling and divided by standard deviation of each connection of RS acquisitions. Sign of task and rest is set to reference bigger or smaller deviation from one another before demeaning to obtain variation to the grand mean. These variations are the independent variables in three linear models aimed at explaining SoM attentiveness.

### Static Connectivity Calculation

<table>
<thead>
<tr>
<th>Static Connectivity</th>
<th>Dynamic Connectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial Correlation (ZPC)</td>
<td>task.pseudo-dynamic connectivity</td>
</tr>
<tr>
<td>RS</td>
<td>difference to the mean task</td>
</tr>
<tr>
<td>task potency</td>
<td>dynamic task potency</td>
</tr>
<tr>
<td>difference to the mean RS</td>
<td></td>
</tr>
</tbody>
</table>

### Static Connectivity Modeling

- SoM e.g. attentiveness $- \beta$ RS $\times$ RS $+ \text{constant} + \text{error}$
- SoM e.g. attentiveness $- \beta$ N back task $\times$ N back task $+ \text{constant} + \text{error}$

### Dynamic Connectivity Modeling

- Z-Poisson Transform
  - Matrix normalization
  - Task and rest
  - Normalized ZPC
  - Defining variations
  - Demeaning
  - Sign adjusting

- Inverse function derivative $\delta \text{PC} = \delta \text{PC} \times \delta \text{PC} \times \delta \text{PC}$

- $\delta \text{PC} = \delta \text{PC} \times \delta \text{PC} \times \delta \text{PC}$
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

RESULTS

ACROSS-SESSION EFFECTS

<table>
<thead>
<tr>
<th>Same evening</th>
<th>Positive-attentiveness</th>
<th>Previous evening</th>
<th>Negativity-fatigue</th>
<th>Negativity-anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>same evening:</td>
<td>PanasX: joviality, serenity, positive scale, self-assurance, attentiveness, surprise</td>
<td>previous evening: PanasX: gut health, alcohol, psoriasis severity, stress,</td>
<td>PanasX: negative scale, fatigue, hostility</td>
<td>PanasX: fear, sadness</td>
</tr>
<tr>
<td>gut health, psoriasis severity, alcohol, time spent outdoors, stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day of week</td>
<td>noise cancelling headphone during scan</td>
<td>date of scan</td>
<td>sleep quality in the previous night</td>
<td>morning soreness</td>
</tr>
<tr>
<td>weight</td>
<td>performance in the N-back task</td>
<td>previous evening: time spend outdoors</td>
<td>anxiety during scan</td>
<td></td>
</tr>
<tr>
<td>LIWC positive emotion in email</td>
<td>LIWC CDI in email</td>
<td>LIWC negative emotion in email</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1: DETAIL OF THE FIVE GROUPS OF MEASUREMENT RESULTING FROM THE HIERARCHICAL DENDROGRAM

Based on the linkage between measurements, three main clusters were defined: the first cluster grouped all measurements related to the evening following the MRI session (same evening); the second cluster grouped measurement related to positive and attentive state; the third cluster was larger and included the performance to the task. We then decided to split the larger cluster into the next lower level of the dendrogram. This allowed us to define a cluster related to measurements of the evening before the MRI session, including the task performance and two clusters related to a negative mindset. One negative cluster related to tiredness including fatigue and sleep quality and the other one related to anxiety with fear, anxiety in the scanner and anxiety during
scan as well as negative emotions in email analysis. Both previous and same evening clusters will later not be used in the analysis of the dynamic connectivity for interpretation purposes. The cluster names and their corresponding behavioural measurements are shown in Table 1.

In order to assess the relationship between connectivity variations and daily changes in SoM, we modelled the linear relationship between daily variations of the 31 behavioural measurements and each matrix entry in the rest, task and task potency connectivity matrices. We summarized the effects across groups of measurements, i.e. SoM cluster, by extracting the main mode of variation from each of the three independent linear models. Figure 3B shows the corresponding eigenvalues of the main modes of variation for rest, task, and task potency. It is clear that the eigenvalues show great similarity between the rest and task linear models, suggesting that a common effect of these daily measurements in the global connectivity is at play.

Indeed, in figure 3C, we observed a general pattern when assessing the loading of the main mode of variation of the rest and task modalities. The matrices in figure three display the strength of each edge’s (or network’s) loading onto the main mode of variation obtained for each SoM. When averaging effects at the network level (figure 3C, lower triangle), we generally observed either a positive or negative pattern. The effect of the same evening and the positive attentiveness clusters is overall positive, meaning that the rest and the task connectivity are getting more similar under these SoM. The same evening cluster shows a mix of negative and positive effects. In contrast, the two negativity-related clusters show a general negative loading into rest and task variations, showing that the task and rest connectivity patterns are less similar under a negative SoM.

When assessing the interaction between rest and task via the task potency metric, we observed a different eigenvalue pattern (figure 3B), showing that the rest-task interaction relates differently to each SoM compared to rest and task separately. Looking at the SoM relationships at the edge and network level (figure 3D), we did not observe the general positive or negative effects. but observed that the direction of the SoM relationship was network-specific. This suggests that the interaction
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between the rest and task states under a certain SoM is related to a specific connectivity pathway.

To assess the significance of our results, we tested connection and network effects against 10,000 null beta-weight maps. We observed a dissociation in the direction of the significant SoM-connectivity modulation relationships between the rest and task assessments. Significant SoM-network interaction relationships under rest were mostly negative, showing that specific networks are moving away from the task state. In contrast, for the task modulations, we observed that the significant SoM-network interaction relationships were positive, moving closer to the rest architecture. The insulo-cingulum and the temporo-frontal networks, in particular, showed a reduced need of modulation across the positive and negative SoM cluster in task and, within insulo-cingulum, moving away from the task state in both positive and negative SoM. Finally, the task potency loadings showed both positive and negative effects that were network-specific, especially SoM related to task potency in the insulo-cingulum and the DMN.
Figure 3: State of Mind connectivity loading. The hierarchy over the similarity in correlation between the measurement is displayed in the top row. The eigenvalues for the first component of principal component analysis on the respective linear models of the rest, task and the task potency for each of the five clusters and first eigenvectors in the three connectivity modalities are represented in each cluster columns. Only the significant connections are displayed in the top triangle of each of the matrices. The lower triangle corresponds to the average value per network interaction, the non-significant networks interaction are represented with a lower opacity such that the gradient on the right applies to the top triangle and the significant values in the lower triangle.
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

**Within session expression of the SoM maps**

In order to assess if a SoM built on daily variation translates into a lower window scale and affects performance during the task, we evaluated the expression of the SoM in the dynamic task connectivity and compared the time series around hit and miss trials. We tested the significant difference of the expression of SoM maps in the average time series between hit and miss trials through comparison with the expression of the 10000 SoM permutation maps.

During the 2-back trials, we observed that most of the significant SoM expression differences are related to their higher expression during miss trials. 35 times points show significantly higher expression of a SoM for one connectivity modality in miss trials compared to 11 times point higher expression in hit trials.

Specifically, during miss trials, we observed that the loading of the negative-fatigue related to resting-state and task potency variations express after the presentation of the stimuli n-2, i.e. the one matching with trial onset, and the stimuli n-1. After missing the trial, before the presentation of the stimulus +1, we observed a significant expression of the negative-anxiety loading from resting state variations. As for the hit trials, we observed a significant expression of the positive-attentiveness loading of the task potency variation after the presentation of the stimulus n-2 and an expression of the negative-fatigue task potency loading after correctly responding to the trial.
**Figure 4:** Within-session representation of three of the SoM clusters. The top graph shows the average dynamic functional task connectivity around one task trial in the case of a hit or a miss trial. The stars show when the SoM clusters load with significant differences between the hit and trial time courses, compared to the permutation null representation of the SoM. The loading is higher in the miss trial time course when the arrow is red, and blue when the loading is higher in the hit trial time course.
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

DISCUSSION
We investigated the effect of day-to-day changes in an individual’s state of mind on functional connectivity while at rest, functional connectivity during task performance, and the interaction between those two contingencies. We observed a general positive-to-negative variation of the overall functional connectivity in line with the positive-to-negative State-of-Mind of the participant. A negative SoM such as fatigue or anxiety increased the distance between resting state and task functional connectivity. In contrast, a positive SoM had the reverse effect, bringing task functional connectivity closer to the resting architecture, suggesting smaller changes in modulation are needed to perform a task when in a positive mindset.

A larger distance between the resting and task connectivity architecture results in larger required modulations to perform a task. Previous research estimated the efficiency of modulation of connectivity by modelling the energy consumption required as represented by the oxygen consumption in the brain (266). They found that more energy is required for higher connectivity modulation, as shown across the local connectivity versus hubs area in the brain. Together, these findings support the idea that more modulation is generally more energy demanding. This hypothesis echoes that less reconfiguration between networks is related to higher intelligence (267), which we can then hypothesise to be a reflection of more efficient, less costly, cognitive processing. In light of these studies and our results, we can therefore interpret required higher modulation as costly and non-beneficial. Accordingly, the relationship between SoM and rest-task connectivity modulations observed here might represent a neural mechanism underlying day-to-day variations in perceived task difficulty.

This general modulation effect that needs to be overcome to reach the task state was different from the specific interaction between rest and task functional connectivity. We found that specific network pathways were affected by SoM across both connectivity states, meaning that the SoM would impact the general flexibility across states for specific networks. Depending on which networks are required to perform the task, their ability to modulate (i.e. their flexibility to reach the task state)
can be affected by the SoM of the participants and impact the perceived task difficulty. Especially for the integration of information between higher cognitive networks such as insulo-cingulum, the DMN, temporo-frontal and attention networks show higher sensitivity to SoM. In addition, a state of tiredness showed a greater effect on sensory networks (visual and somato-motor). A recent study integrates fluorodeoxyglucose-positron emission tomography and fMRI to define the relationship between the cost of glucose metabolism and the level of regional activity (268). The study demonstrates that fronto-parietal regions and DMN are metabolically demanding: these regions show higher activity with signs of a costly glucose metabolism. These findings support our observation that a negative SoM (as particularly evident with negative-fatigue) requires a higher modulation of activity between networks and a fast but inefficient underlying glucose metabolism. A positive-attentive SoM would enhance the pathway between fronto-parietal and cerebellum, being less demanding and having a more efficient metabolism, across rest and task states. In a positive-attentive state, the insulo-cingulum and attention networks connectivity as well as the DMN and subcortical connectivity require less modulation, increasing their ability to switch states. The effect is reverse in a negative-anxious state. As for the negative-tiredness state, we observed an increase inflexibility in sensory networks but an increase flexibility of the insulo-cingulum networks. Whether these networks are required in the task and depending on the SoM of the participants, the cost of performing the task might vary.

In line of this, the frontal, precuneus and cingulum have also been reported to be related to personality traits (269,270). While personality traits are quite stable, studies have shown that they might vary across lifespan (271–273). These Big Five personality traits (Agreeableness, Conscientiousness, Openness, Extraversion and Neuroticism) and the Panas score (currently used in this study and that describe the positive negative state in an individual) are related over time (274). We show that at a smaller time scale, behavioural variations are also related to variations in these networks.
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

The specific networks that are significantly affected by SoM are previously reported as key networks underlying multiple cognitive processes. The cingulum has been characterised as a key hub between networks related to autobiographical information, motivation and emotional processing (131). The fronto-parietal network has been shown to be a flexible hub between multiple tasks and higher cognitive processes (83). Lastly, the DMN is well-known to be a key network anticorrelating with task networks (275) and is also important as a processing hub (276,277). These multi-functional networks are keys to efficient reconfiguration and their level of activity correlates with better task performance (278). Related to our n-back task, we can note particularly that, in working memory, cingulum and fronto-parietal flexible reconfiguration is related to increased accuracy (279). Therefore, we can conclude from our results that these networks are used in multiple tasks and the mindset is key to switching between cognitive processes.

However, fronto-parietal, subcortical, cingulo-opercular and default-mode networks also have a maximum modulation capacity (280) and flexibility of networks are reported to show limitations, particularly in terms of multitasking and the ability to process information for multiple sources (281). For example, emotion and memory have been shown to heavily interact. When an emotional cue is coherent with memory content, recollection is strengthened. When both types of information are incoherent, memory performance is impaired (131,282,283). Their common brain networks are interacting at the level of frontal and attentional connectivity. Non-congruent modulation with the task at hand were observed, suggesting a limitation of networks in multitasking, splitting capabilities between cognitive processing and impairing their optimal functioning. As multi-functional networks are already in high demand, managing a SoM and performing a task would imply splitting this capacity between processes, reducing the optimal and maximal involvement in each of them. These networks are also therefore more highly sensitive to SoM effects that will reduce their ability to optimally process information regarding the task at hand.
We therefore further investigated the representation of these SoM effects within task sessions in order to better understand variations that lead to hit or miss trials and to assess whether task and rest functional connectivity variations affect task performance. Indeed, previous research has shown that the baseline state before trial onset, for example in DMN or attention networks, predicts the outcome of the trial (233,284). Looking at the SoM loading in dynamic connectivity, we observed a generally higher expression of SoM in miss trials, showing more task-unrelated variation in connectivity, suboptimal for task performance. We then focused on the interpretation of the three positivity-negativity related clusters. The observed significance difference in loading of SoM between hit and miss trials follows an interpretable pattern. The positive-attention SoM most notably loads during presentation of the matching stimuli prior to a hit trial, suggesting that variation in baseline enables more flexible and more responsive networks, leading to a success in the trial. In contrast, the negative-fatigue SoM related to baseline and the task-rest interaction mostly affects the connectivity during a miss trial, between presentation of stimuli and the matching (onset) stimuli. This suggests that baseline connectivity variation is also relevant for the ability to integrate information during task and its modulation away from the task state leads to failing task performance. Interestingly, this effect is not observed in related variations in the task connectivity, meaning that a knowledge of both task variation and rest variation is needed to understand the full integration of information and the task performance.

Our results suggest that an individual’s SoM is relevant to understand brain variation during cognitive processing and that to describe SoM effects, we need information from both variations in task-induced modulations as well as from baseline variation. However, by defining the SoM maps in only one individual, we cannot disentangle whether or not observed effects are specific to that individual. Replication of this investigation that would look at similar positive-negative SoM could assess whether they also generally tap into less or more modulation between rest and task. Replicating these results with other participants would give insights into the individual variation of the brain’s representation of SoM in terms of specific network loading, or variation
Daily state-of-mind affects task-rest connectivity modulations: a MyConnectome analysis

in strength of the SoM effect into cognitive processing. However, no other datasets are currently available with such a range of metadata around fMRI acquisition. Even without metadata, only few datasets are available with multiple fMRI acquisition time points within an individual, as the protocol is heavy for the participant. Most of the available high-sampling fMRI datasets are acquired by dedicated researchers. While this enables access to a higher sensitivity of neural correlates of time-varying characteristics, results need to be carefully interpreted as they remain specific to an individual.

While these SoM are not referring to cognitive concepts defined by psychology, their expression within a task informs us about the participant’s reduced ability to process task information by splitting resources into irrelevant cognitive processes towards accurate performance. These SoM processes are also relevant to study neural correlates of a specific cognitive function. Showing the heterogeneity of response across brain networks, where some networks will have an altered task-response, flexibility is important when trying to model the relationship between neural correlates and task parameters such as change in cognitive demand. In the same line of thinking that removing common architecture improves sensitivity to neural correlates in a task study (285), we propose that controlling for the SoM of a participant will improve our understanding of brain mechanisms and network relationships. Additionally, cognitive training is optimal when participants work on their Zone of proximal development, as a task of moderate difficulty (286). Using these individual mindsets could also be used as indices to predict performance within task, by controlling the indexing level of neural correlates of fatigue or attention of an individual, therefore adapting training to each individual. Another application domain would be the travelling head within multicentre neuroimaging studies (287). In this protocol, several subjects travel from site to site to acquire fMRI sessions in order to define differences between sites. These differences are used to adjust data of all other participants across the dataset. If changes in the SoM of these travelling head participants can affect the data, it can be mixed with the analysis of site differences while being an independent and irrelevant effect, therefore altering the correction applied across sites. Defining a sensitivity map to individual
variation across the brain can be a tool to disentangle relevant site effects from behavioural variations in these subjects.

In conclusion, we observed that a participant’s SoM interacts with the rest-task relationship. Indeed, the baseline functional architecture and the task state are closely related. The ability of networks to modulate from one towards the other impacts task performance. Therefore, as the mindset of the participant affects network flexibility, assessing this mindset is relevant to control for individual variabilities and obtain more sensitive results for the cognitive process of interest.
Assessing age-dependent multi-task functional co-activation changes using measures of task-potency

CHAPTER 3

ASSESSING AGE-DEPENDENT MULTI-TASK FUNCTIONAL CO-ACTIVATION CHANGES USING MEASURES OF TASK-POTENCY

**this chapter is based on:** Chauvin RJ, Mennes M, Buitelaar JK, Beckmann CF. Assessing age-dependent multi-task functional co-activation changes using measures of task-potency. Developmental Cognitive Neuroscience, Volume 33, October 2018, Pages 5-16

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ABSTRACT
It is being hypothesised that the developing adolescent brain is increasingly enlisting long-range connectivity, allowing improved communication between spatially distant brain regions. The developmental trajectories of such maturational changes remain elusive. Here, we aim to study how the brain engages in multiple tasks (working memory, reward processing, and inhibition) at the network-level and evaluate how effects of age across these tasks are related to each other. We characterise how the brain departs from its functional baseline architecture towards task-induced functional connectivity modulations using a novel measure called task potency, allowing direct comparison between tasks by defining sensitivity to one or multiple tasks. By applying this method in a sample of healthy participants (N=218) aged 8 to 30 years, we demonstrate maturational changes in task-dependent functional co-activation over and above baseline connectivity maturation. Our results provide evidence for task-specific maturational windows with different cognitive systems probed by different tasks displaying specific age-range dependencies of strongest developmental change. Our results highlight the use of task potency for modelling developmental trajectories and the impact of differential maturation across tasks. This enables better characterisation of cognitive processes disrupted in neurodevelopmental disorders and may explain the increased level of heterogeneity observed in adolescent population studies.
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INTRODUCTION
Understanding human cognition in adolescent cohorts is invariably linked to understanding cognitive maturation and brain development. Multiple theories aimed at modelling development build on the seminal work of Jean Piaget to explain maturation of cognitive abilities (25). The interactive specialization theory states that cognitive functions interact in their maturation (26,137). For instance, the maturation of working memory and processing speed is predictive of language maturation (141).

Experimental evidence for the interactive specialization theory supports its notion that maturation is a combination of planned biological, experience-induced, and learning-induced changes (142,143). Neuroconstructivism further proposes that learning-induced maturation applies to the cellular-, brain network-, and cognitive function-levels. As cognitive functions would not mature independently, brain networks would also not mature independently (138,139), i.e., developmental changes in reward processing will impact the development of inhibition, and would be reflected in neural correlates of this maturational interaction between neural networks. As an example, in maturation of memory, emergence of knowledge can be modelled from interactions between prior knowledge (288). To assess the idea of co-occurring development, it becomes necessary to investigate underlying common maturational processes between cognitive functions and their neural correlates.

Task-based fMRI has been instrumental in assessing hypotheses that relate brain development to such cognitive maturation. However, due to periods of rapid development during adolescence the use of a single task across a large age-range to characterise cognitive maturation remains practically challenging. Moreover, many studies examine changes in a single fMRI task with development, which limits the generalizability of possible conclusions. In this context, resting state fMRI has been put forward as a viable alternative as it can be administered across ages regardless of cognitive abilities. Although resting state fMRI allows investigation of the brain’s baseline functional architecture (12), and can predict task responses (58,74,77), observed changes with age in the brain’s resting architecture might not be sufficient to explain maturation
in cognitive performance. As studies indicate that task-related connectivity builds on the brain’s baseline functional architecture, it is clear that resting state connectivity does not capture all neural processes that are related to task performance (74,75). Therefore, resting state-derived results provide insight into a different aspect of brain functioning yet cannot substitute task-based fMRI studies that aimed to link a specific cognitive function to specific brain areas (289). Assessing the additional value of task-fMRI in understanding cognitive maturation requires dissociating age-related changes in the brain’s baseline architecture from age-related changes in task-induced neural modulations departing from that baseline. Ideally, this would incorporate multiple experimental tasks allowing to obtain insight into task- or function-specific versus common patterns of maturation.

Relying on the availability of both resting-state fMRI and task-fMRI data we use a novel analytical approach to define task-modulated functional connectivity that enables us to look at common maturational effects across multiple tasks. Importantly, we index task-induced modulations independent of generic maturational changes in the brain’s baseline architecture. More specifically, we focus on so-called task-potency, an index that compares functional connectivity under task performance relative to the brain’s generic baseline functional architecture as measured using resting-state functional connectivity. This is based on the idea that engaging in a task causes modification of functional connectivity away from its baseline status (74,75), in a way that allows prediction of the task modality (73,77). This is enabled by the idea that resting state represents the landscape of cognitive states through fluctuation of large-scale networks SMITH 2009 (241,290) and allows to capture specificities of an individual (230,291). As task potency is readily comparable across tasks we can investigate the existence of singular versus common maturational processes across cognitive functions, allowing us to investigate the idea of co-occurring development. We here demonstrate that characterisations on the basis of task potency give rise to interpretable differential developmental trajectories of different cognitive systems.
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Such comparisons between tasks while incorporating resting state fMRI by means of the task potency measure offer great potential in the context of large-scale neuroimaging efforts that include multiple tasks acquired in large cohorts (e.g., NKI-RS (292), the HCP Lifespan Project (263), UK Biobank (293), and FCP-INDI (294)). Instead of analysing individual task responses independently, task potency focuses on integration across multiple tasks (295). Here, we used a local database providing three fMRI tasks (working memory, reward processing and inhibition) acquired alongside a resting-state scan in a large developmental cohort and assessed the impact of age on task-induced connectivity modulations. Specifically, we focussed on the relationship of age effects between tasks and their potentially common underlying maturational processes.

METHODS

PARTICIPANTS

In the current analyses, we use MRI data from healthy control participants only (initial N=385) of the NeuroIMAGE sample (175) who each performed at least one of the following tasks during fMRI scanning: response inhibition (Stop Signal Task (STOP)) (see (45,175,207)), reward processing (REWARD) (see (175,208–210)), spatial working memory (WM) (see (133,175,211,212)). In addition, each participant completed a resting state fMRI session (10 min, eyes open). fMRI acquisition parameters are shown in table 1. All participants also completed an anatomical scan for registration purposes (T1-weighted MPRAGE, TR=2730 ms, TE=2.95 ms, T1=1000ms, flip angle=7, matrix size=256x256, FOV=256mm, 176 slices with 1mm isotropic voxels).

FMRI scans exhibiting limited brain coverage or excessive head motion were excluded from further processing. Limited brain coverage was defined as having less than 97% overlap with the MNI152 standard brain after image registration. Applying this criterion excluded 47 subjects (details in table 1). In addition, we excluded from each task those participants who were among top 5% in terms of head motion as quantified by RMS-FD, the root mean square of the frame-wise displacement computed using MCFLIRT (213). Applying these criteria
resulted in the inclusion of data from 218 healthy controls, comprising 218 resting state acquisitions, 111 STOP acquisitions, 123 REWARD acquisitions, and 144 WM acquisitions. Participants ranged in age between 8.6 and 30.5 years; mean=16.9; sd=3.4; 54.1% were female. Further details are included in Table 1 and Supplementary Figure 1.

**FMRI PREPROCESSING**

All fMRI acquisitions were processed using tools from FSL 5.0.6. (FSL; [http://www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) (214,216,262). We employed the following pipeline: removal of the first volumes to allow magnetization equilibration (Table 1), head movement correction by volume-realignment to the middle volume using MCFLIRT, global 4D mean intensity normalization, spatial filtering with a 6mm FWHM Gaussian kernel. Subsequently we applied ICA-AROMA, an automated algorithm to detect head motion-related artefacts in single-subject fMRI data based on independent component analysis. ICA components identified as related to head motion were subtracted out of the data using fsl_regfilt (66,67). Finally, we regressed out mean signals from CSF and white matter, and applied a 0.01Hz temporal high-pass filter.

For each participant, all acquisitions were registered to its high-resolution T1 image using Boundary-Based Registration (BBR) available in FSL FLIRT (213,218). All high-resolution T1 images were registered to MNI152 space using 12-dof linear registration available in FLIRT and further refined using non-linear registration available in FSL FNIRT (219).

<table>
<thead>
<tr>
<th>Image acquisition parameters</th>
<th>RS</th>
<th>STOP</th>
<th>REWARD</th>
<th>WM</th>
</tr>
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<tr>
<td><strong>General parameters</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE=40 ms, FOV=224mm, 37 axial slices, flip angle=80, matrix size=64x64, in-plane resolution=3.5mm, slice thickness/gap=3.0mm/0.5mm</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N volumes</td>
<td>&gt;260</td>
<td>86 * 4 blocks</td>
<td>&gt;300</td>
<td>107 * 4 blocks</td>
</tr>
<tr>
<td>TR (ms)</td>
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<td>2340**</td>
<td>2340**</td>
<td>2340</td>
</tr>
<tr>
<td>N first volumes rejected*</td>
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<td>4</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
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<td>N used in final analyses</td>
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<td>111</td>
<td>123</td>
<td>144</td>
</tr>
<tr>
<td>RMS-FD min-max</td>
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<td>0.029 - 0.413</td>
<td>0.027 - 0.554</td>
<td>0.033 - 1.504</td>
</tr>
<tr>
<td>RMS-FD mean (std)</td>
<td>0.171 (0.224)</td>
<td>0.09 (0.074)</td>
<td>0.13 (0.099)</td>
<td>0.17 (0.23)</td>
</tr>
<tr>
<td>Age min - max</td>
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<td>8.6 - 27</td>
<td>9.1 - 23.9</td>
<td>8.6 - 27</td>
</tr>
<tr>
<td>Age mean (std)</td>
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<td>17.1 (3.5)</td>
<td>16.8 (3.2)</td>
<td>16.8 (3.2)</td>
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<tr>
<td>% female</td>
<td>54.1%</td>
<td>54.0%</td>
<td>57.8%</td>
<td>52.8%</td>
</tr>
<tr>
<td>IQ mean (std)</td>
<td>104.1 (14)</td>
<td>104.5 (14.5)</td>
<td>104.1 (14.5)</td>
<td>104.3 (12.8)</td>
</tr>
</tbody>
</table>

* The number of initial volumes removed from further analyses varied to ensure comparability with earlier studies that used these data. Note that this variation will have very limited impact on the
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Some subjects were scanned with a different TR: RS - 1860 for 11 subjects; STOP – 2150 for 10; REWARD – 2150 for 10.

**Table 1:** fMRI acquisitions parameters

**Region-of-interest analysis**

For each functional imaging scan we defined connectivity matrices using regions defined in a hierarchical whole-brain functional atlas (220). This atlas contains 185 non-overlapping regions and was defined through Instantaneous Correlation Parcelation (ICP) applied to resting state fMRI data of 100 participants of the Human Connectome Project (HCP; (263)).

In short, ICP aims to parcel larger regions into subregions based on signal homogeneity, where the optimal number of subregions is determined based on split-half reproducibility at the cohort level.

Figure 1 illustrates the hierarchical brain atlas, where areas were grouped into 11 higher-level networks: 9 resting state networks (visual1, visual2, motor, right attention, left attention, auditory, default mode network (DMN), fronto-temporal and striatum), and 2 anatomical structures (subcortical areas, and cerebellum). These higher-level networks respectively contained 19, 12, 22, 22, 18, 8, 18, 13, 7, 23, and 23 subregions.

All analyses were performed in each participant’s native space. To this end we transformed the atlas to each participant’s native space using the inverse of the anatomical to MNI152 non-linear warp, and the inverse of the linear transformation of the functional image to the participant’s high resolution anatomical image. Voxel-membership in brain parcels was established on the basis of majority overlap. Areas that were on average across our population over 50% outside of the brain were rejected from further analyses. This resulted in the rejection of one area in brainstem. For consistency, we removed the 5 other brainstem areas. As a result, we used 179 areas to compute connectivity matrices, as explained in the next section.
Figure 1: 179 areas selected from an ICP-based parcellation of the human brain (van Oort et al). Each area is coloured in accordance to its overarching network. Eleven large-scale networks constitute the first level of the parcellation: visual 1, visual 2, auditory, motor, frontal-temporal (fronto-temp), right and left attention (R_attention, L_attention, respectively), default mode (DMN), cingulum, sub-cortical (sub cort), cerebellum (cereb) networks. We used the 179 regions that are part of the sub-network scale parcellation to obtain functional fingerprints based on 179x179 correlation matrices.
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**CONNECTIVITY CALCULATION**

For each participant and each task (rest, WM, REWARD, STOP) we calculated 179x179 connectivity matrices, by cross-correlating the time series of all regions in our atlas. We obtained each region’s time series through multivariate spatial regression, using all 179 regions as regressors and each task’s preprocessed time series as dependent variable. The resulting regional time series were demeaned. For the WM and STOP task we temporally concatenated the time series of individual runs. Using these time series, we calculated 179x179 partial correlation matrices through inverting covariance matrices estimated by the Ledoit-Wolf normalization algorithm (222) as implemented in nilearn (http://nilearn.github.io/). Finally, all pair-wise correlations were Fisher r-to-Z transformed.

To allow comparison of connectivity values between acquisitions, we normalized the connectivity values within each matrix to fit a Gaussian distribution (Figure 2). Importantly, we were cautious not to affect the tails of the connectivity distributions as these represent the most interesting connectivity values. Therefore, we modelled the obtained connectivity values per task using a Gaussian-gamma mixture-model to obtain “mixture-model-corrected” Z-stat values (225,264). This model fits three curves to represent the data: a central Gaussian distribution representing the noise and two gamma distributions on each side of the central Gaussian that represent the signal as the tails of the data distribution. We used the main Gaussian, i.e., the one fitting the body of the distribution, to normalize our connectivity values with respect to its main distribution (i.e., noise), while not taking into account the extremes (i.e., signal). In practice, we applied the mixture modelling to the upper triangle values of each connectivity matrix and subsequently normalized the connectivity values by subtracting the mean and dividing by the standard deviation of the obtained central Gaussian model. As a result, the values within the normalized, Z-transformed partial correlation matrices are readily comparable across tasks (Feinberg et al. 2010).

To differentiate connectivity changes induced by task modulation from changes in the baseline architecture, we standardized each participant’s task-based connectivity matrix by the population average resting state
matrix. This effectively allows interpretation of the task-based connectivity matrices in terms of their deviation from the resting state baseline connectivity. Accordingly, we can interpret the resulting values as ‘task potency’, referring to the magnitude of the task-induced connectivity modulation. We standardized each individual-level connection, i.e. entry in the correlation matrix, by subtracting its own individual-level connection value from rest across all participants (We did not include participants without resting state acquisition in this study).

As such, each task-based pair-wise correlation or edge quantifies how connectivity for that edge differed from that edge’s connectivity during the resting state. For each participant we obtained a standardized connectivity matrix for each of its task acquisitions, further referred to as task potency matrices. For each task, we finally created group-level task potency matrices by averaging across the participant-level matrices.

**FIGURE 2:** Task-potency pipeline. Using the brain parcellation shown in Figure 1, we calculated 179x179 connectivity matrices for each individual in each task (WM, REWARD, STOP, RS). From the Fisher r-to-Z transformed partial correlation, we obtained task potency by first normalizing the task and rest connectivity and subsequently subtracting the rest from the task connectivity. Through population averaging and thresholding the resulting matrices we obtained a task potency fingerprint for each task (WM, REWARD, STOP).

**TASK-BASED FINGERPRINTS**

To focus on maturational change of connections that characterize a task’s functional fingerprint we selected - for each task - those edges that showed a relevant deviation from rest (see Figure 2 right half). To this
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end we converted the group-level task potency matrices to Z-statistic matrices by subtracting the mean and dividing by the standard deviation calculated for each task matrix. For each task we then selected those edges with an absolute Z-statistic >= 2.3. This threshold was chosen to represent 2.3 standard deviation from the Gaussian noise of the baseline distribution, thereby respect the logic of sparseness, i.e., strong connectivity modulations occur infrequently, and to correspond to a p-value of 0.01 for each end of the task-potency distribution. We refer to those selected edges as task-modulated edges and to the resulting matrices as task-based fingerprints. Here, we defined task-based fingerprints at the group-level by selecting edges in the task potency matrix as averaged across the population. Group fingerprints describe each task-potency architecture and can be used to address common connectivity modulations between tasks. Note that it is also possible to create fingerprints at the individual level, i.e., the individual task connectivity matrix adjusted for its individual resting state connectivity matrix. Individual potency fingerprints reflect individual variability in the task potency architecture and can be directly compared to its group-level equivalent. We did not investigate individual-level potency in this study.

INVESTIGATING EFFECTS OF AGE

We investigated age-related effects on task potency based on the underlying idea that task connectivity modulations that are in common between tasks reflect underlying common mechanisms. Accordingly, we investigated age-related effects on the potency of single edges as well as on an average potency across subgroups of edges. For both analyses, we used least square fitting to investigate the linear change with age, thereby maximising the detection of maturational processes while minimizing the complexity of the model. We applied correction for multiple comparisons across the tested subgroups of edges by implementing FDR correction (q<0.05).

The subgroups of edges we used were, for each task, 1) edges modulated by this task only, 2) edges modulated by this task and one of the two other tasks, 3) edges modulated by all three tasks. See the Venn-diagram in Figure 3 for an overview of potential edge subgroups. We propose that similar changes with age will be observed across tasks in connections that
they co-modulate. For example, if task potency in one task increases with age for an edge modulated by more than one task, we would expect to observe a similar increase with age in all other tasks modulating this edge.

The average potency across edges within each of the edge subgroups specified above reflects an average underlying mechanism, but potentially obscures effects that play at the single edge level. To gain insight into age effects at the level of single edges we compared the slope of the linear relationship between age and potency for each edge within the task-modulation fingerprint of two tasks. Specifically, we plot the slope of each edge in one task against the corresponding slope of that edge in the other task. We then fit an ellipsoid on the resulting scatter plot using least square fitting to quantify the relationship between the two displayed tasks. If the ellipsoid stretched around the $x=y$ diagonal axis, it indicates a strong relationship between the two parameters, which in our case translates into the observation that connectivity modulation would mature similarly in both tasks. We conducted this analysis independently in edges shared by the two tasks or selected in only one task. To further quantify the strength of the relationship we calculated the width/height ratio of the ellipsoid fit. The closer this ratio is to 1, the rounder the ellipsoid, and the weaker the relationship between the two tasks.

Finally, at the single edge level, we further tested for second order changes with age, i.e. we tested whether the speed of the maturational changes varied as a function of age. We assumed that age effects would be stronger in younger than in older participants. To this end, we modelled a linear change over a short age window of 1 year including 7 participants from this window. When more than 7 participants were available within an age window we randomly selected 7. We moved this window across our entire population, each time removing the youngest subject of the window and considering a 1 year age span starting from the age of the subject immediately following in age. We extracted the absolute beta value of the linear regression for each window as a marker for the speed of change with age of the task-potency.
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**Disentangling baseline and task-modulation effects**

In order to confirm that task-potency changes with age were not solely driven by changes with age in the baseline (i.e., resting-state derived) connectivity, we assessed whether age also impacted baseline connectivity and whether potential age effects on the baseline related to age effects on task-based connectivity modulations. To this end we also conducted our age-based analyses on the baseline connectivity, i.e. the normalized $Z$-partial correlation extracted from the resting state scan. We compared age effects obtained for baseline and for task modulation and evaluated whether both measures were related by correlating the baseline connectivity score with the task-potency across subjects. At the edge level, we defined the fingerprint of the baseline connectivity by selecting edges with $|Z| > 2.3$. We assessed the correspondence between age effects on shared selected connections in each task with age-related changes observed at baseline by least-square fitting an ellipsoid as done for the comparison between tasks.

**Results**

**General effects of age on task-potency for selected edges**

For both the STOP and WM task we observed that task-potency across edges modulated by each task decreased significantly with age. This suggests that in each of these tasks, as participants mature, their task-modulation and baseline fingerprint become more similar to each other (Figure 3A and 3B). In addition, we observed a significant decrease with age in baseline connectivity (Figure 4).

To confirm that the task-potency changes with age were not driven by changes with age in the baseline connectivity, we correlated the average potency observed under task modulation to the average connectivity in the baseline condition across the population. The average was computed independently for edges modulated by the STOP and the WM task. We observed no correlation between the resting connectivity and task potency for either task: $r$(STOP, REST)=0.026; $r$(WM, REST)=−0.054. This suggests that the modulation of connectivity under task performance
shows developmental changes that are independent of the maturational changes in baseline functional connectivity.

EFFECT OF AGE ON TASK-POTENCY FOR COMMON EDGES ACROSS TASKS FINGERPRINTS

To investigate common underlying maturational mechanisms across tasks, we estimated the effect of age on average potency across selected edges modulated by multiple tasks. Edges modulated by both the STOP and the WM task showed a significant decrease in average potency as measured under STOP and WM modulation (Figure 3D). To investigate whether the age effect is specific to tasks modulating these edges, we also assessed the average potency of these edges in the REWARD task. While REWARD-related edges did not show a significant change with age in the average potency across selected edges, average REWARD-potency across selected edges shared by STOP and WM shows a significant decrease with age (Figure 3D). The observation that edges sensitive to both WM and STOP also show an age effect under REWARD, although they are not sensitive to modulation by this task, suggests that maturation of task-modulation in one task can be transferred across tasks.

Such common effect of age could be due to the maturation of a subgroup of edges modulated by all three tasks. However, edges shared between all three tasks showed a decrease in average potency with age in the STOP task only (Figure 3E). This result indicates that the age effect detected in edges modulated by STOP and WM is not dependent on shared selected edges with REWARD and supports the idea that task-connectivity modulation can be identical between tasks, even if the edges are not strongly modulated by each of the tasks. Additionally, the STOP task is the only task showing an age effect in edges shared by all tasks, which indicates existence of maturational processes attributed to a single task.
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Figure 3: Effect of age on edges modulated by each task. Each graph illustrates the effect of age for corresponding edges indicated in the Venn diagram. A: edges modulated during WM; B: edges modulated during STOP; C: edges modulated during REWARD; D: edges modulated by WM and STOP; E: edges modulated by all three tasks. All displayed effects, except for C, reached statistical significance at p < 0.05 after FDR correction. The age effect is calculated by linear regression of age against the average potency over the specified subset of edges. The average potency decreases significantly with age for edges selected in STOP and WM, in all tasks for edges shared by WM and STOP, and in STOP for edges shared by all three tasks.
Figure 4: Effect of age on baseline, i.e., resting state connectivity. Age is linearly regressed against the average normalized Z partial correlation over edges selected in the resting state fingerprint. Connectivity decreases significantly with age at p < 0.05.
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**Visualization of areas related to shared edges between tasks showing an age effect**

Figure 5 illustrates which areas are related to the edges exhibiting the top 5% strongest age effects across the edges modulated by both WM and STOP for which we observed age-related effects in all three tasks (see Figure 3E). When comparing the edge representation in Figure 5A, B, and C it is clear that, within the edges modulated by both STOP and WM, all three tasks displayed the strongest age effects between areas of visual1, fronto-temporal, cingulum, DMN, attention, and cerebellum networks. Of note, a subset of the displayed edges is not strongly modulated under REWARD, we have created separate visualizations of the strongest age effect for edges modulated by all tasks and for edge modulated under STOP and WM only. For these we refer to supplementary figures 5a and 5b. Comparison of these separate figures enables differentiation of whether similarity across tasks is due to shared modulation. As the similarity between tasks generalized to both subsets of edges (supplementary figure 5 a and b), the current results suggest non-independence of age effects between these tasks, especially at the level of larger networks.
**Figure 5:** Top 5% areas showing the strongest linear age effects across edges modulated by STOP and WM tasks (darkest subgroup in the Venn-diagram, see also figure 3c). The linear age effect per edge, averaging and selection of the top 5% areas are done independently for each task and represented in A for WM, B for STOP, and C for REWARD. Circles represent the edges included in the top 5% area selection. Thicker edges in the circles represent those edges that formed a connection between two areas within the top selection.

**Effect of Age on Potency at the Single Edge Level**

The age effect on the average potency of edge subgroups as presented in the result section does not provide fine-grained information about single edges. Here, we quantify the similarity of the age effect between tasks by estimating the age effect for each single edge and subsequently
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comparing between tasks. To this end, we computed the effect of age for all selected edges in each task. Using edges related to a pair of tasks, we conducted two comparisons of their age effects: 1) between edges shared by that pair of tasks, and 2) between edges modulated by only one task within the pair. We assessed this relationship by fitting ellipsoids to a scatter plot of the data. When edges showed related age effects between tasks we expected to observe an ellipsoid elongated along the diagonal where x=y. As shown in Figure 6, first column, we observed an ellipsoid around the diagonal axis for edges shared between each pair of tasks (average 9.75 degrees deviation from x=y axis with an average width/height ratio of the ellipsoid of 0.75).

For edges only selected in one of the two tasks, we expected that correspondence between the age effects would be less strong, resulting in rounder ellipsoids. As evident in the two middle columns of Figure 6 we indeed observed rounder ellipsoids with a width/height ratio closer to 1, yet with a conserved orientation towards the x=y diagonal. This result supports the idea that task connectivity modulations share maturational processes that also impact modulation from tasks that are involved a different task fingerprint.

To add further verification that the age effect on task modulation (figure 3) was not related to the age effect on baseline connectivity (figure 4), we compared the baseline and the task modulation age effects at the edge level. We expected that the ellipsoid would show a reduced or absent orientation towards the diagonal as a marker of un-related maturational processes. Using edges selected in the task modulation fingerprint and in the baseline fingerprint, we displayed the effect of age on the resting state connectivity against the effect of age on the task potency for each edge and observed that the resulting ellipsoid fit showed no specific orientation and a strong elongation over the task modulation axis (see Figure 6 right column). This indicates that age effects observed for task potency and baseline connectivity were not related, suggesting that different maturational processes impact task modulation and resting connectivity.
Figure 6: Relationship of age-effects between tasks for specific or common edges. A linear regression against age is computed for each edge in the task potency of each task. The beta parameters corresponding to the slope of the linear regression are extracted for each edge and related between two tasks. Edges displayed in the left column are edges selected in both tasks included in the plot, the two central columns display correspondence for edges selected in only one of the two tasks of the plot. The right column displays correspondence for edges selected in the baseline fingerprint (i.e., the resting state z partial correlation) versus one of the tasks. An ellipsoid is fit over the points in the scatter plot and two values are extracted from the ellipsoid: the deviation from 45° (i.e., x=y) for the main axis of the ellipsoid and the elongation of the ellipsoid (i.e., width divided by height). Bar plots on the bottom illustrate these parameters for each of the left (black), the two central (grey), and the right column (blue).
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DEVELOPMENTAL DYNAMICS AT THE INDIVIDUAL EDGE LEVEL
To assess the dynamics of the observed age effect across the age range of our population we modelled the linear change with age using a sliding window approach. Figure 7, illustrates the maturational dynamics as indexed by the average slope of the effect of age across the selected edges per task. All tasks (Figure 7A, B, C) showed a non-linear trajectory across their maturational window. Compared to STOP, both REWARD and WM exhibited stronger age-related effects before age 15 (Figure 7B & 7C). In contrast (Figure 7A), the STOP task exhibited overall slower and more linear maturational dynamics continuing until age 18, suggesting more gradual maturational effects across our age range. This difference between tasks in the timing of maturational changes suggests that brain activity related to each task has a specific maturational window (Figure 7D). Combined with the finding that maturation is related between tasks at the edge level (Figure 6), the observation that the maturational dynamics have different timing is consistent with the idea that maturation in one task can influence maturation of another task. Here, we can speculate that faster developmental changes of WM and REWARD-related circuitry until age 15 potentially influences the continued STOP task maturation actually requiring smaller (but prolonged) developmental changes.

The resting state connectivity also exhibited more gradual dynamics, with the strongest maturational changes occurring before age 17 (Figure 7E). Importantly, the difference in amplitude of change between tasks and REST cannot be interpreted as the input data are of different nature, i.e., task potency (adjusted for rest) versus functional connectivity.
Figure 7: Average speed of change with age of task potency for STOP (A), REWARD (B), and WM (C). Each plot illustrates the absolute beta-parameters for each window in the sliding-average calculation. For each task we fit a 2nd order polynomial to model the rate of change across development. Graph D overlays each task’s 2nd order fit to allow comparison between tasks. Finally, E illustrates the rate of change for RS. Note that due to different input to the regression models, the amplitude for RS should not be directly compared to the amplitude for the other plots.
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DISCUSSION
We introduced task potency as a sensitive feature to study brain involvement in cognitive tasks across development. The feature is reflecting connectivity modulations under performance of a task relative to functional connectivity observed during a resting state. To study development, task potency enables dissociating changes with age in the brain’s baseline functional connectivity architecture from changes with age in functional connectivity as elicited across multiple tasks.

We observed task-specific maturation independent of age-related effects on the baseline (i.e., resting state) connectivity patterns (Figures 3A, 3B, and 4). For STOP and WM (Figure 3D), we observed that task potency decreased with age. At the same time, we observed that between-region resting state functional connectivity also decreased with age, thereby replicating previous studies (110). Importantly, we showed that the age-related effects on task potency were not related to the resting state maturation, both at the level of task-specific edges, as well as at the single edge level (Figure 6).

Decreasing task potency with age indicates that the task-based and resting state connectivity architectures converge with age, allowing reduced switching costs to transition from a baseline state towards a task state. The convergence between task-based and resting state connectivity exhibited task-specificity, i.e., the REWARD task showed different developmental trajectory relative to WM and STOP. This result replicates earlier findings from a meta-analysis where reward tasks showed significantly different task-dependant connectivity compared to task-independent resting state connectivity in adults (131). Note that the absence of a task-independent maturational effect, does not exclude the possibility of common maturational processes that are shared between select task, e.g., observed that STOP and WM showed a similar age effect as their average potency in the subset of edges shared by these two tasks decreased with age (Figure 3D). This decrease of task potency shared by the two tasks supports the idea of a shared underlying neural maturational process, located in a subset of edges modulated by both tasks. Moreover, this common maturational process did extend to REWARD, as the average potency of edges shared by the STOP and WM
tasks also exhibited decreasing potency with age in REWARD. Such co-maturation could be converging towards or supported by an architecture of flexible multi-task hubs as observed by Cole and colleagues (83).

By comparing common modulations across tasks, task potency enabled to define edges involved in the maturation of multiple cognitive functions. This allows developing new hypotheses to study how cognitive functions relate to one another. For example, if two related cognitive functions mature over two different time windows, the cognitive function that matures earlier will impact the maturation of the second one. We observed support for such hypothesis by investigating the difference in maturational dynamics between tasks. Specifically, we observed that REWARD and WM exhibited the strongest maturational changes at earlier ages compared to the STOP task (Figure 7). However, without a larger observation window, we cannot distinguish whether the STOP task simply displays a more gradual change across development or whether its strongest maturational changes happened in earlier developmental phases. Longitudinal data across a larger age window, would be required to allow investigating whether the bigger individual age effects in WM and REWARD require smaller maturational changes in the STOP task. The difference in timing of maturation between reward processing and inhibition relates to the idea that motivation and executive control interact during maturation through alterations in the communication between striatum and prefrontal cortex (PFC) (296). In the context of detecting salient environmental cues during adolescence, striatum, involved in early temporal coding of reward, would trigger bottom-up maturation of the connection between striatum and PFC. In contrast, top-down connections from PFC to striatal areas, reflecting cognitive control, mature only afterwards. Corroborating this idea, we showed connectivity modulation between areas typically involved in executive functioning (40,297) exhibited the strongest age-related effects (Figure 5). This result is in accordance the fact that executive functioning, being strongly associated to PFC functioning, is one of the cognitive functions that is thought to mature late, not reaching completion until early adulthood (298). Accordingly, through comparison of appropriate tasks and age-windows, task potency could be used, for instance, to predict inhibition-specific maturational changes related to
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PFC maturation. Yet, in this context, we highlight that our approach assumes that our normalisation approach allows isolating task-driven connectivity changes. However, the separation of exogenously-driven modulations from low-frequency fluctuations found in both resting state and task-related fMRI timeseries remains a matter of active empirical examination. While, the current results fit this presumption, it will require additional research of the neurophysiological basis of connectivity and its complex relationship to cross-correlated BOLD signal dynamics throughout the brain to know whether this assumption is fully supported.

Linking changes in connectivity to behavioural changes would provide more insight into how potentiation of edges matters for the maturation of cognitive functioning. Supplementary Figure 8 illustrates the maturational dynamics for the most typical behavioural parameter in each task. Similar to the maturational dynamics observed for task potency (Figure 7), the behavioural parameter for the STOP task (i.e., SSRT) did exhibit a more gradual change across the age window of our sample. In comparison, the behavioural parameters for REWARD (reward-related speeding) and WM (error rate) exhibited faster developmental changes in earlier ages. Our results corroborate behavioural studies providing evidence for maturation of cognitive abilities across our age range. For spatial working memory, a strong increase in the number of remembered items occurs between 11 and 15 years old (Conklin et al., 2007), while response inhibition exhibits a gradual increase in performance until adult-level performance is reached around age 15 (127,300). In addition, studies showing that maturation of reward processing can influence maturation of inhibition provide evidence for underlying common neural correlates of both cognitive process (125,126). However, it is clear that we cannot assume that these different behavioural metrics integrate the same biological underlying processes. A reaction time and an error rate will reflect a different integration of the processes involved in proper task performance. To address the relativeness of task at the behavioural level, common mental processes across task need to be defined (84).
A common concern for developmental studies that make use of functional MRI data is the impact of head motion (68). During preprocessing we have used ICA-AROMA to mitigate effects of participant head motion on the collected data (66,67). (for an independent evaluation of ICA-AROMA see e.g., (5)). However, as some younger subjects showed highest head motion (see supplementary material figure 2), and given that it has been shown that head motion is heritable (301), it is possible that head motion might relate to underlying biological features of interest and will accordingly exhibit maturational changes. To account for this potential interaction effect and to further validate our results, we replicated all results using a linear model including both age and head motion. Results can be found in supplementary figures 3, 4, 6, and 7. Overall, results were comparable between the different models, with limited changes in some relationships not reaching significance anymore, while others did reach significance when including head motion in the model. These changes can be due to the use of a more complex model, and to amplification of the age effect when movement related variance is modelled out, helping some age effects to reach significance.

Observing neural mechanisms of maturation that affect multiple tasks and their associated cognitive functions provides support for the interactive specialization theory (26,137) and neuroconstructivism (138,139), two related developmental theories stating that cognitive functions interact in their maturation. Our results corroborate earlier experimental evidence supporting the notion that maturation is a combination of planned biological, experience-induced, and learning-induced changes (142,143). Neuroconstructivism in particular proposes that learning-induced maturation applies to the cellular-, brain network-, and cognitive function-levels. As cognitive functions would not mature independently, brain networks would also not mature independently (138,139), i.e., developmental changes in reward processing will impact the development of inhibition, and would be reflected in neural correlates of this maturational interaction between neural networks. We observed an age effect on REWARD-related potency in edges that showed strong task involvement and a strong age effect in the STOP and WM tasks (Figure 3 c). The observation that these edges were not
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strongly involved in REWARD processing suggests that theses edges are trained, i.e. matured, by STOP and WM performance. This training then impacts these edges’ connectivity as observed under REWARD processing. We could not differentiate whether the age-related effects on the edges shared by STOP and WM tasks represent a common maturational mechanism or maturation of an independent cognitive function involved in all three tasks that would be evolving on its own (212). Longitudinal investigations would further enable to better understand variability in maturation between individuals and the specificity of task-related maturational processes. In this context, longitudinal measurement of resting state is of key importance to compare local age effects relative to local variability in resting state that is influenced by individual characteristics, experimental manipulations, or environmental factors. Accordingly, we encourage to obtain resting state data in the same session as the task scans (see also Chapter 1).

Future investigations could examine why a reduction in task-induced connectivity modulations is a marker of brain maturity, possibly distinguishing effects of changes at the neurophysiological level from changes in the brain’s response to a task. In connectivity studies, some authors interpret a reduction with age of resting state connectivity as a reduced need for energy for a network to function and a more efficient integration of information (110). This interpretation can also apply to task potency: a reduced switch from the baseline when engaging in a task can reflect a more efficient integration of information. This would support the idea that executive function performance is associated to higher flexibility in connectivity, allowing more frequent switching from one connectivity state to another (302). A lower task potency request facilitates such flexibility by making switching between rest and task less costly. We can hypothesise that a reduced need of modulation to reach the requested connectivity state would be beneficial for a better performance by reducing the cost of involvement in executive tasks. This hypothesis would need further validation. Investigating this hypothesis in the context of ADHD could provide such validation as it has been theorized that individuals with ADHD have difficulty in energizing their brain activity (178). We could investigate whether impairment of ADHD participants in executive functioning is linked to higher task potency.
levels displayed during tasks. If so, we could predict under what cognitive load or when ADHD participants would experience cognitive fatigue as the demand for task-induced modulations becomes too high. In general, investigation of cognitive impairment in developmental disorders such as ADHD is intrinsically linked to understanding deviant task-related modulations related to differences in the baseline brain architecture due to age effects and/or clinical representations. The task potency framework is well suited to enable researchers to detect and understand differences linked to cognitive performance in various domains of impairment, thereby tapping into both cortical and subcortical networks.

In conclusion, understanding how human cognition matures, requires defining not only functional connectivity changes in the baseline, but also changes in functional connectivity that is modulated by tasks (289). Our study shows that task potency defined as the difference in connectivity modulation between rest and task is a promising neural correlate to study cognitive development.
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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FIGURE 1: DISTRIBUTION OF PARTICIPANT AGE FOR EACH OF THE TASKS
Supplementary Figure 2: Relationship between age and head motion-related metrics. The first column illustrates for each task (row) the relationship between age and RMS-FD (213). While age did not strongly correlate with head motion, it is clear that some younger participants displayed more extreme displacements. Column two illustrates the ratio between the number of components selected for correction by ICA-AROMA and the total number of components resulting from the ICA decomposition. This ratio is not related to age, illustrating that across participants there was no age-related bias in the number of components removed from the data. However, the selected components loaded more onto one of the parameters used to select ICs in ICA AROMA (edge fraction), showing that removed components more strongly represented head motion in younger participants. It is clear that this edge fraction is directly associated to head motion (column 4), supporting the notion that we do remove head motion-related noise and not signal of interest.
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Supplementary Figure 3: Effects of age, age and head motion interaction, and head motion only on edges modulated by each task. Each graph corresponds to the analysis of the age effect on the average potency for corresponding edges indicated in the Venn-diagram. A: edges modulated during WM; B: edges modulated during STOP; C: edges modulated during REWARD; D: edges modulated by WM and STOP; E: edges modulated by all three tasks.

Each graph illustrates the additional effects of age only, age and head motion interaction, and head motion only from the following linear model: average task potency (P) = β0 + β1*age + β2*(ageXhead motion) + β3* head motion, where (ageXhead motion) is the interaction term of age and head motion, and βi are the parameters. The dots correspond to the real value, the pink area corresponds to the change in value explained between ‘P = β0’ and ‘P = β0 + β1*age’. The orange area corresponds to the change in value explained between ‘P = β0 + β1*age’ and ‘P = β0 + β1*age + β2*(ageXhead motion)’. The blue area corresponds to the change in value explained between ‘P = β0 + β1*age + β2*(ageXhead motion)’ and ‘P = β0 + β1*age + β2*(ageXhead motion)’.
Chapter 3

motion)’ and ‘P = β0 + β1*age + β2*(ageXhead motion) + β3* head motion’.

Compared to figure 3 in the main text, supplementary figure 3 shows that some significant effects of age are lost possibly due to the loss of degrees of freedom due to using a higher-order model (see A, age effect on the average potency of edges sensitive to WM is not significant and see D, the age effect on edges modulated by all tasks is lost for STOP). In addition, some variance in task potency can be linked to head motion and can thus be modelled out, revealing an underlying age effect in edges sensitive to the REWARD task (see E), or modulated by all tasks in REWARD (see D first graph). However, even if some head motion can be interacting with the age effect, it can’t be simply modelled out, as this interaction is significant in several cases, supporting the idea of a common underlying biology. See B and C (and supplementary table 2), when head motion shows a significant effect while age loses its significant effect compared to results in figure 3, the F-test across the age effect and the age by head motion interaction versus the head motion effect is significant. Modelling head motion without conserving the interaction would thus result in false negative age effects.
Assessing age-dependent multi-task functional co-activation changes using measures of task-potency

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**Supplementary Table 2:** Multifactor linear regression parameters linked to the regression plots shown in supplementary figure 3, the F-test corresponds to the analysis of age + ageXhead motion against head motion.
Supplementary Figure 4: Effect of age only, age and head motion interaction, and head motion only on resting state (RS) connectivity. The figure displays the additional effects of age only, age and head motion interaction, and head motion from the following linear model: average normalized Z partial correlation \( (P) = \beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot (\text{age} \times \text{head motion}) + \beta_3 \cdot \text{head motion} \), where \((\text{age} \times \text{head motion})\) is the interaction term of age and head motion, and \(\beta_i\) are the parameters. The dots correspond to the real value, the pink area corresponds to the change in value explained between \(P = \beta_0\) and \(P = \beta_0 + \beta_1 \cdot \text{age}\). The orange area corresponds to the change in value explained between \(P = \beta_0 + \beta_1 \cdot \text{age}\) and \(P = \beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot (\text{age} \times \text{head motion})\). The blue area corresponds to the change in value explained between \(P = \beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot (\text{age} \times \text{head motion})\) and \(P = \beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot (\text{age} \times \text{head motion}) + \beta_3 \cdot \text{head motion}\). None of the parameters reach significance \((p<0.05)\).
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Supplementary Figure 5A: Top 5% areas showing the strongest linear age effects on average across edges modulated by STOP and WM only (darkest subgroup in the venn-diagram). The linear age effect per edge, average, and selection of the top 5% areas are done independently for each task and represented in A for the WM task, B for the STOP task, and C for the REWARD task. Circles represent the edges selected only in STOP and WM tasks of the top 5% areas selection. Thicker edges in the circle are edges that connect two areas within the top selection.
Supplementary Figure 5B: Top 5% areas showing the strongest linear age effects on average across edges modulated by all three tasks (darkest subgroup in the Venn-diagram). The linear age effect per edge, average, and selection of the top 5% areas are done independently for each task and represented in A for the WM task, B for the STOP task, and C for the REWARD task. Circles represent the edges selected only in STOP and WM tasks of the top 5% areas selection. Thicker edges in the circle are edges that connect two areas within the top selection.
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**Supplementary Figure 6:** Relationship of age effects between tasks for specific or common edges. A linear regression is computed against age, age-head motion interaction, and head motion for each edge in the task potency of each task. The beta parameters corresponding to the slope of the linear regression for the age effect are extracted for each edge and related between two tasks. Edges displayed in the left column are edges selected in both tasks included in the plot, the two central columns display correspondence for edges selected in only one of the two tasks of the plot. The right column displays correspondence for edges selected in the baseline fingerprint (i.e. the resting state Z partial correlation) versus one of the tasks. An ellipsoid is fit over the points in the scatter plot.
Supplementary Figure 7: Average speed of change with age of task potency for STOP (A), REWARD (B), and WM (C). Each plot illustrates the absolute beta-parameters relative to the age effect for each window in the sliding-average calculation using a linear model with age, age by head motion interaction, and head motion included in the model. For each task, we fit a 2nd order polynomial to model the rate of change across development. Graph D overlays each task’s 2nd order fit to allow easy comparison between tasks. Finally, E illustrates the rate of change for RS.
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**Supplementary Figure 8:** Speed of change with age of task performance: stop signal reaction time (A), reward—non reward reaction time difference (B), and working memory performance (C). Each plot illustrates the absolute beta-parameters relative to the age effect for each window in the sliding-average calculation using a linear model. For each task, we fit a 2nd order polynomial to model the rate of change across development. Graph D overlays each task’s 2nd order fit after normalization using the maximal beta of each task to allow comparison of dynamics between tasks.
CHAPTER 4

INEFFICIENT FUNCTIONAL PROCESSING IN THE ADHD BRAIN: AN INTEGRATED ANALYSIS ACROSS THREE SEPARATE TASK DOMAINS

This chapter is based on: Chauvin RJ, Buitelaar JK, Oldehinkel M, Franke B, Hartman C, Heslenfeld DJ, Hoekstra PJ, Oosterlaan J, Beckmann CF, Mennes M, Inefficient functional processing in the ADHD brain: an integrated analysis across three separate task domains (submitted)
ABSTRACT

**Objective:** Multiple cognitive theories have been proposed to explain the cognitive impairments observed in Attention-deficit/Hyperactivity Disorder (ADHD). Functional imaging studies building on these theories reveal a heterogeneous and wide-spread pattern of neuronal dysfunction without providing an overarching perspective on the pathophysiology of ADHD. To determine whether a common alteration underlies deficits in reward processing, inhibition, and working memory, we integrated across these three paradigms to investigate common versus task-specific functional architecture of the ADHD brain.

**Method:** We used multiple functional magnetic resonance imaging acquisitions: resting-state, and working memory, monetary incentive delay, and stop signal tasks collected in 96 participants with ADHD, 78 unaffected siblings, and 156 controls (total N=330, age range=8-27 years). We calculated task-specific connectivity modulations away from the resting-state baseline and indexed connections that were modulated in none, one, two, or all three of the included tasks. We then assessed how group membership affected the fingerprint of observed modulations.

**Results:** Participants with ADHD and unaffected siblings modulated significantly fewer connections compared to controls, due to reduced modulation of connections that were modulated regardless of task. Instead, to perform each task, siblings over-modulated connections also modulated by the other groups, while participants with ADHD relied on over-modulating task-specific patterns of connectivity.

**Conclusions:** When performing multiple cognitive tasks, controls efficiently modulate a set of core common connections. In contrast, participants with ADHD use task-tailored alternative strategies which are more demanding and might result in suboptimal task performance. Our results support theories emphasizing neural inflexibility and aberrant cognitive-energetic states in ADHD.
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INTRODUCTION

Attention-deficit/Hyperactivity Disorder (ADHD) is an early onset neurodevelopmental disorder characterised by symptoms of inattention and/or hyperactivity-impulsivity that result in impairments in multiple functional domains (27). Different cognitive theories have been proposed to explain the disorder, including a dysfunction in state and arousal regulation (303), deficient response inhibition (304) or a broader deficit in executive functioning (37), a motivational dysfunction (305), and delay aversion (37). Functional imaging studies building on these cognitive explanations tried to uncover the neural underpinnings of ADHD, but have revealed a heterogeneous and wide-spread pattern of neuronal dysfunction (27,176,306,307). This fragmented pattern of findings asks for new approaches that provide an overarching perspective on the functional architecture of the ADHD brain.

Here, we aim to provide such a perspective by applying task potency analyses to the ADHD brain (255). This approach entails integrating findings of cognitive tasks across multiple cognitive domains to assess the role of task-dependent localised effects. We thereby capitalize on the idea that regional task-induced activity builds on the brain’s functional connectivity architecture as revealed by resting-state MRI analyses (12,75,188), and index the potency of task-induced connectivity modulations in light of their underlying baseline connectivity (255). Assessing potency across tasks then allows disentangling modulations that are shared across multiple cognitive functions, thus forming a cognitive core (77,236,308), from those that are unique to a single task.

This approach allows examining overarching cognitive theories about ADHD by studying the relationship between tasks that probe key cognitive dysfunctions. For example, suppose that a comparison of probes for working memory, response inhibition, and reward shows a core alteration across tasks that mainly relates to inhibition networks. This would then provide support for theories that claim a prominent role for poor response inhibition in ADHD (304). Alternatively, theories suggesting inefficient management of resources would be supported by observing an pattern of overall more ‘expensive’ modulation in ADHD.
compared to typically developing controls in an otherwise similar functional architecture (45,210). Both types of theories are not antinomic as alterations could be overcome in a suboptimal way, making the whole system less (energy) efficient. In light of these possibilities we hypothesized that alterations in how the brain’s functional core interacts with more specialized modulations would result in inefficient use of the brain’s resources in ADHD. Regarding unaffected siblings and their genetic vulnerability (100), we expected to observe some overlap with the ADHD profile, but potentially also mechanisms compensating for altered connectivity preventing cognitive impairments to emerge in this group.

To test our hypothesis, we applied the task-potency paradigm to a large cohort of participants with ADHD, their unaffected siblings, and healthy controls (N=330) and describe functional connectivity patterns relative to the cognitive requirements of response inhibition (45), WM (309), and reward processing (210). This allowed for assessing the impact of ADHD on the brain’s functional architecture in terms of commonality versus specificity as well as in terms of magnitude of modulations.

METHODS

PARTICIPANTS AND (f)MRI ACQUISITIONS
We selected participants with ADHD, unaffected siblings of individuals with ADHD (but not related to the participants with ADHD included in this study), and typically developing controls (unrelated to any participant) from the NeuroIMAGE sample (175). All selected participants completed an anatomical MRI scan, a resting state fMRI scan (RS), and at least one of the following task fMRI scans: a spatial working memory task (WM), a monetary-incentive-delay reward task (REWARD), and/or a stop signal response inhibition task (STOP) (see ST2). Table 1 summarizes the demographics of the 96 participants with ADHD, 78 unaffected siblings, and 156 controls included in the current analyses. A full description of the selection criteria, task paradigms, and MRI acquisition parameters is provided in ST3 and SA.
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<table>
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<th></th>
<th>N used in final analyses</th>
<th>Age min - max</th>
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<th>Site¹</th>
<th>Inattention¹ (std)</th>
<th>Hyperactivity¹ (std)</th>
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<td>94.9 (13.9)</td>
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<tr>
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<td>44%</td>
<td>7.0 (1.7)</td>
<td>5.6 (2.2)</td>
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</table>

**Table 1:** Participants’ information: descriptive, clinical variables, and distribution of scan modalities, for each group sample and tasks: Resting state (RS), stop signal paradigm (STOP), reward processing (REWARD), working memory (WM). 1 Combined symptoms from KSADS and Conners. 2 Ratio of Amsterdam/Nijmegen scan localisation. For participant exclusion, see ST1. For more detail on age and gender representation, see SF1.

**Task potency calculation**

Our task potency approach is described in detail in Chauvin et al. 2019 (255). In brief, for each participant and each pre-processed RS, WM, REWARD, and STOP fMRI acquisition (see eMethod for pre-processing procedures) we defined functional connectivity matrices using 179 regions from a hierarchical whole-brain atlas (220) (see SF2). We calculated connectivity as the normalized Fisher-Z partial correlation between the timeseries of each pair of regions in the atlas (see eMethod). To isolate connectivity changes induced by task modulation (WM, REWARD, STOP) from changes in the brain’s baseline architecture (RS), we standardized each individual-level pair-wise correlation obtained during task acquisition by subtracting the corresponding pair-wise correlation value calculated for the RS scan of that participant. This effectively allows interpretation of the task connectivity matrices in terms of their deviation from that participant’s resting baseline.
Accordingly, we refer to the magnitude of the task-induced connectivity modulations as ‘task potency’ (255).

For each task, we created group-level task potency matrices by averaging the individual-level potency matrices across all participants in each diagnostic group. Within these group-level matrices we aimed to select those connections that were sensitive to task modulation. Using the values within each potency matrix, we used a mixture modelling approach featuring a Gaussian curve to model the main (noise) distribution of the potency values and two gamma distributions to model the left and right (signal) tails (224). We subsequently defined a limit for each signal tail and selected potency values exceeding this limit as being sensitive to task modulation.

We further subdivided the sensitive connections depending on their modulation by one or more of the tasks. In particular, we referred to connections that were modulated by one task only as task-specific, to connections that were modulated by more than one but not all tasks as task-unspecific, and to connections that were modulated regardless of task as common.

**GROUP DIFFERENCES IN TASK CONNECTION TYPE**

To assess whether ADHD was associated with a deviant distribution of task-induced modulations across the brain and across tasks, we compared the distribution of task-sensitive, task-specific, common, and task-unspecific connections across the three diagnostic groups. We compared the amount of sensitive connections between groups by indexing the percentage of connections included for each group relative to the total number of sensitive connections. To assess between-group differences in the specificity of connections, we obtained for each group the percentage of connections per type relative to the total number of sensitive connections for that group. In addition, we assessed the ratio of connections uniquely modulated by each diagnostic group (unique connections) versus those connections that were also modulated by one or both of the other groups (shared connections). To allow statistical inference, we calculated group-level distributions for each of these percentages through bootstrapping, using 10000 repetitions each including 80% of participants (see eMethod). Using the variance across
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these bootstraps, we conducted pair-wise group comparisons for each percentage. We here report results averaged across the three tasks.

To further investigate whether differences in the selection of connections were associated with differences in the amplitude of the associated modulations (i.e., the actual task potency), we extracted the group-level average task potency for selected connections and tested for between-group differences in task-potency amplitude by computing a p-value across the 10000 bootstraps. P-values were assessed for significance using FDR correction at p<0.05. Replication of the analyses in light of possible confounder effects (medication, gender, scanner of acquisition, and comorbidity) are presented in SF4.

Finally, we investigated the reproducibility of the selection of connections to estimate the stability versus the heterogeneity of task connection types in the different groups. To this end, we computed across bootstraps each connection’s selection rate at the group level and its associated shared selection rate between two groups. We computed these rates for sensitive, common, task-specific, and task-unspecific selections. These group-level selection rates index how specific a selected connection is to one particular group by computing the difference in selection rate at the connection level between groups. We can then display the uniqueness versus the sharedness of each connection. By comparing both rates, we can estimate which connections are uniquely and reproducibly selected in one group only, potentially representing idiosyncratic strategies to solve the task.

RESULTS

COMPARING TASK-MODULATED CONNECTIVITY PROFILES ACROSS GROUPS

Using the selection of connections that yielded significant connectivity modulations, we compared the diagnostic groups in terms of the sensitivity and specificity of their connectome to task performance. Figure 1 illustrates the sensitivity and task-specificity for each diagnostic group averaged across the three tasks. The top row in Figure 1 shows that controls modulated a significantly higher percentage of connections (20.2% corresponding to 61.9%, sd=7.9 of all sensitive connections)
compared to participants with ADHD (16.7% corresponding to 38.9%, sd=8.2 of all sensitive connections, p<0.006) and compared to the siblings (11.8% corresponding to 30.9%, sd=6.9 of all sensitive connections, p<0.0005). Within their respective sets of sensitive connections, siblings exhibited a larger percentage of shared connections (i.e., connections also modulated by another group; 58.2%, sd=7.5) compared to controls (39.7%, sd=5.1, p<0.01) and participants with ADHD (44.9%, sd=7.6, p=0.058 after FDR correction). This illustrates that the control and ADHD groups exhibited a higher rate of connections that only they modulated, compared to siblings whose modulations displayed greater overlap with both other groups.

The bottom half of Figure 1 displays the proportion of selected connections that were common across tasks, specific to one task, or task-unspecific. As shown in Figure 1, controls modulated more than 20% of their sensitive connections regardless of task. This was significantly higher compared to the siblings (13%, p<0.005) and the ADHD group (10%, p<0.001). In addition, about 70% of the controls’ common connections were unique to this group, compared to only 20% unique connections observed for the siblings (21%, p<0.005) and the ADHD group (22%, p<0.02). Accordingly, the common connections observed for ADHD and siblings are mostly connections that controls also modulated. Conversely, the set of common connections that controls used across tasks were mostly unique to them and not modulated by either ADHD participants or siblings.

In contrast to the lower number of common connections, both the ADHD and sibling groups exhibited a significantly higher percentage of task-specific connections compared to controls (see Figure 1). We observed no between-group differences in the uniqueness of the task-specific connections, with on average 80% of the task-specific connections being unique to each diagnostic group. In comparison, task-unspecific connections did not yield between-group differences in terms of their relative percentage or their group-specificity.
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**Figure 1:** Description of connectivity modulations across the three tasks and diagnostic groups (ADHD, siblings, controls). The first row shows for each group the percentage of connections they modulated across the three tasks (sensitive connections) and within these selected connections, the percentage of connections unique to one group or shared across groups. We further split the selected connections of each group into task-specific, task-unspecific, and common connections, corresponding to connections modulated in only one, two, or all three tasks, respectively. The second row quantifies the relative percentage of each connection type within the sensitive connections of each group. For the connections described in the second row, the third row then quantifies whether these connections were unique to that group or shared across groups. Finally, the fourth row quantifies the average task potency across unique or shared connections for each group and connection type. All reported values show the average and standard deviation across 10000 independent bootstraps. Indicated p-values shown significant differences after FDR correction. Full ANOVA results for the task potency results shown in row 4 are available in ST4-5. Replication of this findings for possible confounder effect (scanner, gender, medication, comorbidity) is available in SF4.
To assess whether the group differences in specificity were associated with group differences in the amplitude of modulations, we compared the task-potency values across unique and shared connections for the common, task-specific, and task un-specific selections. In the common connections that groups shared with each other, we observed a siblings > controls > ADHD effect on task-potency amplitude. In contrast, for task-specific connections that were uniquely modulated by each group we observed that controls showed significantly lower modulation compared to both the siblings (p<0.05) and ADHD groups (p<0.01)(see ST4). Although participants with ADHD showed higher modulation compared to the siblings group, this difference did not reach significance (p=0.078).

**Within Group Variability of Task Connection Types**

To examine the bio-marker potential of our findings we assessed the variability of task connection types across participants within groups. Figure 2 shows that sensitive connections displayed a distribution shifted toward controls when comparing their selectivity to siblings or ADHD (Figure 2 top row). This indicates that task connection types observed for controls were more stable across bootstraps and less heterogeneous across participants. Moreover, especially the common connections displayed strong homogeneity across the control participants. This demonstrates that controls reliably selected connections across tasks that were not present in other groups, further validating results from Figure 1. Consequently, as common connections are highly reproducible in controls yet missing in ADHD and siblings they could potentially be used to optimally differentiate controls. In contrast, the task-specific connections observed in ADHD and siblings (see Figure 1) were variable and heterogeneous across participants, as illustrated by an absence of a shift in the distributions shown in Figure 2 towards the ADHD and sibling groups.

Finally, Figure 3 shows the brain areas associated with the most reliably modulated common connections in controls (above 50% across bootstraps). Within those connections, we further differentiated between those connections that were almost never modulated by ADHD (ratio of modulation percentage is above 50%) and those that were relatively more modulated by ADHD participants. Overall, controls most
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reliably modulated connections involving a widespread pattern of areas typically associated with reward, salience and executive networks (310). Observed areas included subcortical, motor, fronto-parietal areas, and left dorso-lateral prefrontal cortex. When compared to participants with ADHD, controls exhibited higher selectivity of connections corresponding to the sensory-motor execution pathway connecting the visual networks, auditory and motor areas, cerebellum, and the left attention network, as well as connecting between networks: auditory (including insula), cingulum, attention, and fronto-temporal. In contrast, only putamen, insula, Heschl gyrus, and visual regions exhibited relatively reliable modulation across tasks in participants with ADHD.

**Figure 2: Comparison of selection reliability across bootstraps.** By investigating the reproducibility of the selection of connections across bootstraps we inferred on the uniqueness (x-axis) and shareability (y-axis) of each connection between two groups. A connection that was always selected in both groups, shown at the top corner of each triangle, would represent a connection that cannot be used to differentiate between those two groups. A connection that was always selected in one group only, located in the lower corners of the triangles, would be unique to a group and could be used to predict the group. Connections that would be heterogeneously selected in the population would have a low uniqueness (around 0 on the x-axis) and a low shareability (bottom of y-axis). The distribution at the basis of the triangle informs about the density of connections represented in the triangle, i.e. the spread of the distribution indicates whether only a small subset or a larger representation of connections are most often selected in one group relatively to the total amount of selected connections. Random labelling correspond to a random selection of participants while keeping percentages of participants across groups.
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Figure 3: Representation of areas with most reproducible common connections in controls and comparison to ADHD participants. The brain slices on the left show areas with at least one connection showing a selectivity in at least 50% of the control bootstraps. The circular connectivity plot and the brain slices on the right illustrate how these connections and areas differed between ADHD and controls. The comparison with the ADHD group is computed as the ratio for each connection of the difference in selectivity between both groups and the relative selectivity percentage in controls. The connectivity graph displays connections that show a difference above 50% of selectivity in controls in blue, i.e. connections not reliably selected in ADHD, and the connections below 50% of relative difference, i.e. those preserved in ADHD, in red. The opacity in the bundles is related to the reliability of those connections in controls. Connections selected below 50% in controls are shown with lower opacity. Note that the darker lines correspond to the regions shown on the left. The brain slices on the right display the areas involved in the dark connections shown in the connectivity graph. One visual area exhibited both a loss and a preservation of connections and is displayed in pink.
DISCUSSION

In this study, we used a novel framework to infer the efficiency of observed connectivity modulations in ADHD under working memory, reward processing, and response inhibition task demands. Participants with ADHD and unaffected siblings both used significantly fewer connections compared to controls to complete each task. Furthermore, the functional architecture of participants with ADHD and siblings was characterised by a low percentage of common connections that allow sharing resources across tasks. Instead, both groups relied more strongly on unique sets of task-specific connections requiring more independent resources and potentially inducing high switching costs. Participants with ADHD under-modulated the ‘efficient’ common connections, while siblings strongly over-modulated these connections, suggesting a potential compensatory mechanism.

Collectively our results suggest that participants with ADHD lack a common core of modulations that can be efficiently used regardless of task, and try to overcome this deficit through implementing task-tailored patterns of connectivity. These observations may be interpreted as a neural inflexibility of participants with ADHD (311,312), as using task-tailored connectivity patterns makes switching more demanding, more expensive and inefficient, making task performance more challenging. As such, this connectivity profile provides support for the cognitive-energetic model (303). In this model, the limitations in arousal observed in ADHD could be a consequence of a higher level of energy required to perform cognitive tasks; possibly because of having to micro-manage task-specific patterns instead of keeping a general processing core ready to perform.

Fitting with the hypothesis of inefficient processing is the observation that participants with ADHD typically do not demonstrate a striking inability to perform tasks but rather exhibit large variability in the way they perform tasks (45,313,314). Some studies have reported an inefficient use of resources for specific networks or functions in ADHD including the attention network (314,315), executive functioning (316), or cognitive control (314,317). However, as these studies focus on specific cognitive aspects, they do not allow identifying a potential common
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underlying deficit, as demonstrated in the present study. Alternative approaches to investigating the efficiency of the brain’s organization have used graph theory and shown that the functional architecture of the ADHD brain is associated with differences in the balance of local and global efficiency (176,318–320). However, these graph theory metrics provide no information on localized effects affecting specific cognitive functions. In contrast, our integrated approach provides a bridge between cognitive tasks and the functional architecture of the brain to understand the interaction between neural systems.

Unaffected siblings of individuals with ADHD share on average 50% of their genetic make-up with the ADHD probands. Accordingly, they are hypothesized to share part of the ADHD endophenotype, i.e. biological deficits underpinning the ADHD phenotype, yet without crossing the diagnostic threshold, exhibiting a behavioural pattern intermediate between ADHD and controls (100,309,321). Here, siblings displayed a similar task connectivity profile as ADHD participants. However, in addition siblings exhibited increased modulation of common and shared connectivity, suggestive of a potential compensatory mechanism that enables successful task performance (see ST6). Previous research suggests that ADHD participants could compensate by using higher order executive systems or by relying on lower-order visual, spatial, and motoric processing (168,169,322,323). Our results suggest that siblings are potentially still able to recruit more efficient connections, yet they require extra modulation.

The results shown in Figure 2 highlight that task-specific connections can be used to investigate such compensatory mechanisms at the level of individual participants, as task-specific connections are highly variable across participants, which is also described in previous work on task potency (255). For instance, using longitudinal designs and models of compensatory strategies (323), we can focus on those connections that are subject-specific and highly reproducible at the individual level to investigate a progressive specialization of individual compensatory mechanisms. In contrast, at the group level the absence of part of the common connections is the most reproducible pattern across ADHD and siblings compared to controls (Figure 2). As such, it has potential as a
biomarker of an “at risk profile”, where participants exhibiting a connectivity profile that includes these common connectivity modulations are unlikely to be related to the ADHD phenotype.

At the brain regional level, participants with ADHD mainly missed modulations that connect regions within the executive control, reward and salience pathways, including cerebellum, striatal, cingulum and cortical areas during task performance (318). As shown in Figure 3, participants with ADHD preserved only few common connections, interestingly involving striatal regions known to be involved in reward processing. Note that these results do not contradict typical findings of aberrant brain activity in reward-related regions in participants with ADHD (305) as we showed that participants with ADHD used these connections with greater inconsistency and decreased modulation compared to controls. Knowing that ADHD participants make less efficient use of common pathways among multiple cognitive functions, will inform next studies aimed at understanding task response variability in ADHD.

In conclusion, we integrated task-specific connectivity modulations across three tasks and demonstrated that individuals with ADHD had a more specific and variable pattern of connectivity in response to each task compared to controls who displayed more commonly potentiated connections across all tasks. Our work provides an important stepping stone towards new integrative theories explaining how multiple neural alterations interact and result into multiple cognitive impairments in ADHD.
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SUPPLEMENTARY MATERIAL

SUPPLEMENTAL APPENDIX: PARTICIPANT SELECTION CRITERIA

All subjects participated in the NeuroIMAGE project, the Dutch follow-up of the International Multicenter ADHD Genetics (IMAGE) study. Details about ethics approval, recruitment, assessment, and the general testing procedures can be found in the general methods and design paper of the NeuroIMAGE project (309). In short, ADHD diagnosis was based on semi-structured interviews (the Schedule for Affective Disorders and Schizophrenia for SchoolAge Children [K-SADS] (324)) as well as the Conners ADHD questionnaires (325,326). Probands with ADHD had to have six or more hyperactive/impulsive and/or inattentive symptoms according to DSM-IV criteria (327); unaffected siblings and unrelated controls had to have less than two symptoms overall, based on a structured psychiatric interview (K-SADS) and Conners questionnaires (328,329). Inclusion criteria for MRI participation consisted of the absence of claustrophobia and any metal in the body. Informed consent was acquired from all participants, with parents supplying consent for participants less than 16 years old.

fMRI scans exhibiting limited brain coverage or excessive head motion were excluded from further processing. Limited brain coverage was defined as having less than 97% overlap with the MNI152 standard brain after registration of the fMRI scan to the MNI152 template. In addition, we excluded from each task those participants who were among top 5% in terms of head motion as quantified by RMS-FD, the root mean square of the frame-wise displacement, computed using MCFLIRT (213). From this selection, we selected one participant per family to avoid enhancing similarity between or within groups.
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**Supplemental Table 1: Overview of participant exclusion and final inclusion**

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<td>3</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>STOP</td>
<td>119</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>REWARD</td>
<td>127</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>127</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>ADHD participants</td>
<td>RS</td>
<td>382</td>
<td>17</td>
<td>6</td>
<td>8</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>STOP</td>
<td>379</td>
<td>15</td>
<td>9</td>
<td>7</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>REWARD</td>
<td>409</td>
<td>16</td>
<td>7</td>
<td>5</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>423</td>
<td>18</td>
<td>9</td>
<td>11</td>
<td>94</td>
<td>14</td>
</tr>
</tbody>
</table>

**Supplemental Table 2: Number of participants having performed multiple tasks. In grey, in the diagonal is the total number of participants in final sample**

<table>
<thead>
<tr>
<th></th>
<th>STOP</th>
<th>REWARD</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy control participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP</td>
<td>87</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>REWARD</td>
<td>-</td>
<td>92</td>
<td>43</td>
</tr>
<tr>
<td>WM</td>
<td>-</td>
<td>-</td>
<td>102</td>
</tr>
<tr>
<td>Unaffected siblings of ADHD participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP</td>
<td>46</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>REWARD</td>
<td>-</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>WM</td>
<td>-</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td>ADHD participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP</td>
<td>44</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>REWARD</td>
<td>-</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>WM</td>
<td>-</td>
<td>-</td>
<td>57</td>
</tr>
</tbody>
</table>
### Supplemental Table 3: fMRI Acquisition Parameters and Characteristics

<table>
<thead>
<tr>
<th>Image acquisition parameters</th>
<th>RS</th>
<th>STOP</th>
<th>REWARD</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE=40 ms, FOV=224 mm, 37 axial slices, flip angle=80, matrix size=64x64, in-plane resolution=3.5 mm, slice thickness/gap=3.0 mm/0.5 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N volumes</strong></td>
<td>&gt;260</td>
<td>86 * 4 blocks</td>
<td>&gt;300</td>
<td>107 * 4 blocks</td>
</tr>
<tr>
<td><strong>N first volumes rejected</strong></td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Healthy control participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N used in final analyses</td>
<td>156</td>
<td>87</td>
<td>92</td>
<td>102</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>1960**</td>
<td>2340**</td>
<td>2340</td>
<td>2340</td>
</tr>
<tr>
<td>RMS-FD min-max</td>
<td>0.026 - 1.357</td>
<td>0.029 - 0.413</td>
<td>0.032 - 0.420</td>
<td>0.033 - 1.504</td>
</tr>
<tr>
<td>RMS-FD mean (std)</td>
<td>0.165 (0.207)</td>
<td>0.094 (0.079)</td>
<td>0.127 (0.091)</td>
<td>0.175 (0.241)</td>
</tr>
<tr>
<td>N ICs extracted – mean (std)</td>
<td>36.61 (9.61)</td>
<td>26.13 (3.93)</td>
<td>64.10 (11.96)</td>
<td>31.66 (5.248)</td>
</tr>
<tr>
<td>NICs defined as noise – mean (std)</td>
<td>11.81 (4.31)</td>
<td>7.83 (2.09)</td>
<td>21.34 (4.94)</td>
<td>9.33 (2.32)</td>
</tr>
<tr>
<td><strong>Unaffected siblings of ADHD participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N used in final analyses</td>
<td>78</td>
<td>46</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>1960**</td>
<td>2340**</td>
<td>2340</td>
<td>2340</td>
</tr>
<tr>
<td>RMS-FD min-max</td>
<td>0.027 - 1.357</td>
<td>0.033 - 0.413</td>
<td>0.043 - 0.330</td>
<td>0.039 - 1.504</td>
</tr>
<tr>
<td>RMS-FD mean (std)</td>
<td>0.177 (0.224)</td>
<td>0.096 (0.086)</td>
<td>0.124 (0.081)</td>
<td>0.211 (0.309)</td>
</tr>
<tr>
<td>N ICs extracted – mean (std)</td>
<td>36.91 (10.02)</td>
<td>26.28 (4.22)</td>
<td>61.94 (11.35)</td>
<td>31.90 (4.87)</td>
</tr>
<tr>
<td>NICs defined as noise – mean (std)</td>
<td>11.64 (4.57)</td>
<td>7.83 (2.05)</td>
<td>20.66 (4.71)</td>
<td>8.88 (2.12)</td>
</tr>
<tr>
<td><strong>ADHD participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N used in final analyses</td>
<td>96</td>
<td>44</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>1960**</td>
<td>2340**</td>
<td>2340</td>
<td>2340</td>
</tr>
<tr>
<td>RMS-FD min-max</td>
<td>0.033 – 3.189</td>
<td>0.027 - 0.478</td>
<td>0.035 – 1.393</td>
<td>0.034 – 0.834</td>
</tr>
<tr>
<td>RMS-FD mean (std)</td>
<td>0.264 (0.381)</td>
<td>0.126 (0.109)</td>
<td>0.196 (0.243)</td>
<td>0.238 (0.205)</td>
</tr>
<tr>
<td>N ICs extracted – mean (std)</td>
<td>40.84 (9.57)</td>
<td>26.83 (4.34)</td>
<td>65.39 (14.07)</td>
<td>33.99 (5.30)</td>
</tr>
<tr>
<td>NICs defined as noise – mean (std)</td>
<td>12.33 (3.74)</td>
<td>7.89 (1.81)</td>
<td>21.28 (5.85)</td>
<td>9.31 (2.31)</td>
</tr>
</tbody>
</table>

* The number of initial volumes removed from further analyses varied to ensure comparability with earlier studies that used these data. Note that this variation will have very limited impact on the current analyses.

** some subjects were scanned with a different TR. In control participants: RS - 1860 for 1 subject; STOP – 2150 for 1; REWARD – 2280 for 1, in siblings: RS - 1860 for 1 subject; STOP – 2150 for 1; REWARD – 2280 for 1, in ADHD participants: RS - 1860 for 7 subjects; STOP – 2150 for 4 and 2280 for 1; REWARD – 2150 for 5 and 2280 for 1.
Inefficient functional processing in the ADHD brain: an integrated analysis across three separate task domains

SUPPLEMENTAL APPENDIX: MRI PREPROCESSING
All fMRI acquisitions were processed using tools from FSL 5.0.6. (FSL; http://www.fmrib.ox.ac.uk/fsl) (214–216). We employed the following pipeline: removal of the first 4 or 5 volumes to allow magnetization equilibration (see Supplemental Table 1), head movement correction by volume-realignment to the middle volume using MCFLIRT, global 4D mean intensity normalization, and 6mm FWHM smoothing. We denoised all preprocessed data for secondary motion-related artefacts using ICA-AROMA (66,67). Finally, we regressed out signal from CSF and white matter, and applied a 0.01Hz high-pass filter.

For each participant, all acquisitions were registered to its high-resolution T1 anatomical image using Boundary-Based Registration (BBR) available in FSL FLIRT (213,218). All high-resolution T1 images were registered to MNI152 space using 12-dof linear registration available in FLIRT and further refined using non-linear registration available in FSL FNIRT(219). We used the inverse of the obtained transformations to bring a brain atlas to each participant’s native space, and performed all further analyses in participant native space.

SUPPLEMENTAL APPENDIX: PERMUTATION TESTING IN SELECTIVITY
The reproducibility and significance of the group differences in task fingerprint is estimated by doing a permutation testing of the fingerprint similarity. To this aim, we repeated the analysis 10,000 times using 80% of each group, randomly selected and picked with replacement. Using the 10,000 bootstraps we obtained confidence intervals around each group’s percentages in main Figure 1.
**GROUP X SHARED TASK POTENCY DIFFERENCES**

*Supplemental Table 4: Group x Shared ANOVA on average task potency (see also main Figure 1). We performed Group x Shared ANOVA with subject and task as a random effect is performed on the average task potency across edges weighted by the reproducibility of selection of edges across bootstraps for each of the edge conditions (specific, unspecific and common). The condition and group effects are FDR corrected independently for specific, unspecific and common tests and reported in the top table.*

### Group x Shared ANOVA

<table>
<thead>
<tr>
<th>Group</th>
<th>Unique/Shared</th>
<th>Group x U/S</th>
<th>ADHD</th>
<th>Sibling</th>
<th>Ctrl</th>
<th>A vs S</th>
<th>A vs C</th>
<th>S vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common edges</td>
<td>0.17</td>
<td>$1.9 \times 10^{-4}$</td>
<td>$8 \times 10^{-7}$</td>
<td>Shared vs Unique</td>
<td>0.031</td>
<td>0.002</td>
<td>0.002</td>
<td>0.269</td>
</tr>
<tr>
<td>Unspecified edges</td>
<td>0.15</td>
<td>0.57</td>
<td>0.44</td>
<td>Shared vs Unique</td>
<td>0.289</td>
<td>0.028</td>
<td>0.189</td>
<td>0.377</td>
</tr>
<tr>
<td>Specific edges</td>
<td>0.15</td>
<td>$3.1 \times 10^{-4}$</td>
<td>0.034</td>
<td>Shared vs Unique</td>
<td>0.313</td>
<td>0.004</td>
<td>0.005</td>
<td>0.078</td>
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</table>

### Supplemental Table 5: Mean potency and standard deviation for each condition

<table>
<thead>
<tr>
<th>Common</th>
<th>Unspecified</th>
<th>Specific</th>
</tr>
</thead>
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<tr>
<td>ADHD</td>
<td>Shared</td>
<td>Unique</td>
</tr>
<tr>
<td></td>
<td>sd 0.182</td>
<td>sd 0.117</td>
</tr>
<tr>
<td></td>
<td>1.156</td>
<td>0.879</td>
</tr>
<tr>
<td>Siblings</td>
<td>Shared</td>
<td>Unique</td>
</tr>
<tr>
<td></td>
<td>sd 0.236</td>
<td>sd 0.286</td>
</tr>
<tr>
<td></td>
<td>2.030</td>
<td>0.977</td>
</tr>
<tr>
<td>Controls</td>
<td>Shared</td>
<td>Unique</td>
</tr>
<tr>
<td></td>
<td>sd 0.123</td>
<td>sd 0.189</td>
</tr>
<tr>
<td></td>
<td>1.408</td>
<td>0.804</td>
</tr>
</tbody>
</table>
Inefficient functional processing in the ADHD brain: an integrated analysis across three separate task domains

**Task Performance Differences Between Groups**

*Supplemental Table 6: Independent t-test between task performances of the ADHD, Siblings and Controls. The strongest differences are observed in the stop signal reaction time variability for ADHD participants. No differences in performance is observed between Siblings of ADHD and the control participants.*

<table>
<thead>
<tr>
<th>Task performance</th>
<th>ADHD mean (sd)</th>
<th>Siblings mean (sd)</th>
<th>Control mean (sd)</th>
<th>ADHD vs Control p-val (t)</th>
<th>ADHD vs Siblings p-val (t)</th>
<th>Siblings vs Control p-val (t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP - Stop signal reaction time</td>
<td>260.6 (55.8)</td>
<td>251.4 (48.5)</td>
<td>254.1 (50.0)</td>
<td>0.176</td>
<td>0.146</td>
<td>0.654</td>
</tr>
<tr>
<td>STOP - reaction time variability</td>
<td>104.6 (39.7)</td>
<td>93.5 (37.2)</td>
<td>87.8 (34.2)</td>
<td>9.56 x 10^-7 (2.42)</td>
<td>10^-7 (2.42)</td>
<td>-1.35</td>
</tr>
<tr>
<td>REWARD – reward and non-reward reaction time differences</td>
<td>40.5 (44.3)</td>
<td>34.6 (31.3)</td>
<td>31.7 (31.7)</td>
<td>0.010</td>
<td>0.213</td>
<td>0.442</td>
</tr>
<tr>
<td>WM – working memory performance</td>
<td>0.24 (0.04)</td>
<td>0.24 (0.04)</td>
<td>0.24 (0.04)</td>
<td>0.975</td>
<td>0.968</td>
<td>0.951</td>
</tr>
</tbody>
</table>

**Confounder Effects**

*Supplemental Figure 4: Replication of the results presented in figure 1 in subsamples to evaluate possible confounder effects of medication (top graphs corresponds to the comparison of ADHD off (left) and on (right) medication with Siblings and Controls), gender (second row of graphs corresponds to the subsamples of only female (left) or only male (right) for each groups), scanner (third row of graph corresponds to the subsamples of participants acquired with the Siemens Avanto (left) or the Siemens Sonata (right)), and co-morbidity (bottom graphs corresponds to the comparison of ADHD with another comorbid disorder (ODD, CD, Tourette or/and TIC) (left) or without comorbid disorders (right) compared to Siblings and Controls. Conclusions from the main analysis on common edges hold for each condition, conclusions on task-specific edges shows less robustness as also concluded from figure 2. Differences are more strongly expressed in females than in males, however, the reduction of power does not enable to draw firm conclusions from these differences.*
Inefficient functional processing in the ADHD brain: an integrated analysis across three separate task domains

Supplemental Figure 5: Gender differences in common edges. Brain areas with edges used across the three tasks by the female ADHD population but not the male ADHD population. Colours of areas characterize networks as in Supplemental Appendix 2.
**Supplemental Figure 5bis:** Gender differences in common edges. Brain areas with edges used across the three tasks by the male ADHD population but not the female ADHD population. Colours of areas characterize networks as in Supplemental Appendix 2.
Chapter 5

HETEROGENEITY IN ASD FUNCTIONAL CONNECTIVITY REVEALS ADHD-RELATED SYMPTOMS SUBPROFILES

This chapter is based on: Looden T, Chauvin RJ, Mennes M, Buitelaar JK, Beckmann CF Heterogeneity in ASD functional connectivity reveals ADHD-related symptoms subprofiles (in preparation)
ABSTRACT

Autism Spectrum Disorder (ASD) is a developmental disorder characterised by social and communicative deficits and repetitive behaviour [1]. Research into ASD is challenging due to a large heterogeneity in the population and a high prevalence of co-morbid disorders [2,3] such as Attention Deficit Hyperactivity Disorder (ADHD), a developmental disorder characterised by impulsivity, hyperactivity and/or inattention [1]. Both ASD and ADHD are associated with functional brain alterations, observed in rest- and in task-fMRI studies. To better characterise functional connectivity alterations specific to task domains, we propose the task potency pipeline [4] to compare 282 participants with ASD and 221 typically developing (TD) participants from the EU-AIMS LEAP dataset. We compare the task modulation connectivity of five task domains: Hariri emotion processing, Flanker Go-NoGo, animated shapes theory of mind, social and non-social reward anticipation [7]. To investigate a co-morbidity effect, we split the ASD participants (ASDTOTAL) into two subgroups, those that met clinical criteria for ADHD (ASDADHD+, 81 subjects) and those that did not (ASDADHD-, 201 subjects) and repeated the above analysis for each subgroup. We find that task modulation amplitude in these five tasks is altered in ASD. However, participants co-morbid with ADHD strongly impact that population effect. They displayed a task potency profile showing ADHD characteristics with less edges modulated and stronger modulation of these edges. Differences in task potency profiles show significant correlation with ADHD symptoms scores, validating a potential stratification biomarker for ASD with ADHD comorbidity.
Heterogeneity in ASD functional connectivity reveals ADHD-related symptoms subprofiles

INTRODUCTION
Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder marked by social and communicative deficits as well as repetitive and restricted behaviours and interests and abnormal sensory processing (327). There exists significant phenotypic, etiologic and biologic heterogeneity within ASD populations (330,331). This has made investigation into any underlying commonalities that might bring us to a better understanding of the disorder challenging. As part of the phenotypic heterogeneity, ASD is known to display a high rate of comorbidity with other disorders (51,52). 81% of the ASD population meets diagnostic criteria for another psychiatric disorder, most commonly ADHD, anxiety disorder, depression and epilepsy (332).

In this multifactorial landscape, attempts at describing ASD at a cognitive level have led to the emergence of multiple theories (183). Prominent theories include the empathizing-systemizing hypothesis – related to a tendency in autistic patients to interpret events based on too few observations and create over-generalized rules (47). This theory follows up on the disfunction in theory of mind hypothesis, which refers to the ability to represent others’ mental states and to make inferences about others’ intentions, also called mentalization or mentalizing. It is a broad ability which involves the capacity to understand feelings, intentions, beliefs and metaphors (49). Because of low executive processing performance, ASD has also been linked to executive dysfunction (48). It has furthermore been proposed that abnormal reward processing could influence learning mechanisms during development (333) Alternatively, according to the weak central coherence hypothesis, autistic patients integrate only the spatially nearest information available to interpret their environment (50). This series of current theories displays the difficulty of obtaining a global view on the disorder and to pinpoint whether one or more dysfunctions are at play.

Relevant work has been published on how these various theories about ASD might interrelate at the cognitive level (330). However, thus far our knowledge is limited about how the neural processes underlying tasks which tap into these cognitive domains, interrelate. In order to investigate neural pathways which might support existing ASD theories,
we need to obtain a holistic view on alterations across task domains where ASD participants show impairment. The current research aims to advance our understanding of these cognitive interrelations in terms of their associated neural patterns at the functional connectivity level through a method called ‘Task Potency’. The task potency method incorporates both resting state and task-fMRI based measures of functional connectivity to disentangle task-specific modulations and compare these modulations across task domains. Using task potency to define connectivity modulation induced by tasks, for ASD and typically developing groups independently, enables us to investigate differences in their ability to respond to tasks. We can specifically disentangle task effect from domain unspecific differences existing in the baseline functional connectivity.

From a cognitive domain unspecific viewpoint, i.e. resting state studies, findings from the ASD functional connectivity literature show patterns of over-connectivity and under-connectivity relative to typically developing controls depending on the network and the chosen connectivity metrics (183). Whereas previous studies focus on areas of interest, looking at whole brain connectivity or averages across networks might provide different results. Such results are not necessarily antinomic but could underwrite the complexity of the neural pathway alterations in the ASD brain. A local diffuse over-connectivity with an aberrant pattern (334), especially in sensory and subcortical networks (335), does not discredit observing a globally weaker connectivity with an abnormal functional organisation (184), observed principally in posterior cingulate, medial prefrontal cortex and default mode networks (336). A complex pattern can be identified where brain regions are under-connected with typically associated brain regions (53) but over-connected with non-traditional areas (63). In fact, multiple studies started to look at whole brain, data driven approaches and observed there a reduced segregation (underconnectivity within functional systems) and an increased integration (overconnectivity between functional systems) (337). However, between children, and adolescents/adults, different connectivity alterations are observed, which point toward developmental changes interacting with connectivity profiles in ASD (338). Additionally, different subtypes of ASD might also be characterized
Heterogeneity in ASD functional connectivity reveals ADHD-related symptoms subprofiles with different alterations. A recent rsMRI study in high-functioning adults with ASD challenged the hypo- versus hyperconnectivity dichotomization by observing either changes in degree of connectivity and or changes in amplitude of connection strength, in an idiosyncratic pattern (162).

In order to unravel the neural underpinnings of cognition in ASD, we should not only consider resting state studies. Even though resting state analyses provide a solid foundation of the functional architecture of the brain (12), it cannot tap into the processing underlying specific cognitive functions. This means that task-based fMRI measures are crucial to include if the aim is to understand why deficits might be present in specific cognitive domains. Results from task studies show evidence of underconnectivity during voice perception or also language development between typically implicated regions. Intents to understand task results in relation to resting state findings have therefore led to the hypothesis that ASD brain fail to deactivate connection during tasks (337,339,340). These findings highlight the complexity and the difficulty of obtaining a clear view of the connectivity pattern in ASD. Information that can be extracted from probing cognitive processes can predict very accurately ASD diagnoses from functional connectivity matrices, e.g. social reward tasks (341) and theory of mind tasks (342). However, a review of prediction studies shows that sample sizes have a major effect on prediction results. Due to heterogeneity in the population, too small sample size might create specific population bias in selection (343).

Seemingly incongruent findings may further be driven by different factors such as age, sex, or comorbidities that would interact with developmental mechanisms (183). ADHD is one of the most common co-morbid disorders of ASD and research has investigated the effect of this co-morbidity. ASD individuals with ADHD symptoms interestingly shared specific connectivity patterns of ADHD, such as increased connectivity in the basal ganglia (344,345). Not accounting for the effect of comorbidity might lead to wrong conclusions as to which factors drive the results in brain structure, function, or connectivity. As such, the field of ASD research is still evolving to account for newly discovered confounders: moving from small to large samples with regard to the population
heterogeneity and using better movement correction, as movement is known to be a prominent confound in the study of young populations (346). These findings already underline the challenge in integrating results across studies and coming to a scientific consensus as to what might be characterizing the brains of individuals diagnosed with ASD.

In order to integrate results across cognitive domains, we propose an analysis across multiple tasks using the task potency method, in a large ASD population and addressing the question of heterogeneity by looking at the effect of ADHD co-morbidity. The EU-AIMS Longitudinal European Autism Project (LEAP), a multi-centre and multimodal prospective longitudinal observational study, offers this opportunity by having gathered a large dataset aimed at identifying stratification biomarkers for ASD (186). In the fMRI dataset, the inclusion of a battery of resting state and five tasks targeting different cognitive domains (theory of mind, social and non-social reward, inhibition, emotional face processing (see details in supplementary material)) offers a great opportunity to assess common neural pathways across cognitive domains where ASD participants show impairments. The task potency framework takes the assumption that functional connectivity during tasks builds upon the ongoing activity architecture that resting-state fMRI aims to estimate (58). Using the task potency framework enables us to disentangle observed baseline connectivity differences from task-specific differences and to study alterations visible under specific cognitive constraints. The contribution of task-induced functional connectivity relative to that of the baseline architecture potentially allows a more precise interpretation of task-based functional connectivity findings and its contribution to the understanding of the ASD brain.

In this study, we make use of task potency to study task-induced connectivity modulations of the five fMRI tasks of the EU-AIMS LEAP dataset in order to assess whether the task modulation is altered in ASD compared to healthy participants. We further identify neural pathways common between tasks to characterize whether specific subprocesses - which are shared across cognitive domains impaired in ASD - are altered and could result in such a complex landscape of multiple impairments. Such findings would support the existence of local alterations, which can
Heterogeneity in ASD functional connectivity reveals ADHD-related symptoms subprofiles

be specific to a functional system. This could, for example, support theories such as executive functioning deficit. In order to address global alterations and get a general understanding of the brain connectivity response to tasks, we will characterize the level of integration and segregation of information under cognitive constraints, by looking at differences in task-modulation within and between networks. These analyses will also be repeated in the ASD subpopulations with high and low scores on ADHD scales, in order to address whether there is a specific effect of co-morbidity with ADHD. As previously reported (344), we expect to observe alterations typical to ADHD which were described in an earlier study using task-potency (see chapter 4).

MATERIALS AND METHODS

PARTICIPANTS.

![Demographical characteristics of the sample used in this study.](image)

*Fig. 1. Demographical characteristics of the sample used in this study.*
The dataset from the EU-AIMS LEAP project was used for the current analyses (185,186). Data from participants with intellectual impairments (IQ<75) was excluded. Participants with brain abnormalities were removed from the analysis. Participants performed a resting state fMRI and one or more of the following task fMRI scans: Hariri emotion processing (Emotion) (347), Flanker and Go-NoGo (Flanker) (348), non-social reward anticipation (Reward_ns), social reward anticipation (Reward_s) (349), animated shapes theory of mind (ToM) (350,351) (see details on the tasks in supplementary material). Additionally, each participant completed an anatomical scan for the purpose of registration. fMRI parameters are shown in the next paragraph. We further removed participants from the analysis for data quality using the following criteria. All participants had acceptable overlap (>94%) with the MNI152 standard brain after image registration. We excluded 57 Participants due to poor overlap (<50%) with one or more regions from the brain parcellation atlas that has been chosen for the analysis (220). Participants were further excluded on the basis of incidental findings, incomplete scans, and those in the top 5% in terms of head motion quantified through RMS-FD (213). The above criteria resulted in the inclusion of data for analyses from the following participants: 282 participants with autism spectrum disorder (age range 7.5-30.3 years; mean = 17.1; sd = 5.4; 72.3% male), and 221 typically developing controls (age range 6.9-29.8 years; mean = 17.0; sd = 5.5; 63.8% = male) (see Fig. 1) (see supplementary table for population characteristics).

**fMRI SCANNING PARAMETERS**

MRI data were acquired on 3T scanners at multiple sites in Europe. Structural images were obtained using a 5.5 minutes MPRAGE sequence (TR=2300ms, TE=2.93ms, T1=900ms, voxels size=1.1x1.1x1.2mm, flip angle=9°, matrix size=256x256, FOV=270mm, 176slices). An eight-to-ten minute resting-state fMRI (R-fMRI) scan was acquired using a multiecho planar imaging (ME-EPI) sequence; TR=2300ms, TE 12ms, 31ms, and 48ms (slight variations are present across centres), flip angle=80°, matrix size=64x64, in-plane resolution=3.8mm, FOV=240mm, 33 axial slices, slice thickness/gap=3.8mm/0.4mm, volumes=200 (UMCU), 215 (KCL, CIMH), or 265 (RUNMC, UCAM). Participants were instructed to relax and...
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fixate on a cross presented on the screen for the duration of the R-fMRI scan. Details can be found in (346).

FMRI PREPROCESSING
Preprocessing of the fMRI data was performed with tools from FSL 5.0.6. (214). The first 5 volumes for each acquisition were removed to allow for equilibration of the magnetization. To correct for head movement, we performed volume realignment to the middle volume using MCFLIRT. Then followed global 4D mean intensity normalization and smoothing with a 6mm FWHM kernel. ICA-aroma was used to identify and remove secondary motion-related artefacts (66,67). Next, signal from white matter and CSF was regressed out and we applied a 0.01Hz highpass filter. For each participant, we registered acquisitions to their respective high-resolution T1 anatomical images by means of the Boundary-Based Registration (BBR) tool from FSL-FLIRT (213). The high-resolution T1 image belonging to each participant was registered to MNI152 space with FLIRT 12-dof linear registration, and further refined using FNIRT non-linear registration (219). We used the inverse of these transformations to take a brain atlas to the native space of each participant, where all further analyses were performed.

CLINICAL DATA
We used clinical variables related to ASD and in order to analysis possible co-morbidity effect - ADHD symptomatology in our analysis. For ASD these were the total scores for the Social responsiveness scale second edition (SRS-2)(352), the Repetitive Behaviours Scale - Revised (RBS-R) (353), and the Short Sensory Profile (SSP) (354). The SRS-2 contains questions about broad, characteristic ASD behaviours. The RBS-R contains questions specifically about repetitive and restrictive behaviours associated with ASD. The SSP scores abnormalities in sensory processing. For our analyses we summed the SRS-2, RBS-R, and SSP scores for each participant in order to produce an ASD symptom sum-score. Parent report were selected for all participants for consistency. For ADHD symptomatology, we used parent report due to the age range of the population in order to keep our measure consistent. The ADHD DSM-IV rating scales comprise two clinical domains: inattentive symptoms and hyperactivity/compulsive symptoms (327). We summed the ADHD
hyperactivity and inattentiveness score for each participant in order to produce an ADHD symptom sum-score.

**TASK-POTENCY CALCULATION**

At its core, task-potency aim at quantifying the connectivity modulation that build upon the underlying baseline functional connectivity. This baseline is estimated from the resting state (58). Through this modelling we attain a new connectivity matrix which can be interpreted as the modulation away from the baseline - or ‘potentiation’ - that is instantiated in each edge due to engaging in the task for any particular participant. From each individual task potency matrix, we can define a group average to define the group-specific task profile and which edge are significantly modulated. Some tasks and some groups might potentiate a greater number of edges than others, different localization of edges or show differences in amplitude of modulation.

To this aim, we used a hierarchical brain atlas with 168 brain regions (distributed across 11 larger-scale networks) (220) to superimpose on the native space of each subject and for each fMRI acquisition to define the regions. For each participant, we calculated the covariance between the average BOLD time series extracted from each brain region pair. Using Ledoit-Wolf regularization we estimated partial correlations from the covariance matrix (222), and consecutively apply the Fisher-Z transformation. This provided us with 168x168 connectivity matrices, one resting state matrix and one or more task matrices for each participant. The main gaussian from a mixture gaussian-gamma model that was applied on each individual matrix supplied us with parameterised information about the distribution of values in each matrix. We used these parameters to normalize the elements in each matrix.

In order to produce individual matrices of connectivity modulations induced by the task, i.e. task potency, we standardized each participant’s task matrices by subtracting that participant’s resting state matrix. The resulting matrices are interpreted as containing the connectivity modulations away from the resting state baseline that the respective task induces in the brain - we refer to these modulations as task-potency (Fig. 3) (255).
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**Fig. 3. The task-potency pipeline.** The rest and task connectivity matrices are normalize before subtracting the first to the second at the level of each individual in order to obtain the task potency. A group task potency is then define by average individual task potency, for each task and group. A mixture modelling thresholding on each group average task potency is applied to obtain the set of significantly modulated edges.

**Task-fingerprints.**
We obtained group-level task-potency matrices by averaging across participant potency matrices for each task, within each participant group (ASD and TD). Within these group level matrices we identified the most strongly and consistently modulated edges by applying a threshold informed by a mixture modelling procedure (224). The resulting binary matrices for each task and diagnostic group are referred to as task-fingerprints and consist of those edges sensitive to their respective task. We refer to the edges passing the threshold as ‘selected edges’ for that task. Within each diagnostic group we now have 5 task-fingerprints, one per task. From these five fingerprint matrices we can now identify those edges that are modulated by one particular task, as well as those edges that are modulated by 2, 3, 4, or all of the 5 tasks. Any edge can therefore be modulated by a combination of the 5 tasks, resulting in 32 (including the set of edges modulated by none of the tasks - the null set) possibilities across the tasks. We can report the proportion of edges modulated across tasks in as a Venn diagram containing each of the 31 non-null sets of edges. To simplify our interpretation of these sets, we decided to define 5 categories as ‘levels of modulation’, which we can interpret as the level of generalization in the use of an edge. Essentially, we define
five concentric ‘rings’ within this Venn-diagram representation, where each ring consists of all of the sets that have the same sensitivity ‘level’. For example, ring 1 consists of those five sets that are modulated in only one of the respective five tasks, and ring 5 consists of the one set that is modulated in each of the five tasks (Fig. 2). This representation allows us to make inferences about whether any connectivity differences which we will test between ASD and TD might be situated in e.g. a task-general or a task specific domain.

**Statistical Testing.**

For ASD and TD we investigated and compared edges that were selected in a particular task, or in a particular ring. Four types of clinical measures were investigated in the above conditions. 1. The percentage of selected edges, 2. the mean amplitude within the selected edges, 3. The normalized distribution of selected edges across the five sensitivity-levels 4. the ratio of edges connecting areas within or between networks, as defined in our atlas - across the five sensitivity-levels. For point 4, we average information across networks as we do not aim at investigating network-specific differences. Bootstrapping was used to provide a robust estimate of the variance within these measures. Here, 10000 samples were taken from the original data, each including a random 80% of participants of the groups involved, selected with replacement. This allowed us to produce an estimate of the uncertainty of the particular metric within the populations which we need to quantify the uncertainty as to their difference. Any differences between ASD and TD in the obtained metrics above were then assessed using significance testing where we assessed how surprising our findings were given the distributions that were obtained from the sample bootstrapping.
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RESULTS

DATA
We have so far thus obtained 2 (groups) x 5 (tasks) = 10 separate mean functional connectivity matrices which were thresholded to reveal the connectivity fingerprints consisting of a selection of modulated edges for each of these 10 groups. We compare the modulation strength, amount, and spatial pattern of these selected edges between groups and tasks.

COMPARISONS BETWEEN DIAGNOSTIC GROUPS.
As the first step in analysing the data, we focus on the connectivity fingerprints and compare the amount of selected edges in each of these fingerprints between diagnostic categories for each task. Differences in the amount of selected edges present in the task connectivity fingerprint of diagnostic groups can provide insight into a global connectivity alteration where more or less edges are modulated to achieve the same task-goal. This could indicate more diffuse or more focused network involvement. In this measure the specific spatial connectivity modulation profile e.g. which networks connect where, is not taken into consideration. On first inspection there appears to be a trend for a
greater amount of edges being recruited in performing the tasks in ASD as compared to TD across the tasks (Fig. 4). This could suggest a more diffuse modulation of edges across networks in ASD. However, the overall modulation across selected edges between groups is not significant in any of the five particular tasks (pairwise comparisons with FDR corrected across tasks). Additionally, we notice that different tasks modulated a different amount of edges in both diagnostic groups.

As a second step, we can analyse the mean amplitude of modulation within the selected edges present in the fingerprints. For each diagnosis x task combination, we identified the mean amplitude of edge modulation across the edges (Fig. 4). After FDR correction across groups, we see significant differences in tasks flanker (p=0.005), social reward (p=0.001), non-social reward (p=0.002), and theory of mind (p=0.026). In each of these tasks, the amplitude is lower for the ASD group, suggesting that the brain connectivity profile in the ASD group is not as strongly modulated in the face of any of these tasks as is the case for the TD group.

**Fig. 5.** The distribution (normalized) of selected edges across the rings. On the extremes we have ring 1, which contains only those edges selected in one task, and ring 5 which contains only those edges selected in all of the tasks.
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![Graph showing percentage of edges modulated consistently and strongly](image1)

![Graph showing mean potency amplitude of selected edges](image2)

**Fig. 4.** Top: The percentage of edges that were consistently and strongly modulated in ASD/TOTAL. Bottom: The mean potency amplitude of the selected edges in ASD/TOTAL.

**Comparisons between tasks.**

One of the primary goals of this investigation was to attempt to integrate brain connectivity findings across different task- i.e. cognitive domains in the ASD population. As described earlier, for each task x group combination we have a task-fingerprint - containing those edges that passed our threshold for being consistently and strongly potentiated in their respective condition. If we consider these ‘selected edges’ for each of the tasks, we can represent edges that are modulated by one or a
combination of tasks in a Venn-diagram. This allows us to describe similarity in terms of connectivity patterns between tasks. We focus our analysis on the level of selectivity across tasks, as edges can be modulated by one, two, three, four or all five of the tasks. (Fig. 2). The five areas defined as ‘rings’ within this diagram represent advancing levels of generalized modulation across tasks, with ring one being a combination of the five sets of edges that are only modulated in one specific task, and ring five consisting of that set of edges which are modulated in each task. We investigate the way in which the amount of selected edges is distributed across these five rings, and how this might differ between ASD and TD. For better visualization, the distributions were normalized within diagnosis group - meaning that the sum of the values across the five tasks, within diagnosis group, equals one. Because this makes the data dependent across rings, we model the representation of edges across the five rings using a parametric fit. We chose an exponential for this fit, based on visual inspection as well as for model simplicity. Using one fit per bootstrap, we extract the distribution of the exponential coefficients for each group and compared if the representation of shared edges across rings shows a different pattern between the groups. We find that the first parameter of the exponential fit is estimated as significantly greater in the ASD group (p=0.04). This parameter indicates the intersect with the y-axis rather than the rate of decay, suggesting that the ASD group has a relatively greater proportion of edges that are unique to one task.

We have furthermore mapped the connectivity profile of each ring of edges, here defined as being edges that connect nodes either within- or between networks. We quantify this per ring by taking the fraction of the amount of Within network edges to the amount of Between network edges (W/B ratio). Higher values here correspond to greater within network connectivity. Firstly, we observe that this ratio is always greater than 1 - replicating the finding that tasks preferentially modulate within-network edges (240). We further model a mean linear relationship between W/B ratio and the ring level using one fit per bootstrap (β=5.66, sd=0.60 for ASD, β=6.49, sd=0.95 for TD) where we find that edges shared by more tasks are increasingly more likely to be a within-network edge. We did not find evidence of these linear effects differing between ASD
Heterogeneity in ASD functional connectivity reveals ADHD-related symptoms subprofiles and TD (p=0.14). Visually, the TD group appears to recruit more within network edges across each of the rings, however this is only significant in ring 3 (p=0.018) (FDR corrected across the five rings) (Fig. 6).

**Fig. 6.** Displays the ratio of the amount of within-network edges to the amount of between-network edges in each ring set. Higher values correspond to greater within network connectivity. The lines indicate the linear fit for the respective diagnosis type of the ring on the W/B ratio ($\beta=5.66$, SD=0.60 for ASD, $\beta=6.49$, SD=0.95 for TD).

**ASD and ADHD.**

Previous work has shown that task-potency measures in an ADHD sample have displayed opposite effects, i.e. less modulated edges with higher modulation, to those found in the current study (see chapter 4). It is further known that ASD and ADHD are often co-morbid. To investigate this possible confound, we separated our sample into ‘ASD/ADHD+’ consisting of those ASD subjects that met clinical classification cutoffs for an unofficial ADHD diagnosis, and ‘ASD/ADHD-’, consisting of those subjects that did not meet the ADHD cutoff. The cutoff is in both cases defined as having a score of 5 or greater on either the hyperactivity or inattentiveness ADHD subscales as measured by parent-report. Out of our total sample of 282 ASD subjects, 201 fell into the ASD/ADHD-subgroup, and 81 fell into the ASD/ADHD+ subgroup. Note that this means that some ADHD comorbidity may be registered in almost 30% of the participants.

**Potency profile of the different subgroups.**

In order to visualize any posited heterogeneity of the subgroups in relation to the total population with respect to their set of selected edges.
for each of the five tasks, we compute five Venn-diagrams (Fig. 7 top). Inspecting the diagrams, we show a number of trends occurring across the tasks: 1. Selection sizes appear to be smaller for the subgroups than they are for the total. 2. The ASD/ADHD- and the ASD/ADHD+ subpopulations appear to cover large unique areas in the ASD/TOTAL selected edges profile (yellow and purple areas in the figure). 3. There is negligible overlap between the ASD/ADHD- and the ASD/ADHD+ subpopulations outside of the ASD/TOTAL selected edges profile. In order to check whether effects might have been driven by comorbid ADHD, we re-ran the above analyses of Fig. 4 in both the ASD/ADHD- and ASD/ADHD+ subgroups. As the subgroups do not represent well-posed subpopulations, we only look for similarities or divergences in results compared to our original group.

**Task-analysis in ASD/ADHD-.**

The amount of edges selected by the mixture model as showing strong connectivity modulation in each task appears lower, and hence more similar to TD, when we use only the ASD/ADHD- subgroup in the analysis (Fig. 8 top). Just as was the case for the comparison for the selection of edges between the ASD/TOTAL group and TD, we do not find significant differences for a particular task. Furthermore, when we look at the amplitude present in these edges, we see that the values for ASD/ADHD-subgroup appear closer to normal TD values (Fig. 8 bottom). None of the current comparisons exceed the significance threshold for differences.

**Task-analysis in ASD/ADHD+.**

We find that the ASD/ADHD+ group as a whole recruits significantly less edges compared to TD in all but the Flanker task (Fig. 9 top). Moreover, inspecting the mean potency amplitude of these edges show us that the potentiation taking place is more powerful in the ASD/ADHD+ group compared to TD for all of the tasks (Fig. 9 bottom).
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**Fig. 8.** Top: The percentage of edges that were consistently and strongly modulated in ASD/ADHD-. Bottom: The mean potency amplitude of the selected edges in ASD/ADHD-.
**Fig. 9.** Top: The percentage of edges that were consistently and strongly modulated in ASD/ADHD+. Bottom: The mean potency amplitude of the selected edges in ASD/ADHD+. 
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Modelling potency from symptom scores in ASD and ADHD. As a way of investigating whether we can link potency to ASD and ADHD severity and to control for differences in clinical characteristics (see supplementary table 1), we model the mean potency amplitude of the edges in the respective sets from ASD and ADHD aggregate symptom scores (Fig. 7 bottom). Interestingly, for the flanker, non-social reward, and theory of mind tasks, we find significant positive associations between ADHD symptom scores and the set of edges that was selected in both the ASD/TOTAL and ASD/ADHD+ groups but not the ASD/ADHD- group (yellow area in the figure). We furthermore find a significant positive association between ADHD scores and the set of edges selected in all three conditions for the flanker task. We do not find significant associations between ASD symptom scores and a particular set of edges in any of the current tasks. All significance values are FDR corrected for the 15 possible set x task combinations.
### Table: Significance Values for Linear Model Predicting Mean Potency Amplitude of Edges within Venn-Set from ASD and ADHD Symptom Scores and Age

<table>
<thead>
<tr>
<th>Venn-Set</th>
<th>ASD Score</th>
<th>ADHD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD/ADHD -</td>
<td>0.65</td>
<td>0.79</td>
</tr>
<tr>
<td>ASD/ADHD +</td>
<td>0.99</td>
<td>0.34</td>
</tr>
<tr>
<td>ASD/ADHD +</td>
<td>0.89</td>
<td>0.99</td>
</tr>
<tr>
<td>ASD/ADHD +</td>
<td>0.80</td>
<td>0.34</td>
</tr>
<tr>
<td>ASD/ADHD +</td>
<td>0.56</td>
<td>0.98</td>
</tr>
</tbody>
</table>

### Venn Diagrams

**Fig. 7.** Venn diagrams displaying percentage of shared and unique modulated edges for the ASD/TOTAL group and its two subgroups ASD/ADHD-, and ASD/ADHD+. The numbers denote the amount of modulated edges in each Venn-set. The table shows significance values for a linear model predicting the mean potency amplitude of edges within the respective Venn-set from ASD and ADHD symptom scores and age. We find significantly positive relations between ADHD symptom scores and mean potency from the set of edges shared between ASD/TOTAL and ASD/ADHD+ for Flanker, non-social reward, and Theory of Mind tasks.
DISCUSSION

We hypothesize that, by integrating multiple task domains, we assess common (i.e. across tasks) altered connectivity patterns during task response and assess global alterations in response to these tasks by comparing ASD to typically developing individuals. These two aspects would enable us to give an unbiased integrated viewpoint and find support for either theories implying specific disfunction of a subsystem, or for a more general alteration of the brain functional architecture. For this reason, we have focused our first inquiry on general alterations in the way brain connectivity is modulated in five tasks: emotion processing, Flanker, social and non-social reward, and theory of mind.

When we compare the percentage of modulated edges away from the baseline architecture of the brain in the overall ASD group (ASD_total) to the TD group, we do not find case-control differences. However, the amplitude of the connectivity modulation is significantly lower in the whole ASD group for 4 of the 5 tasks under consideration (Flanker, social reward, monetary reward, ToM). This could mean that even though participants with ASD engage a normal percentage of their connectome in performing a task, the particular strength of these modulations could be a reason for their impairments in achieving these cognitive goals. We did not find this alteration for the Hariri emotion processing task, suggesting that the lower modulation present in ASD may be specific to certain tasks, or rather to a cognitive process underlying the above tasks, but not emotion processing. Alternatively, differences in task difficulty can create differences in sensitivity to differences between ASD and healthy participants. In other words, the task profiles - i.e. which edges are potentiated for a particular task - are similar between ASD and TD, but not the amplitude of this modulation. Importantly, as the influence of the base resting state connectivity architecture is explicitly removed from the analyses in this paper, we only assessed the connectivity modulation. Differences in baseline between groups are not assessed. Therefore, existing connectivity alterations previously observed in the resting state (183) might be interacting with observed task-induced modulations. For example, an underlying over-connectivity might need
to be down-modulated to avoid interacting with the required system requested to performed the task. An underlying under-connectivity should be up-modulated to match the requirement of the task. If the underlying baseline architecture supporting the task-induced modulation is altered, not observing differences in task potency between ASD and control group could mean that the task response is adequate, but lack flexibility to adapt.

As the tasks involved in this study have been selected for their implication in ASD (185), finding altered connectivity in a set of edges common to these tasks could help us in searching for the brain processes at the root of ASD symptoms. The thinking behind this approach was that it might help us in identifying if any alterations are primarily found in those edges that are specific to certain tasks, or rather to edges that are involved in multiple, or all of the tasks. In order to explore similarities and differences between task modulation profiles - as well as how these might differ between groups, we constructed a Venn-diagram of the sets of edges (task-profile) involved in each of the five current tasks. We found for both groups that the majority of edges across the five tasks are task specific, with fewer edges modulated across tasks as we go towards considering sets selected in higher numbers of tasks, i.e. each consecutive ring. Very few edges were common across all five tasks. In order to find out whether this pattern differed between the groups, we modelled this ‘decay’ from specific to common edges for both groups with an exponential curve. We found that the model showed some difference in the initial state, but importantly no difference in the rate of decay, providing no evidence that the task-profile in ASD is altered. This contrasts sharply with what has been found for ADHD (see chapter 4), where a lack of common processing compared to TD has been identified.

The weak central coherence theory of autism refers to the apparent cognitive deficits individuals with ASD have with fluently integrating/segregating information e.g. ‘not seeing the forest for the trees’ (330). If we make the biologically plausible assumption that adjacent types of information processing occur in adjacent brain regions, this allows us to investigate this cognitive theory aided by fMRI data. Adjacency can be defined, for instance, in terms of graph theoretical
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distance, or Euclidean distance. And indeed, previous evidence in line with the weak central coherence hypothesis of ASD suggests that there may be resting-state underconnectivity at short range and overconnectivity at long range in the ASD brain (50,183). Adjacency can however also be defined in functional terms e.g. as resting-state networks. The task-potency method allowed us to assess whether such a pattern can also be observed when it comes to the connectivity modulation that occurs during a task. Because we make use of a hierarchical atlas (11 large-scale networks, in which are situated 168 smaller scale areas) we have the ability to classify edges as being either within- or between-networks, which served as our measure for adjacency of processing. We found that edges in both groups become more likely to be within network edges as we look at the sets that are selected in more tasks. In other words, processing that is more general, and shared across multiple cognitive domains is much more likely to take place within the same networks when compared to processing that is only implicated in a single task.

Contrary to the literature that has associated ASD with short range overconnectivity, we have not found evidence for this in our analyses. We find rather that in ring 3, the TD group has significantly greater within-network oriented edges. We can hypothesise that only observing an effect in ring 3 might be due to a particular interaction between three of the tasks, which fall under this umbrella. More investigation is needed by selecting specific tasks together as we cannot compare our results to the existing literature on short- and long-range connectivity. Indeed, we analysed modulation of connectivity during tasks rather than resting-state connectivity, and we cannot compute the distance in terms of graph theoretical metrics as we focused on a subset of edges modulated during the task and removed the underlying architecture that connects them.

In order to investigate variability and heterogeneity in our ASD sample and because previous findings have shown that the task profile is altered in ADHD (see chapter 4), we decided to compare the task profiles of an ASD group which also scored high on ADHD symptoms to the rest of the ASD sample. Because of the high levels of ADHD co-morbidities known to exist in ASD cohorts, we were able to split the ASD group up into two
groups, ASD/ADHD- and ASD/ADHD+ with respectable sample sizes. In the ASD/ADHD- group where participants which met unofficial clinical scores for ADHD were excluded, we did not find any effect for either percentage of modulated edges or their amplitude. This might suggest that the amplitude effect that was found in the original whole ASD group (ASD\textsubscript{total}) could have been in fact driven by the subjects with ADHD. Though we do find a significant amplitude effect in ASD/ADHD+ for each of the tasks, they have an opposite direction to the effects found for ASD\textsubscript{total}, with the ASD/ADHD+ group rather having greater modulation amplitudes than TD. The fact that the amplitude findings of ASD\textsubscript{total} are not a simple weighted average of ASD/ADHD+ and ASD/ADHD-, implies that these groups must have had differences in the set of edges from which this amplitude was calculated. This led us to computing the selected edges for each of the five tasks, for these new groups and found they mostly make use of different sets of edges to perform tasks. What appeared to be a confound due to heterogeneity in the population now makes it clear that our method is highly sensitive to group differences even if they come from subgroups. Further research is needed to investigate how this generalises to other ways of splitting populations, and whether it can be used to correctly classify individual participants. For example, we can try to assess whether observed differences are characteristics of the entire population by using this as input in a normative modelling analysis (355). In this approach, participants’ deviance from a norm defined in the sample is assessed in order to capture subgroups effect or even individual profiles.

We found a significant positive association of ADHD symptom scores and mean potency amplitude in the flanker, non-social reward, and theory of mind tasks. This was the case when we considered a set of selected edges that was common between ASD\textsubscript{total} and ASD/ADHD+, but not ASD/ADHD-. These particular tasks have a strong executive function component, which is known to be impaired in ADHD (332). This finding may form a steppingstone to a possible clinical/diagnostic application of task-potency in ADHD. Further research can be done in a cohort of ADHD participants to narrow down which edges are responsible for driving this effect, and find out whether we have identified an ADHD-related effect or rather an ASD-ADHD comorbidity effect.
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In the current research we take a holistic perspective at brain connectivity modulation. We analyse characteristics of the sets of selected edges independently of their spatial localisation, taking a general view on whole brain connectivity. Even when investigating edges as being within or between networks, where we carry out a slightly finer grained analysis, we still aggregate across tasks and lose some resolution in that dimension. It stands to reason there may exist many relevant differences between (and within) the groups under consideration with respect to task-potency that we have not detected, which are left to future research. As it is known that ASD has a component of sensory processing abnormalities, it could for instance be interesting to compare and contrast the task-profiles of sensory versus higher-order regions.

In summary, when observing differences between the ASD population and the typically developed individuals, the ASD group displayed a more diffuse and weaker connectivity modulation across tasks. When accounting for heterogeneity in the population in regard to ADHD comorbidity, the ASD subpopulation with high ADHD symptoms demonstrated a pattern of connectivity typical to the ADHD population with less modulated edges showing a higher amplitude of modulation. The ASD subpopulation without high symptoms did not display significant differences with typically developing participants. Lastly, we related ADHD symptom scores to mean potency amplitude in a set of edges, but were not able to do the same for ASD symptom scores. We have showed that task potency is a method of integrating task fMRI data which shows promise in the domains of parsing heterogeneous clinical groups as well as predicting symptom scores from fMRI data.
SUPPLEMENTARY MATERIAL

DESCRIPTION OF THE TASK

HARIRI TASK (347)
Participants are presented with blocks of trials that either ask them to decide which of two faces presented on the bottom of the screen match the face at the top of the screen, or which of two shapes presented at the bottom of the screen match the shape at the top of the screen. The faces have either an angry or fearful expression. 56 trials are presented in blocks of 6 trials of the same task (face or shape), with the stimulus presented for 2000 ms and a 1000 ms ITI. Each block is preceded by a 3000 ms task cue, so that each block is 21 seconds including the cue. Each of the two runs includes 3 face blocks and 3 shape blocks, with 8 seconds of fixation at the end of each run.

FLANKER TASK (348)
A task in which participants view stimuli (arrows) presented one at a time and to which they must make a simple lexical response. These stimuli are surrounded by either distracting or facilitating items. Distracting items are associated with an opposite response ("incongruent" = pointing in opposite direction to target stimulus), whereas facilitating items are typically associated with the same response as the target stimulus ("congruent" = pointing in the same direction as the target stimulus). 202 trials are presented every 300ms.

MONETARY/SOCIAL REWARD TASKS (349)
In both tasks, participants had to respond as quickly as possible to a trigger (white square) while it remained on screen. The amount of time the participant had to respond to the trigger depended on the number of correct or incorrect prior responses. Trigger cues were preceded by an instruction cue signalling the level of potential reward. For ‘reward’ trials a circle denoted that participants would be rewarded if they responded quickly enough (n per task = 60) while for ‘no reward’ trials a triangle denoted that the participant would not receive a reward, regardless of whether or not they responded quickly enough to the trigger (n = 30). Reward magnitude varied on two levels indicated by the number of horizontal lines on a cue stimulus. In the MID the levels of monetary
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reward were €0.20 (n = 30, preceded by a cue depicting a circle with one horizontal line) and €1.00 (n = 30, preceded by a cue showing a circle with two horizontal lines). Success was acknowledged by showing a picture of a coin with the money earned on that trial. In the case of a ‘no reward’ trial, or when participants did not respond to the trigger quickly enough, they were shown a coin stimulus of the same size and luminance but with no features. SID instruction cues were identical to MID instruction cue except in color. Feedback was a female face from the NimStim set of Facial Expressions with a happy facial expression at two levels of intensity (small smile and larger smile). This face stimulus was presented as it was rated as the most pleasant and attractive of the Caucasian faces in the NimStim set by a sample of 20 male participants. Two levels of social reward were used to reduce task duration. The ‘no reward’ facial stimulus was the same but graphically dysmorphed face, with facial features eliminated but size and luminance retained.

THEORY OF MIND TASK (ANIMATED SHAPES) (350,351)
Subjects are asked to perform a task involving the understanding of another’s personal beliefs and feelings or forming hypotheses regarding the mental states of others by looking at animated sequences. The animations depicted two triangles moving about on a screen in three different conditions: moving randomly, moving in a goal-directed fashion (chasing, fighting), and moving interactively with implied intentions (coaxing, tricking). The last condition frequently elicited descriptions in terms of mental states that viewers attributed to the triangles (mentalizing). 12 animated sequences are presented.
## Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TD mean (sd)</th>
<th>ASDtotal mean (sd)</th>
<th>ASDadhd- mean(sd)</th>
<th>ASDadhd+ mean (sd)</th>
<th>ASDadhd- vs. ASDadhd+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (number of subj)</strong></td>
<td>194</td>
<td>252</td>
<td>171</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (% of male)</strong></td>
<td>66.5%</td>
<td>71.0%</td>
<td>70.8%</td>
<td>71.6%</td>
<td>ASD-~ASD+ P=0.891</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>17,001 (5,700)</td>
<td>17,116 (5,548)</td>
<td>17,854 (5,694)</td>
<td>15,560 (4,872)</td>
<td>ASD-&lt;ASD+ P=0.002</td>
</tr>
<tr>
<td><strong>head motion (meanFD)</strong></td>
<td>0.092 (0.077)</td>
<td>0.110 (0.088)</td>
<td>0.104 (0.082)</td>
<td>0.123 (0.099)</td>
<td>ASD-~ASD+ P=0.102</td>
</tr>
<tr>
<td><strong>IQ (full scale)</strong></td>
<td>105,139 (16,499)</td>
<td>101,130 (18,863)</td>
<td>103,125 (18,028)</td>
<td>96,918 (19,867)</td>
<td>ASD-&gt;ASD+ P=0.015</td>
</tr>
<tr>
<td><strong>SRS (raw_comb)</strong></td>
<td>28,012 (20,613)</td>
<td>87,700 (31,657)</td>
<td>77,098 (28,986)</td>
<td>107,975 (26,190)</td>
<td>ASD-&lt;ASD+ P&lt;0.001</td>
</tr>
<tr>
<td><strong>ADOS (total)</strong></td>
<td>na</td>
<td>5,139 (2,725)</td>
<td>4,932 (2,666)</td>
<td>5,579 (2,797)</td>
<td>ASD-~ASD+ P=0.089</td>
</tr>
<tr>
<td><strong>ADI communication</strong></td>
<td>na</td>
<td>5,117 (2,720)</td>
<td>4,902 (2,655)</td>
<td>5,439 (2,840)</td>
<td>ASD-&lt;ASD+ P=0.005</td>
</tr>
<tr>
<td><strong>ADI RRB</strong></td>
<td>na</td>
<td>13,124 (5,509)</td>
<td>12,436 (5,535)</td>
<td>14,544 (5,172)</td>
<td>ASD-&lt;ASD+ P=0.003</td>
</tr>
<tr>
<td><strong>ADI social</strong></td>
<td>na</td>
<td>4,120 (2,545)</td>
<td>3,785 (2,516)</td>
<td>4,810 (2,465)</td>
<td>ASD-&lt;ASD+ P=0.005</td>
</tr>
</tbody>
</table>
DISCUSSION
DISCUSSION

SUMMARY OF MAIN FINDINGS
The general aim of this thesis was to investigate how functional connectivity is modulated under task performance in order to understand its task-specificity. We made the initial assumption that functional connectivity induced by performing a task builds upon ongoing network activity structured into a general functional architecture. We used functional connectivity estimated during resting state as a proxy for functional architecture and extracted the modulation from this architecture to characterize a task’s functional activity. Through the estimation of task-specific connectivity modulations, we obtained a metric, i.e. task potency, which enhances sensitivity to the neural correlates of cognition in describing the task-related changes in functional connectivity. We used this metric to investigate the commonality of functional connectivity modulations across multiple tasks and to uncover how modulated neural pathways structure cognitive processing. With task potency, we aimed to better understand how functional connectivity modulation participates in task performance, and how this modulation creates efficient processing of information. To this aim, we investigated whether the task-rest modulation exhibited task-specific maturational patterns and validated our potency framework in the context of cognitive mindsets. In addition, we investigated how developmental disorders could be characterized by a disorder-specific pattern of modulations thereby highlighting potential vulnerabilities in the efficiency of the brain’s functional architecture.

Chapter 1 of this thesis describes the task potency pipeline and includes proof of concept analyses that demonstrate that task functional connectivity modulations away from the extracted resting-state baseline correspond to meaningful task networks. These analyses were carried out using data from healthy participants and three tasks available in the NeuroIMAGE database targeting different cognitive domains (inhibition, working memory and reward anticipation). As this metric is defined in a common space, i.e. normalized connectivity, we can perform direct task comparisons and compare common patterns of network modulation across cognitive domains. Generalizing this concept would enable one to
Discussion

study the building blocks of target cognitive processes used across multiple tasks. We observed more modulation taking place in edges connecting areas within well-known resting state networks. This within-networks modulation is mostly represented by edges common to multiple tasks, while the modulation between networks are mostly task-specific. We conclude that resting state networks represent general processing units and are commonly modulated across cognitive domains, while task-specific processing is exhibited in the way networks integrate and exchange information with one another.

To shed light on the relationship between baseline architecture and task response, chapter 2 investigated how a participant’s state of mind influences task performance by shaping task-induced connectivity modulations. We used the MyConnectome dataset that offers a hypersampling of one subject in task fMRI, rest fMRI and several domains of behavioural metadata. We observed that the task potency generally reduces with positivity and increases with negativity, e.g. a positive and attentive mindset is associated with smaller task-induced connectivity modulations. Therefore, assuming that reduced modulations during task performance translates into reduced energy request, a positive-attentive state sets networks into an efficient neural state. These mindsets also explained within-task performance. We observed that the dynamic task potency during missed trials displays an expression of fatigue after stimulus presentation, leading to miss trials. In contrast, we observed a greater expression of positive-attentiveness in hit trials. This result demonstrates that the amplitude of connectivity modulation between rest and task is an index of the efficiency of task performance in an individual and is influenced by a participant’s state of mind.

In chapter 3, using healthy participants from the NeuroIMAGE database, we investigated the effects of age on task potency in a cross-sectional analysis. We observed that the older participants are, the smaller the task potency is, thus requiring less modulation to perform each task because the architecture during rest and during task performance are more similar. Additionally, each of the tasks showed a different dynamic in time with specific time windows of maximal change. However, these differences with age were observed across tasks in a common
Discussion

connectivity path, which demonstrates that cognitive processes do not mature independently—supporting the interactive specialization theory.

In chapter 4, we used the full NeuroIMAGE dataset and compared participants with ADHD (probands), their unaffected siblings and healthy participants. The database targets three cognitive domains in which ADHD patients show impairment: reward processing, inhibition and working memory. We investigated possible alterations in the common connectivity modulation across the three available tasks for probands and their unaffected siblings when compared to healthy controls. By proband siblings into the analysis, we were able to address the theory that proposes that unaffected siblings of ADHD patients share some endophenotypic traits with probands. We observed that ADHD participants and unaffected siblings, compared to controls, are lacking most of the common connections shared by all three tasks and display an overrepresentation of task-specific connectivity. However, both groups use two different alternative strategies. Siblings displayed increased modulation of the connectivity that they shared with healthy participants, prioritizing their conserved connectivity instead of compensating with task-tailored alternative connectivity—as ADHD participants do. The missing common connections were consistent in the ADHD and siblings groups and could be candidate biomarkers for a deviant profile from normality. In contrast, the task-tailored connectivity displayed by ADHD participants was much more idiosyncratic, i.e. showed large differences between participants with ADHD. This task-tailored connectivity might be related to individual strategies developed over time, contributing to the heterogeneity within the ADHD population.

In order to get a better understanding of developmental disorders mechanisms, in Chapter 5, we investigated the task potency across five tasks performed by participants with ASD and healthy controls from the EU-AIMS LEAP dataset and assessed the effect of comorbidity with ADHD. In the entire population, we observed a higher percentage of selected edges together with an overall decreased amplitude of modulation across these selected edges. However, this effect was driven by a subgroup of participants who displayed a high number of ADHD symptoms and different task fingerprints which replicated results from
Discussion

Chapter 4, namely a different set of selected edges with higher connectivity modulation. These ADHD comorbidity task fingerprints were related to ADHD symptoms and, in particular, to tasks where ADHD is known to be impaired like reward processing and executive functioning tasks. This result shows that our metric enhances the sensitivity to multiple group effects within a heterogeneous population. After describing the task fingerprints, we further investigated how our metric could be supporting current ASD theories related to a general disfunction of networks such as the imbalance of integration and segregation in brain networks, the weak coherence theory and the emphasizing-systemizing theory (47,50) versus theories related to local dysfunction such as the dysfunction of executive functioning or of reward processing or of theory of mind (48,49). We investigated the ratio of within and between network edges to reflect the imbalance of integration and segregation and observed indices of imbalance. We also looked for a core disrupted pattern involved in multiple tasks, as we did in Chapter 4 for the ADHD population, but we hypothesized a representation of one of the networks related to the local mechanisms disfunction theories, yet we did not find such alterations in the ASD population. These results show that ASD is associated with preserved task fingerprints. A next step in understanding how ASD patients perform tasks would therefore be to look for differences in the baseline connectivity that we remove from our task potency analysis, which also plays an important role in the overall information processing during task performance but is not specific to a given task.

Overall, through the integration of results from the different chapters that address connectivity modulation between rest and task according to changes in mindset, or across normal or abnormal development, I demonstrated that functional architecture shapes cognitive processing. Across development, the functional baseline architecture and the task connectivity state become more alike, showing that a more mature brain tends to modulate tasks-related functional connectivity less than an immature brain. A positive mindset also translates into less modulation. Additionally, an ADHD profile is associated with a smaller pattern of selected edges and a higher modulation of that connectivity pattern. Together, my findings suggest that a reduced and well-structured task
Discussion

potency is a marker of brain efficiency in task processing in ADHD. These results give new insights into the importance of functional brain organization and network relationships.

DISCUSSION ON FINDINGS

UNDERSTANDING THE INFORMATION FLOW
In this thesis, we disentangle task-induced modulation from the baseline architecture of the brain. By describing this task-induced modulation, we are able to better map task connectivity as we enhance the sensitivity to connectivity signal. We remove part of the individual variation in the connectivity as we consider individual functional baseline and remove common processing that is not task-specific (256). While we characterise this task-specific modulation, the task potency should not be considered as the only processing relevant for performing a task. Both baseline activity and supplemental modulation are required for processing information in the brain during task performance. Additionally, local processing of information within an area was also not characterised and would need to be integrated to more fully define the underlying neural processing of cognition. Overall, this transfer of information across networks extends beyond the observed local activation (356). The information flows between networks and is processed across specific network modulations and general processing (357). This general processing has both a component represented in the resting state topology, as well as a task-general component particularly loading into flexible hubs (77,83,196,358,359). Disentangling the task-specific modulation from the baseline activity is then the first step to understand task-specific processing and can be followed by information flow modelling. Previous studies have investigated such information flow and their successful ability to predict task activation based on individual baseline architecture (4,5). Such models can be extended to integrate multiple tasks and define what network relationships are needed to process information for a specific cognitive state. An investigation of how the baseline architecture supports the task modulation and this information flow would shed light on the optimal neural functioning.
Discussion

Indeed, information flow has been modelled out of the neural organization of a series of species and is a feature that follows evolution, demonstrating its importance in neural processing (360).

Additionally, understanding the information flow in the brain through the rest-task interaction may lead to new hypotheses on why disruption of the baseline activity in the brain could impact cognitive function. For instance, there have been strong and reproducible results of disrupted baseline activity of the brain in ASD patients (361). However, in Chapter 5 of this thesis, the task modulation was globally preserved compared to controls. Even though more local investigations could still provide specific ASD differences with healthy participants, such large behavioural differences must come from a larger difference in information integration, thus highlighting the importance of a subsequent study towards the understanding of whether the baseline architecture that supports the task modulation displays differences between groups. As these differences would not be specific to task-processing, their localisations might be interacting with the task-specific modulation localisation, therefore impacting specific cognitive processes. In any case, to validate that differences relate to cognitive impairment, additional analysis steps are required to confirm common variation between alteration and symptom dimensions.

As a general statement, relating functional connectivity to behavioural outcome such as task performance or behavioural differences is necessary to validate the underlying neural activity resulting in observed psychological metrics. This validation remains a challenge; even if we can define the neural basis of interest for psychological metrics, whole-brain processing is at play, integrating and processing signal before resulting in behaviour (362). Therefore, the sensitivity between local neural variation and behavioural variation is low and its study challenging. Additionally, due to the massive involvement of the brain and its networks organization, a specific neural basis will also ripple in the activity of other networks across the brain, resulting in the detection of a large representation of a specific psychological metric variation across the brain. Interestingly, in Chapter 5, the ADHD-comorbidity connectivity differences within the ASD population show significant correlation with
ADHD symptoms score, showing that the task potency might provide more sensitivity to psychological metric and help address the challenge of linking behaviour to neural basis.

DISCOVERING SHARED NEURAL PATHWAYS
To understand the structure of connectivity modulation, we can compare tasks to access similarities between cognitive states and disentangle common processes. As such, we might be able to understand how cognitive functions, as defined from a behavioural point of view, can influence each other. For example, emotions interact with memory either by helping or by interfering with the fixation of information. Emotions are beneficial when the emotional event is coherent with the information stored memory, but they become distracting and will impair memory performance when emotional cues are unrelated to the memory task. In the latter case, the prefrontal cortex interacts with two independent cognitive processes, namely one related to the emotional pathway and another related to the memory network(282). It is hypothesised that prefrontal resources are then used in either a coherent manner, which enforces encoding of information, or in a distributed fashion between two tasks, which reduces the ability to work optimally in the memory task. To validate this point, we can define the rest-task modulation that is required to perform each task and its amplitude limitation. Coherently with the idea that the task potency could be used as an index of brain efficiency, we can investigate the interpretability of the modulation in term of brain resources. As we earlier showed that common pathways across tasks are preferred in the healthy brain, we can investigate whether such architecture limits the spread of resources used across the brain, making the integration of information more efficient. Indeed, neurons respond to a mix of non-linear task-relevant information and select which information to process(363). The global workspace theory implements this concept at the level of networks, describing conscious experience as a graph of incoming information that either does or does not pass an integration threshold (364). We can then first define the shared modulated connectivity across cognitive domains and investigate their non-linear relationship in more complex tasks to further understand how information is processed in the brain.
To assess the neural architecture modulated in multiple cognitive states, we should adapt our metrics to benefit from the different conditions available in a task design because they are created to pinpoint cognitive processes. Indeed, task contrasts are aimed to control for most of the other cognitive processes involved in solving a task. To obtain a connectivity pattern that is specific to the condition in the task design, previous research introduced methodologies such as beta series (79) or dynamic connectivity (365). Such methodology could also be adapted to be used as alternative input to the task potency pipeline. Chapter 2 introduces a possible application of the task potency in terms of dynamic effects. This type of utilization permits the study of changes in modulation, connectivity pathways that have specific time-windows, and connectivity pathways that bind different cognitive processing within a task. Recent electrophysiology research has shed new light on the timed relationship between attention and default mode network activity, often assimilated as task positive and task negative (366). While the use of electrocorticography in humans is very limited as it can only be performed in pre-surgical investigation, more sensitive methodology to study spatiotemporal neural process in a non-invasive investigation is required. A dynamic task potency analysis would then enhance the sensitivity to condition-specific modulation.

However, the current pipeline is already a tool that can enable the exploration of a range of new research questions. For example, executive functioning refers to multiple cognitive functions such as planning or problem solving that build upon three basic functions: working memory, inhibition and cognitive flexibility (40). Usually, cognitive flexibility is studied in task switching paradigms. However, a gap exists between observation of human behaviour and how psychology defines tasks that target cognitive flexibility. Autistic patients are thought to show inflexibility in their way of thinking and ability to switch attention or speech, however paradigms to study behavioural and cognitive flexibility fail to ecologically represent the observed deficit (367). ASD participants perform normally on task switching paradigm. This may be due to the fact that the task switching paradigm is not challenging enough and does not
providing sensitivity to the altered neural underpinning of cognitive flexibility. Alternatively, this split between performance and observed behaviour in ASD patients might be related to the setup of a task, its structure and constraints, wherein ASD patients have to initiate the cognitive process—versus real life situations, wherein ASD patients need to react and initiate. More ecologically valid paradigms are therefore required. However, such paradigms involve multiple cognitive processes and results are challenging to interpret. By comparing multiple ecological paradigms using the task potency, we can capture common pathways that would represent an ecologically valid cognitive flexibility pathway. We can therefore address whether alterations are related to the cognitive flexibility pathway or to the way it interacts with other specific cognitive processing.

THE EFFICIENT BRAIN

In general, we may assume that the smaller the distance between network activations at rest and the task network requirements, the quicker the brain can respond and the more efficient the subject can perform. In that sense, quantifying the magnitude of the rest-to-task modulation in the form of task potency for a certain task fingerprint could inform us about brain efficiency. Indeed, our results provide evidence for such interpretation. In Chapter 2, we observe that a more attentive state reduces the rest-to-task distance and, in contrast, a state of tiredness or anxiety increases that distance. Furthermore, in Chapter 3, the modulation required to perform a task reduces with age as the brain matures. We can interpret that the brain displays a general increase in efficiency in the form of smaller required connectivity modulations toward an optimal mature architecture. This view is supported by other recent studies that have used the Human Connectome Project (HCP) data (204). Here, participants with a higher IQ had a much smaller gap between resting-state network and task-related functional architecture than those with a lower IQ (i.e. there was much less need for reconfiguration of networks to perform a task; (278)). At a smaller timescale, the pseudo-rest before a trial is also predictive of the success of a trial, where a network’s pre-activation before the stimulus presentation results in a more quick and accurate response from a subject(284).
Discussion

studies have investigated the underlying neural activity related to this rest-to-task switch by investigating the balance of neurotransmitter release that corresponds to the main effect of inhibition and excitation of neurons, i.e. GABA and glutamate (368). They demonstrate that, for example, in the working memory task, the balance of these neurotransmitters in the frontal cortex is lower in subjects that perform better. Interestingly, again, higher is not better as it would probably be more energy consuming for the brain. Networks evolve to require less communication for the same processing, thus evolving towards greater efficiency (369).

Another index of brain efficiency can be extracted from the diffuse versus generalized pattern of connectivity across cognitive domains. Across development, through the maturation and organisation of network architecture, on-going baseline activity could be directed towards building more general pathways. These highways of communication could facilitate the switch from one state to another by being used very often and without the need to deactivate. Indeed, in ADHD, an early onset neurodevelopmental disorder, we observed a reduction in the use of connections across tasks and a more tailored network pattern for each task that might contribute to an inefficient response. This difference in the use of common edges might come from a failing developmental mechanism that aims to build and strengthen general processing.

Inference on the efficiency of the system has been drawn from theoretical and computational modelling studies (194, 195, 370). These studies provide some biological evidence of the concepts of an efficient structure by using them to build a model of glucose consumption (266). Using positron emission tomography, they compare the glucose metabolism to the connectivity degree of brain areas extracted from fMRI. While brain hubs require more energy consumption than other brain areas, they still enable relative energy saving, making the hub structure more efficient. However, a higher energy request makes them vulnerable to disfunction in energy distribution. More biological correlates of these growing concepts would enable more generalizable interpretations and propose further theories on the underlying brain structure and pathways involved in cognitive processing. Our results
Discussion

could provide a further explanation of biological underpinnings and of metrics that come from graph theory research in fMRI, including path length or hubness, that have been used to describe the structure and efficiency of brain architecture (371). To fully validate that the task potency is a marker of efficiency, the relationship between task performance and rest-to-task modulation needs to be validated and compared in the context of diverse cognitive functions and diverse cognitive processes. For example, through a learning task, we might be able to observe a reduction of modulation and a change toward a specific set of modulated edges.

Nevertheless, perhaps the evolution of neural organization toward general pathways and a system of segregated subfunctions hyper-connected by a backbone of hubs (194, 371–375) is not an optimal system and, instead, offers greater vulnerability. Chapter 4 shows that connectivity alteration during development is not easily overcome by alternative pathway maturation and impacts multiple cognitive functions. While both probands with ADHD and their unaffected siblings show differences in amount of common edges modulated across tasks, when compared to controls, they both display different alternative strategies. These results could lead to a better understanding of compensatory mechanisms and their relative efficiency, as the siblings do not show behavioural impairment and perform as well as controls. Compensatory mechanisms are difficult to define and study (169, 309, 321, 376). Depending of the level of alteration, the brains of patients with neurodevelopmental disorders might use a different set of optimal mechanisms by building on what resources are readily available. The path to remittance and possible effect of interventions or therapies can only be studied within the population sharing the same biological profile.

HUMAN NORMAL AND ABNORMAL DEVELOPMENT
In Chapter 3, we provided evidence for the interactive specialization theory, an influential theory in the field of developmental neuroscience. This theory explains cognitive maturation as an interactive mechanism.
Discussion

between cognitive functions and we demonstrate that we can observe common maturation effects on edges that are shared between tasks. As the brain matures during childhood and until young adulthood, networks become organized and process information more efficiently. Contrary to the previous view on cognitive development where cognitive function was thought to come “online” at a certain age, the interactive theory stipulates that it is the continuous inter-network interaction that enables a course of maturation that unlocks function progressively.

To study the network’s developmental maturation, we can model their developmental trajectories as they interact and mature together. Computational modelling research has used this theory to create models of causal mechanisms that successfully replicate Piaget’s stages of development(140). We can extend this research to understand the neural maturation and model causal maturation between networks as a function of their maturation stages across development. By modelling the interactive specialization theory with a directed graph describing the interaction of networks during maturation, we observed continuous effects and discovered specific time windows of changes linked to developmental events. Additionally, by defining a model of network interaction during development, we can provide new hypotheses on developmental disorders and predict the outcome of network maturation in the presence of alterations in another network. Such predictions could inform us on the optimal time window of intervention and what type of training would be more beneficial to minimize the effect of an altered neural network pattern on maturation of other brain functions. For example, in Chapter 4, our results demonstrate that ADHD participants display an under re-utilisation of edges across three cognitive domains that we know, from chapter 3, have specific time-windows of maturation and show common maturation effects. We can therefore imagine the prioritization of training in each of these domains at different ages. Additionally, by starting with working memory, we might observe a causal effect on reward processing and inhibition pathways and thus the facilitation of subsequent training of these functions.
The common connectivity pattern observed between working memory, reward processing and inhibition might support the maturation of all three cognitive functions in their specific time window of maturation in regard to the interactive specialization theory and as observe in a previous analysis (see Chapter 3). This missing pattern would explain the theorised maturation delay in ADHD as each function would have reduced interactive support, creating a longer maturation process and a need for involving alternative connectivity patterns (see figure 1)(377).

Alternatively, this common core might have an even more important role in shaping which specialized edges need to be involved in each cognitive domain. With a weak common core, ADHD brains might start to involve alternatives to standard edges toward “individualized specialization” in an attempt to cope with the dysfunction. This mechanism would therefore provoke a progressive deviance from the norm. By using a longitudinal design, we could then observe that ADHD participants display changes in their task fingerprint with a progressive use of more shared edges across tasks, showing the same but delayed mechanisms of maturation than healthy participants. Such cases could then provide insight in the ability to remit from ADHD or to persist in ADHD. The amplitude of the delay and the remaining time in the maturation sensitivity window could be used as an index of probability to remit from ADHD. As ASD has an earlier onset than ADHD, the same type of analysis could be applied to the ASD population to understand if our null result could be linked to an earlier stabilization of connectivity. In general, to understand neurodevelopmental disorders, age and sensitivity windows for developmental mechanisms need to be integrated to capture the dynamics of a patient’s growth.
Discussion
FIGURE 1: AVERAGE SPEED OF CHANGE WITH AGE OF TASK POTENCY FOR STOP (A), REWARD (B), AND WM (C). EACH PLOT ILLUSTRATES THE ABSOLUTE BETA-PARAMETERS RELATIVE TO THE AGE EFFECT FOR EACH WINDOW IN A SLIDING-AVERAGE CALCULATION USING A LINEAR MODELLING OF AGE. FOR EACH TASK, WE FIT A 2ND ORDER POLYNOMIAL TO MODEL THE RATE OF CHANGE ACROSS DEVELOPMENT. GRAPH D OVERLAYS EACH TASK’S 2ND ORDER FIT TO ALLOW EASY COMPARISON BETWEEN TASKS.

WE TESTED FOR SECOND ORDER CHANGES WITH AGE, I.E. WE TESTED WHETHER THE SPEED OF THE MATURATIONAL CHANGES VARIED AS A FUNCTION OF AGE. WE ASSUMED THAT AGE EFFECTS WOULD BE STRONGER IN YOUNGER THAN IN OLDER PARTICIPANTS. TO THIS END, WE MODELLED A LINEAR CHANGE OVER A SHORT AGE WINDOW OF 2 YEAR INCLUDING 5 PARTICIPANTS FROM THIS WINDOW. WHEN MORE THAN 5 PARTICIPANTS WERE AVAILABLE WITHIN AN AGE WINDOW WE RANDOMLY SELECTED 5. WE MOVED THIS WINDOW ACROSS OUR ENTIRE POPULATION, EACH TIME REMOVING THE YOUNGEST SUBJECT OF THE WINDOW AND CONSIDERING A 2 YEARS AGE SPAN STARTING FROM THE AGE OF THE SUBJECT IMMEDIATELY FOLLOWING IN AGE. WE EXTRACTED THE ABSOLUTE BETA VALUE OF THE LINEAR REGRESSION FOR EACH WINDOW AS A MARKER FOR THE SPEED OF CHANGE WITH AGE OF THE TASK-POTENCY.

As for the normal development, even if the progressive organization into efficient networks could be described in a general model, each individual will still follow a unique path due to individual factors and experience in life. This will shape the individual differences in the baseline organization of the brain. Understanding those dynamic trajectories is not only useful to predict disorder outcome, but also might benefit children more generally. For instance, stressful events modify the interaction between the prefrontal cortex and amygdala(378,379). During childhood, the prefrontal cortex and its connectivity pattern has not been fully matured. Learning early in life how to manage emotional states or stressful situations has an important preventive role in tackling adversities or when entering teenage years to avoid perturbing the normal maturation of the brain(380–383). School interventions to train soft skills or cognitive functions that impact learning or well-being in schools are currently under evaluation(384–388). Indeed, academic achievement is not only related to memory and attention in the classroom but also evolving in a non-aggressive environment and being able to regulate emotion and leaving preoccupation at the door of the classroom(389–392). Extrapolating from this idea, understanding the relationship between cognitive states and maturation mechanisms could aid in defining programs or interventions that could be proposed to schools to optimize children’s development within specific time-windows and offer an integrative program to target the most important learning processes.
LIMITATIONS
We introduced a new metric to describe task-specific functional connectivity. We demonstrated that task performances and variation in state-of-mind support the relevance of this connectivity modulation to understand the brain processes across the different chapters, and that the pipeline is robust to variation in the population (see Chapters 1 and 5) or change in the input data (see Chapter 1). However, several issues need to be investigated further to assess the generalizability of this pipeline in a broader setting.

TASK AS A CONSTRAINT
Instruction and differences in task protocol will affect what and how cognitive processes will be involved in solving the task. Such effects are well known from task activation studies and as the connectivity modulation is intrinsically linked to the BOLD response, the same effects apply. In the ideal case, within a study, all known sources of variance are controlled for. For example, stimuli are standardized within a task to avoid provoking variable intensity response from the sensory system. Another example can be to avoid having multiple experimenters across participants in one study. When it comes to comparing results across tasks, other variables need to be considered. The BOLD signal is known to be affected by modification in task design such as number of trials or time length of tasks(393). How these differences in design affect the estimation of the overall covariance between areas is poorly defined. In this thesis, we described results at the level of the task and do not infer strongly on specific cognitive processing across tasks. However, specifying the relationship between task parameters such as length and number of trials, is necessary before starting to investigate some cognitive processes such as the linear or non-linear dynamic of the task potency relative to the cognitive load of a task. Using a larger representation of tasks could enable us to investigate effects of cognitive load and estimate whether variations in design need to be accounted for in our understanding of the task potency and its link with cognition. For example, using tasks available in OpenfMRI, a large open data repository, we can replicate results described in this thesis and make progress in the development of the task potency framework.
RESTING STATE AS A CONSTRAINT
The pipeline is generally based on comparing tasks to rest acquisition. Studies have shown that resting state is the best representation of the functional underlying architecture (12). This concept can be discussed as it also depends on our understanding of cognitive processes at play when a participant lies without cognitive constraints in a scanner. We therefore assume that the baseline neural state of a participant includes integration of external stimuli (sound and visual aspects of the environment) and more or less spontaneous thinking depending on the participant, which is ecologically relevant. However, this baseline is therefore dynamic and may differ from one network to another. A better understanding of this localized variability would enhance the definition of our baseline to understand the amplitude and flexibility of the task potency across the brain. In further development of the task potency concept, we can consider to account for the dynamic expression of the functional connectivity in the resting state.

Additionally, even if the resting state acquisition is easy and more frequently acquired in fMRI studies, the use of the task potency as described in this thesis is not adapted to studies that have not acquired resting state data. The analysis of data previously acquired and now released openly might be challenged by the availability of resting state data for every participant. Alternative to an independent resting state acquisition, we can consider pseudo-rest around task trials. Such a pseudo-rest might provide less variation toward unrelated thoughts, which can be beneficial depending on the experimental question at hand. For example, to study mind-wandering or introspection tasks, using a pure resting state as baseline would reduce our sensitivity to relevant cognitive processes. However, using pseudo-rest might not perfectly describe the task modulation as some of the task effects can be present in the close time window around trials. For example, the attention system would not be at the baseline activity level as the subject stays focused on the instruction to solve the task at hand. Indeed, it was shown that a non-baseline attention level before stimulus presentation is necessary for performing the task and is predictive of the success of the trial (284). The use of pseudo-rest to define the baseline functional architecture of a
participant brain remains a possible alternative when an independent resting state is not available.

FUTURE DIRECTIONS

A NEW ANGLE FOR NEW HYPOTHESES

The task potency pipeline can be a great tool to study clinical populations because it increases sensitivity to task effects at both the level of the individual (Chapter 1), as well as at the level of multiple subpopulations (Chapter 5). The field of neuroimaging for clinical applications is moving towards the study of the biology of an individual rather than that at the group level (394–396). The great variability in neural structure, function and connectivity observed across individuals in neuroimaging studies needs to be better understood to enable individualized treatment. By increasing sensitivity to task effects, we will better capture any dimensional effects related to symptoms or behavioural scales. Removing the common effect and individual characteristics of the baseline will maximize variation in neural underpinnings related to parameters of interest (174). Considering dimensional effects instead of group (i.e. diagnostic categories) effects increases the power of analysis by including both healthy and clinical populations. We can consider the representation of the population for a given behavioural parameter as a normative distribution, with individuals varying away from the norm, and employ normative modelling analysis (163). Using the task potency in this context, we can then start to investigate the heterogeneity in terms of cognitive processes that are tied to task design. Once the building blocks for these processes are better described in healthy populations, we can use this prior information to understand how disruptions in the baseline will impact the overall system and which alterations are the most useful features in aiding in diagnosis. Additionally, by defining the interaction between cognitive processes and the connectivity patterns that support them, we can define new hypotheses on which subprocess might be altered in complex disorders where multiple cognitive impairments intertwine.

Looking at the development of the brain, according to the interactive specialization theory, the interaction between cognitive processes is
hypothesised to support the continuous maturation of certain functions (25, 26, 138). A cognitive function such as inhibition displays a slower maturation process and reaches maturation as late as young adulthood. As such, we can imagine creating interventions and school programs targeting specific cognitive function in specific age-windows to optimise brain maturation and maximise cognitive development and soft skills maturation. These programs could also include knowledge about the maturation state of an individual and evolve dynamically with the needs of an individual. To this aim, more knowledge on brain learning processes and effects of cognitive training is required. Additionally, longitudinal studies and training studies could benefit from the use of the task potency pipeline to enhance the sensitivity to changes in cognitive processes. Longitudinal population screening like the one proposed by the ABCD study (397) is key to understanding the variability in individual maturation and learning processes. The ABCD study, providing neuroimaging and behavioural assessment over 10,000 children with a longitudinal protocol and yearly acquisition, enables the investigation of such variability and defines a standard of brain development that can be used to test school program effect.

Knowing is empowering

Regarding the promotion of brain development, I believe that self-awareness of learning processes can empower children and reset prejudices that may have been imposed on them as a result of adverse early-life experiences and socio-economic environment. To prevent the long-term impact of their own background from an early age, we can use the latest knowledge in cognitive science and provide tools that not only propose practical exercises targeting emotional regulation or attentional control, but also explain cognitive functioning to enable a deep understanding of one’s metacognition. Providing an introduction to validated school programs could have a great impact on the self-development of children. To this aim and to provide a bridge between my research line and a possible application, in parallel to this thesis, I developed a teaching kit to provide such tools to primary school teachers (OCEANA program [http://oceana.education]) and involved a team of 20 dedicated individuals from various working areas. This kit is a meaningful
Discussion

opportunity to bring the knowledge from the lab to the general public and to have a significant impact to society, even though to most neuroimagers, neuroimaging investigations often seem far from application.

A first version of this kit was released online and available for free download halfway through my PhD. Through the course of my PhD and the study of the interaction of cognitive processes, it appeared to me that understanding the implication of various cognitive functions in the learning process wasn’t enough, and that the kit should be enhanced by explaining the relationship between cognitive functions. Building on the timing and relationship between cognitive functions, the kit was reorganized with a progressive presentation of cognitive functions and their relationships. After presenting the neurobiology of the brain, we started with introducing the memory systems and continued with teaching about emotions before addressing the relationship between memory and emotions. Thereafter, the kit continues to extend knowledge by progressively integrating attention and ending with executive functioning, while always pointing out how these functions are involved in learning.

According to the knowledge that I extracted from my PhD, I aim to continue investigating human development and better understand the timing of maturation to further develop and fine-tune these teaching tools. By defining the timing of maturation of different cognitive functions, I hope to implement a set of kits for different developmental ages that would be able to target age-related needs of children and optimize their cognitive maturation.

However, while this knowledge comes from cognitive research (neuroimaging and psychology studies), tools and programs need to be validated in the setting of the classroom, which correspond to a less controlled and complex environment than the lab. Evaluating such tools is therefore challenging, but required in order to adapt methodology from cognitive science protocols developed in the lab that have so far remained imperfect(398–401). For that evaluation, I aim to collaborate with researchers from the field of educational science and cognitive science applied to education in order to bridge knowledge and
methodology across scientific fields. Cognitive science is a young field, reflecting the current evolution of disciplines that increasingly re bridge skill and knowledge, and requiring the multidisciplinary integration of scientific fields.

FIRST STEP TOWARD CHANGING OUR PATHS
The studies included in this dissertation show that the functional connectivity modulation away from the baseline functional architecture is a potential marker of efficiency and is a metric that can help understand the global complex structure and relationship between cognitive processes. They demonstrate that modulation from rest to task is dependant on the state-of-life of the subject, such as age or mental state. They inform us about the optimal processing of the brain that shows a preference for using common connectivity across tasks and how it is also a vulnerable organization that can be disrupted in disorders.

We propose a new metric that shows interesting features to revise task-fMRI study as it offers high sensitivity to individual and group effects. It can therefore be used to define new tools to help diagnosis and develop stratification biomarkers. More applications are required to demonstrate the generalizability of these new results. We may look forward to new types of applications such as the implementation and testing of cognitive training aimed at strengthening alternative connectivity paths based on a future deeper understanding of network relationships and that can overcome altered path in this architecture.

In the Greek mythology, the three Moirai were in charge of the thread of life. One of them allotted a length of thread, one spun it into a spindle, i.e. organized it and the last would cut it, i.e. decided inevitable fate. The metaphor of the thread of life could apply to brain connectivity; it has a certain capacity to evolve through life, gets organized and can define your fate. Indeed, as a wrong twist on fibres could create fragility in the thread, making it less flexible and resistant, fragility in the functional connectivity would impact the response of the architecture and its ability to modulate under cognitive request. We might not be able to change the work already done on the brain connectivity thread by the Moirai, but we might be able to supervise them and ensure that they reinforce the structure if they make a mistake. Science can then beat fate.
APPENDIX

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Access to the data

Access to the data

All scripts for replication of the analysis are available either on the author’s github: https://github.com/roscha/task_potency or on request to the author: r.chauvin@donders.ru.nl

The MyConnectome dataset is part of the open repository OpenNeuro: https://openneuro.org

The EU-AIMS dataset and NeuroIMAGE dataset can be assessed by submission of a project proposal via: https://www.eu-aims.eu and http://neuroimage.nl
Supplemental Appendix 1: Description of Task-fMRI Paradigms from NeuroImage

This supplement is related to chapter 1, 3 and 4

STOP SIGNAL TASK (STOP)
A visual version of the stop signal task (45,175,207) was used to measure response inhibition during fMRI acquisition. In this task, participants had to respond as quickly as possible to a go-stimulus by left or right button press, unless shortly after presentation it was followed by a stop signal, in which case they were to withhold their response (25% of trials). The task consisted of two practice blocks and four test blocks, each consisting of 60 trials. For further details of the task and its acquisition parameters we refer to van Rooij et al., 2015.

MONETARY REWARD PROCESSING TASK (REWARD)
A modified version of the MID task (175,208–210) was used to measure reward processing during fMRI acquisition. Participants were asked to respond as quickly as possible to a target by pressing a button. Prior to this target, a cue indicated the possibility to gain a reward after a button press within a given time window. Every trial ended with a feedback screen informing about the outcome of the current trial. Depending on the participants’ performance, the response window for a correct response was adapted in the next trial resulting in an expected hit rate of 33%. The experiment lasted 12 minutes and a total of € 5 could be gained. For further details of the task and its acquisition parameters we refer to von Rhein et al., 2015.

SPATIAL WORKING MEMORY (WM)
The spatial span task used to measure spatial working memory is an adapted version of a task developed by Klingberg and colleagues (133,175,211,402). Two trial types (baseline and working memory) and two memory loads (low and high) were implemented in the task. Each trial consisted of a sequence of either three or six yellow circles (low and
high memory load, respectively), displayed on a 4×4 grid for 500 ms each, with a 500 ms inter-stimulus interval in between. Subsequently, during a 2000 ms response window, a probe consisting of a number with a question mark was presented in one of the 16 locations. During working memory trials, participants were asked to remember the spatial location and temporal order of the presentation of cues, and indicate with a ‘yes’ or ‘no’ response (left or right button, respectively) whether the location of the probe had been stimulated before, at the indicated temporal position. During baseline trials, red circles followed by the probe (always the number 8) were presented sequentially in the four corners of the grid in a predictive manner, and participants were required to pay attention but not to try to remember the sequence, and always had to press the ‘no’ button. During both conditions, feedback was presented after the response in the form of a green or red coloured bar below the probe (for correct and incorrect responses, respectively), for the remainder of the response window. The task was administered in four blocks of 24 trials each (presented in fixed random order), with a short break in between blocks to motivate participants and to avoid fatigue effects, with a total task duration of approximately 16 min. For further details of the task and its acquisition parameters we refer to van Ewijk et al., 2015.

Supplemental Appendix 2: Brain Atlas Used for Computing Connectivity
This supplement is related to chapter 1,3 and 4

For each functional imaging scan we defined connectivity matrices using regions defined in a hierarchical whole-brain functional atlas (van Oort et al., 2017). This atlas contains 185 non-overlapping regions and was defined through Instantaneous Correlation Parcelation (ICP) applied to resting state fMRI data of 100 participants of the Human Connectome Project (HCP; (Glasser et al., 2013)). In short, ICP aims to parcel larger regions into subregions based on signal homogeneity, where the optimal number of subregions is determined based on split-half reproducibility at the cohort level.

Supplemental Figure 2 illustrates the hierarchical brain atlas, where areas were grouped into 11 higher-level networks: 9 resting state networks (visual1, visual2, motor, right attention, left attention, auditory, default
mode network (DMN), fronto-temporal and striatum), and 2 anatomical structures (subcortical areas, and cerebellum). These higher-level networks respectively contained 19, 12, 22, 22, 18, 18, 13, 7, 23, and 23 subregions.

All analyses were performed in each participant’s native space. To this end we transformed the atlas to each participant’s native space using the inverse of the anatomical to MNI152 non-linear warp, and the inverse of the linear transformation of the functional image to the participant’s high resolution anatomical image. Voxel-membership in brain parcels was established on the basis of majority overlap. Areas that were on average across our population over 50% outside of the brain were rejected from further analyses. This resulted in the rejection of one area in brainstem. For consistency, we removed the 5 others brainstem areas. As a result, we used 179 areas to compute connectivity matrices, as explained below.

*Supplemental Figure 2: 179 areas selected from an ICP-based parcellation of the human brain (van Oort et al). Each area is coloured in accordance to its overarching network. Eleven large-scale networks constitute the first level of the parcellation: visual 1, visual 2, auditory, motor, fronto-temporal (fronto temp), right and left attention (R_attention, L_attention, respectively), default mode (DMN), cingulum, sub-cortical (sub cort), cerebellum (cereb) networks. We used the 179 regions that are part of the sub-network scale parcellation to obtain functional fingerprints based on 179x179 correlation matrices.*
Supplemental Appendix 3: Task Potency Calculation

This supplement is related to all chapters.

To compute the partial correlation for each pair of regions we obtained each region’s time series through multivariate spatial regression, using all 179 regions as regressors and each task’s preprocessed full acquisition time series as dependent variable. The resulting regional time series were demeaned. For the WM and STOP task we temporally concatenated the time series of individual runs. Using these time series, we calculated 179x179 partial correlation matrices through inverting covariance matrices estimated by the Ledoit-Wolf normalization algorithm (Ledoit & Wolf, 2004) as implemented in nilearn (http://nilearn.github.io/). Finally, all pair-wise correlations were Fisher r-to-Z transformed.

To allow comparing connectivity values between acquisitions, we normalized the connectivity values within each matrix to fit a Gaussian distribution (Supplemental Figure 3). Importantly, we were cautious not to affect the tails of the connectivity distributions as these represent the most interesting connectivity values. Therefore, we modelled the obtained connectivity values per task using a Gaussian-gamma mixture-model to obtain “mixture-model-corrected” Z-stat values (Feinberg et al., 2010; Llera, Vidaurre, Pruim, & Beckmann, 2016). This model fits three curves to represent the data: a central Gaussian distribution representing the noise and two gamma distributions on each side of the central Gaussian that represent the signal as the tails of the data distribution. We used the main Gaussian, i.e., the one fitting the body of the distribution, to normalize our connectivity values with respect to its main distribution (i.e., noise), while not taking into account the extremes (i.e., signal). In practice, we applied the mixture modelling to the upper triangle values of each connectivity matrix and subsequently normalized the connectivity values by subtracting the mean and dividing by the standard deviation of the obtained central Gaussian model. As a result, the values within the normalized, Z-transformed partial correlation matrices are readily comparable across tasks (Feinberg et al. 2010).
Supplemental Figure 3: Task-potency pipeline. Using the brain parcellation shown in Supplemental Figure 2, we calculated 179x179 connectivity matrices for each individual in each task (WM, REWARD, STOP, RS). From the Fisher r-to-z transformed partial correlation, we obtained task potency by first normalizing the task and rest connectivity and subsequently subtracting the rest from the task connectivity. Through population averaging and thresholding the resulting matrices we obtained a task potency fingerprint for each task (WM, REWARD, STOP).
SUMMARY
Cognitive functions interact by exchanging information across complex and distributed networks of brain areas. During task performance, specific networks modulate their activity in order to process input information and to produce appropriate output. This thesis is about the functional organization of the brain during cognitive performance and addresses network commonalities and specificities between cognitive tasks. Using functional magnetic resonance imaging, this thesis describes a new framework for the examination of changes in communication between brain areas compared to the state of their baseline activity. This enables a direct comparison between tasks, offers a new viewpoint on brain function, and integrates knowledge across different cognitive domains.

The validation of the utility of this new perspective and method covers the understanding of modulation of the functional connectivity under different state of mind such as tiredness, attention fluctuation or change in mood and also addresses changes in efficiency of this modulation during normal and abnormal development. In normal development, changes in modulation characterize maturation mechanisms coherent with skills improvement in working memory, reward processing and inhibition-attention systems. In abnormal development, here attention deficit and hyperactivity disorder and autism spectrum disorder, the method addresses how alterations in this functional organization can be linked to multiple current theories.

This thesis ends with a discussion on the benefits and possible applications of this new method and new knowledge that results from this new approach to the organization of the brain.
SAMENVATTING

Cognitieve functies werken op elkaar in door informatie uit te wisselen via complexe en gedistribueerde netwerken van hersengebieden. Bij het uitvoeren van een taak moduleren specifieke netwerken hun activiteit om inkomende informatie te verwerken en passende output te produceren. Deze theses betreft de functionele organisatie van het brein gedurende het uitvoeren van taken en behandelt de gemeenschappelijke en specifieke aspecten van netwerken tussen cognitieve taken onderling. Met gebruik van functionele MRI beschrijft deze these een nieuw raamwerk voor het beschouwen van veranderingen van communicatie tussen hersengebieden tijdens taken in relatie tot hun staat in rust. Dit verschaft de mogelijkheid tot directe vergelijkingen tussen taken, biedt een nieuw gezichtspunt op hersenfunctie, en integreert kennis over verschillende cognitieve domeinen. De validatie van het nut van deze nieuwe methode omvat het in kaart brengen van de modulatie van functionele connectiviteit in verscheidene gemoedstoestanden zoals moeheid, aandachtswisselingen, en humeur. Daarnaast beschouwt het de veranderingen in de efficiëntie van deze modulaties gedurende normale en abnormale ontwikkeling. In normale ontwikkeling karakteriseren veranderingen in modulatie mechanismen die samenhangen met vooruitgang in werkgeheugen, beloningsverwerking, en aandachtsorientatie. Bij abnormale ontwikkeling echter – specifiek autisme spectrum stoornis en aandachtsstekort-hyperactiviteitsstoornis – herkent de methode veranderingen in de functionele organisatie die gelinkt kunnen worden aan verschillende huidige theorieën over deze stoornissen. De theses eindigt met een discussie over de baten en mogelijke toepassingen van de nieuwe methode, en de nieuwe kennis die resulteert van deze nieuwe benadering van hersenorganisatie.
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To my supervisors for the opportunities,
We could adopt her

to the mstats group for their expertise and kindness, especially Maarten for keeping me on track.

congrat. spade

normative modelling

Be aware, we are watching

to my parents and friends for the moral support
for sharing the journey and adventures
to all crazy people that made me forget my worries with parties and dinners

thank you all.

I made these during 4 years

I am now ready to pursue my academic life.

And now, you will need these fangs to get grants and continue your journey
The successful production of this manuscript would have been impossible if not for countless individuals who generously contributed their minds and talents in so many ways. Since the beginning of my PhD, I have met a multitude of people who have further furnished me with not only scientific skills and knowledge, but also emotional depth and breadth. I grew into a scientist who is ready to continue her path in academia. So it’s time to thank them for the most important things that they’ve given me, even if there is much more to thank them for.

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Andrea, Lonja, Wei, Thomas, Christian and lately Matthias, without forgetting Nils, Neda and all the ones that shared the flex room with me during my first year, and with whom I’ve made great friendships.

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I would like to thank everyone from the Donders Wonders Blog for showing the way to more outreach in the Institute and how this benefits science. You are very passionate people who give your energy to sci comm and make the Donders Institute even more well-known to the general public. Particularly, I want to thank Lieneke as one of the founders and as someone with whom I enjoyed discussing the importance of sci comm and how we can improve it.

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Appendix

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ABOUT THE AUTHOR
Roselyne was born in Bois-Guillaume, France. She studied health information technology in the engineering school Polytech’Grenoble before entering the Cogmaster in ENS Ulm (Paris) and later the Physiology and integrative biology – speciality neuroscience in Jussieu University (Paris). She worked over the years as monitor in multiple holiday camps for children or for disabled adults. There, she developed a great curiosity for understanding the developing mind. This path led her to start her PhD studies at the Donders Institute and to study developmental clinical cohorts with new methodology. Next to her work and studies, Roselyne was involved in multiple non-profit organizations for science outreach and science communication. She used her artistic skills to create a number of documents and tools (comics, picture books, games) to teach neuroscience to laypeople and especially to the young audience. She was part of the Donders Wonders Blog and the OHBM Communication Committee but most importantly, in 2013, she started a project that in 2016 turned into a non-profit organization called Cogni’Junior, which aimed at providing freely available and ready-to-use tools for talking about cognitive science to children. One of the latest and biggest tools developed was the teaching kit OCEANA. Supported by the Donders Institute, this kit has been translated into 4 languages and is in continuous development thanks to a devoted team. Roselyne was also involved in multiple teaching activities in the neuroimaging field, as well as the field of cognitive science applied to education. Particularly, she participated in the making of three MOOCs and several trainings, and was part of the main organization team of two PhD conferences.

**PhD tract:**

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PUBLICATIONS


Chauvin R, Lucchesi A, Massonié J, Rodo C et al., Le conte comme moyen de changer les représentations des enfants sur le cerveau, Grand N - n° 105, 2019 - pp. 5 à 22


DONDERS GRADUATE SCHOOL FOR COGNITIVE NEUROSCIENCE

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master’s and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute. The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students. The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy. For more information on the DGCN as well as past and upcoming defenses please visit: http://www.ru.nl/donders/graduate-school/phd/