Brain–behaviour relationships and individual variability in cognitive and emotional processing

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Nevena Kraljević

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1 Abstract

Human experience and behaviour is subject to multiple different mental processes, which can be separated into cognitive and socio-affective processes. Many studies investigate how experience and behaviour is linked to brain structure and function, and also how much influence can be attributed to our genetic makeup. However, little is known about how behavioural domains are subject to different influencing factors of inter-individual differences of the brain. In particular, how overlapping genetic influences exhibit in brain structure, and which influence different functional task states drive in predictability of individual behaviour. Therefore, in my dissertation I investigated the phenotypic and genetic correlations of cognitive and affective traits and brain structure (cortical thickness, surface area and subcortical volumes; study 1). I further examined to what extent the correspondence of functional network priors and task states with behavioural target domains influenced the predictability of individual performance in cognitive, social, and affective tasks (study 2).

Using phenotypic correlation and heritability-analysis the first study investigated heritability and genes as influencing factors on inter-individual differences of the brain. Cognition revealed several associations with brain morphology, while trait affect revealed only few significant correlations with subcortical volumes and local cortical thickness, where it overlaps in left superior frontal cortex with cognition. Decomposing the phenotypic association into genetic and environmental components, revealed that the associations were accounted for by shared genetic effects between the traits. Using functional correlation and predictability of task states and network priors the second study investigated state- and network-specificity as influencing factors on brain–behaviour relationships, by predicting individual performance in cognitive, social, and affective tasks. Predictions from whole-brain FC were slightly better than those from FC in task-specific networks, and a slight benefit of predictions based on FC from task versus resting state was observed for performance in the cognitive domain.

With my dissertation I provide an integrative model of how cognition and affect relate to the human brain. By combining insights from structural anatomy, heritability modelling, and functional connectivity-based prediction, my results reveal that these traditionally distinct domains share common neural substrates. The superior frontal cortex has been identified as a heritable anatomical hub for both cognitive and affective traits. However, multivariate FC patterns during both task and resting states carried only moderate predictability of individual performance levels of cognition and socio-affective processes, manifesting nevertheless the influence of brain state and network dynamics in shaping individual behaviour. In sum, with these studies I replicated previous findings, but also extended insights into the interplay of cognitive and socio-affective processes with brain–behaviour relationships, and how different factors influence inter-individual differences in the brain.

2 Zusammenfassung

Menschliches Erleben und Verhalten unterliegt vielen verschiedenen mentalen Prozessen, die in kognitive und sozio-affektive Prozesse unterteilt werden können. In vielen Studien wird untersucht, wie Erleben und Verhalten mit der Struktur und Funktion des Gehirns zusammenhängen und welchen Einfluss genetischen Veranlagung spielen. Es ist jedoch nur wenig darüber bekannt, wie unterschiedliches Verhalten den verschiedenen Einflussfaktoren interindividueller Unterschiede des Gehirns unterliegt. Insbesondere, wie sich überlappende genetische Einflüsse in der Gehirnstruktur zeigen und welchen Einfluss verschiedene funktionelle Aufgaben auf die Vorhersagbarkeit des individuellen Verhaltens haben. In meiner Dissertation untersuchte ich daher die phänotypischen und genetischen Korrelationen von kognitiven und affektiven Merkmalen und der Hirnstruktur (kortikale Dicke, Fläche und subkortikale Volumina; Studie 1). Darüber hinaus habe ich untersucht, inwieweit die Übereinstimmung von funktionellen Netzwerken und Aufgabenzuständen die Vorhersagbarkeit der individuellen Leistung bei kognitiven, sozialen und affektiven Aufgaben beeinflusst (Studie 2).

Mit Hilfe phänotypischer Korrelationen und Heritabilitätsanalysen untersuchte die erste Studie die Heritabilität und Gene als Einflussfaktoren auf interindividuelle Unterschiede des Gehirns. Kognitive Prozesse zeigten mehrere Assoziationen mit Hirnstruktur, während Affekt nur wenige signifikante Korrelationen mit den subkortikalen Volumina und der lokalen kortikalen Dicke aufwies, wobei es im linken superioren frontalen Kortex Übereinstimmungen mit Kognition gab. Die Analyse der phänotypischen Assoziation in genetische und umweltbedingte Komponenten ergab, dass die Assoziationen durch gemeinsame genetische Effekte zwischen den Domänen erklärt werden konnten. Mit Hilfe der funktionellen Korrelation (functional connectivity; FC) und der Prädiktion von Aufgabenzuständen und Netzwerken untersuchte die zweite Studie die Zustands- und Netzwerkspezifität als Einflussfaktoren auf die Beziehungen zwischen Gehirn und Verhalten, indem sie die individuelle Leistung bei kognitiven, sozialen und affektiven Aufgaben vorhersagte. Die Vorhersagen aus der FC des gesamten Gehirns waren etwas besser als die aus der FC in aufgabenspezifischen Netzwerken. Für die Leistung im kognitiven Bereich wurde ein leichter Vorteil der Vorhersagen auf der Grundlage der FC aus dem Aufgaben- gegenüber dem Ruhezustand festgestellt.

In meiner Dissertation stelle ich ein integratives Modell vor, wie Kognition und Affekt mit dem menschlichen Gehirn zusammenhängen. Durch die Kombination von Erkenntnissen aus der strukturellen Anatomie, der Modellierung der Vererbbarkeit und der auf FC basierenden Vorhersage zeigen meine Ergebnisse, dass diese traditionell unterschiedlichen Bereiche gemeinsame neuronale Substrate aufweisen. Der superiore frontale Kortex wurde als vererbbarer anatomischer Knotenpunkt sowohl für kognitive als auch für affektive Merkmale identifiziert. Die multivariaten

FC-Muster sowohl im Aufgaben- als auch im Ruhezustand zeigten jedoch nur eine mäßige Vorhersagbarkeit des individuellen Leistungsniveaus bei kognitiven und sozio-affektiven Prozessen, was den Einfluss des Hirnzustands und der Netzwerkdynamik auf die Gestaltung des individuellen Verhaltens deutlich macht.

Zusammenfassend lässt sich sagen, dass ich mit diesen Studien nicht nur frühere Ergebnisse replizieren konnte, sondern um Erkenntnisse über das Zusammenspiel von kognitiven und sozio-affektiven Prozessen mit Gehirn-Verhaltens-Beziehungen erweitern konnte und darüber, wie verschiedene Faktoren interindividuelle Unterschiede im Gehirn beeinflussen.

3 General Introduction

Everyone is unique in experience, thought and behaviour, affect and cognition, but also brain structure and function. Understanding the link between the human brain, individual behaviour, thoughts and feelings, remains one of the greatest questions in neuroscience. Researching the link between brain and behaviour is a scientific pursuit that offers great potential for mental health and personalized medicine, by offering pathways to more precise diagnostic and therapeutic approaches. Therefore, investigating the human brain helps us to elucidate human inter-individual variability. Both within healthy individuals, and with regards to mental health and the treatment of brain disorders.

Human experience and behaviour is subject to multiple different mental processes. Roughly, these processes can be separated into cognitive and socio-affective processes. Many studies investigate how experience and behaviour is linked to brain structure and function, and how much influence can be attributed to our genetic makeup. However, little is known about how behavioural domains are subject to different influencing factors of inter-individual differences of the brain. In particular, how overlapping genetic influences exhibit in brain structure, and which influence different functional task states drive predictability of individual behaviour.

There are various neuroscientific approaches in the quest to study human brain–behaviour relationships and to investigate how experience and behaviour is linked to brain structure and function: Some studies use electrophysiological methods, such as electroencephalography. Some use neuroimaging methods, such as structural magnetic resonance imaging (MRI), or functional imaging methods, such as functional MRI (fMRI). Some use genetic tools, such as genome-wide association studies or twin studies. Some use specific analytic tools, such as machine learning (ML) or predictive modelling, connectomics or network analysis, or functional decoding and meta-analytic annotation. But irrespective which are the chosen measures, in order to study behaviour, there need to be behavioural and psychometric measures. These can be conducted in tasks or in self-report questionnaires.

My dissertation focuses on the influencing factors of inter-individual differences of the brain, specifically, how genetic influences exhibit in brain structure, and how task states drive predictability of individual behaviour. For this, I will first elaborate on the specific behaviours investigated here – cognition and affect – and their relationship to the brain. Then, I will elaborate on heritability and functional task states, as influencing factors of inter-individual differences of the brain.

3.1 Individual differences in behaviour

Human behaviour is driven by different complex mental processes, that can be roughly separated into cognitive and socio-affective processes. Therefore, I decided to investigate cognition and affect as representations of human complex and rich behavioural variability. Despite covering only a fraction, they provide insight into how individuals perceive, interpret, and respond to their environment (Gross, 2015; Langner et al., 2018; Pessoa, 2008). As such, they serve as robust, multidimensional phenotypes for linking behaviour to underlying neural and genetic mechanisms.

3.1.1 Cognition

Cognition refers to mental processes involved in acquiring, processing, storing, and applying information. These processes include perception, attention, memory, language, reasoning, and executive control, including working memory, enabling individuals to interpret and respond to their environment. Intelligence is described as the capacity to carry out cognitive tasks effectively. It reflects how efficiently and flexibly cognitive processes are deployed, usually in novel or complex situations.

The human interest and contemplation about cognition and intelligence have a long history. A scientific approach on cognition dates back to the early nineteen hundreds, where Spearman framed the “general ability factor g” (Spearman, 1904). This was further investigated and developed by Cattel into two sub-constructs: crystallised and fluid intelligence (Cattell, 1943, 1963).

Crystallized intelligence refers to the ability to recognise and apply solutions through previously acquired knowledge and past experiences. It involves knowledge and skills accumulated over time, such as cultural and general knowledge. It can therefore improve with age, peaking in adult life, with only a slow decline until the age of 70 (Cattell, 1963; Hunt, 2001; Jones & Conrad, 1933; Salthouse, 2019).

In contrast, fluid intelligence refers to the ability to solve novel problems without relying on prior knowledge. Therefore, fluid intelligence is usually involved in tasks of non-verbal nature, such as solving mathematical or spatial problems. This involves quick, abstract, and flexible reasoning, as well as the ability to comprehend and manage multiple information simultaneously and manage the amount of information needed to solve the problem (Cattell, 1963). A core component of fluid intelligence is therefore working memory, the ability to maintain and update or manipulating relevant information (Baddeley, 2012; Hofmann et al., 2012; Little et al., 2014). On average, fluid intelligence reaches the maximum in ability in early adulthood and declines with age (Baltes et al., 1999; Jones & Conrad, 1933; Salthouse, 2019).

Crystallised and fluid intelligence are distinct but interconnected cognitive systems (Cattell, 1963; Tucker-Drob, 2009). The ability of fluid intelligence to solve novel problems, reason abstractly, and adapt to new situations is required for acquiring and integrating new knowledge – which over time consolidates and contributes to crystallized intelligence. Furthermore, crystallized intelligence can support fluid intelligence by providing context and meaning. This bidirectional support is especially interesting, given that crystallised and fluid intelligence have different decline rates throughout life (Baddeley, 2012; Tucker-Drob, 2009).

Moreover, while working memory (WM) represents only one aspect of fluid intelligence, it has been shown to be a good proxy and representation for fluid intelligence (Colom et al., 2015). Furthermore, it has been investigated, that working memory capacity predict variation not only in fluid intelligence, but also crystallised intelligence (Alloway & Alloway, 2009; Martinez, 2019).

3.1.2 Affect: Emotion, Social Cognition

As a clear distinction between "emotion" and "affect" remains unresolved, the terms are often used interchangeably in the literature (Bradley & Lang, 2002; Pessoa, 2008; Salsman et al., 2013). Broadly, affect is a complex and multifaceted construct used to refer to emotional experience (Lindquist et al., 2012). Its elusive definition and inherently subjective, bodily nature makes it difficult to be measured in a standardized fashion (Nummenmaa et al., 2014). Therefore, measurement methods include self-reports, physiological indicators (such as heart rate or skin conductance), or the behavioural response to stimuli (Bradley & Lang, 2002). Nevertheless, in the assessment a distinction can be made between emotional processes and trait affect. On the one hand, affective traits can be assessed with self-reports, which are then divided into positive and negative traits. On the other hand, emotional processes, that pertain to identification and responding, can be assessed using tasks.

Trait affect is commonly measured through self-reports and divided into a positive and negative dimension, which are considered independent, instead of opposites. Hence, allowing both to be experienced at the same time (Diener & Emmons, 1984; Salsman et al., 2013). Positive affect includes emotions such as happiness, enthusiasm, and contentment, contributing to psychological well-being, including life satisfaction and a sense of purpose (Salsman et al., 2014). Conversely, negative affect includes emotions like anger, fear, and sadness, which can also manifest in varying intensities and are linked to negative self-evaluation or life dissatisfaction (Pilkonis et al., 2013; Salsman et al., 2013).

Emotion processing starts with a trigger and ends with a mental and behavioural response. Importantly, an emotional response can only be elicited with a relevant stimulus. Emotion processing refers to identifying, interpreting, and responding to emotional cues in oneself and others (Gross, 2015; Langner et al., 2018). It is closely linked to social cognition, which includes the understanding of others' thoughts and feelings. It is crucial in engaging in effective social interactions, since it includes understanding both oneself and others as social beings.

Social cognition spans across both the cognitive and affective domain. Social cognition is linked to theory of mind, which is described as the ability to infer others' mental states, beliefs, intentions, and emotions. Theory of mind allows individuals to make sense of others' behaviour, predict and interpret social interactions and communicate effectively and appropriately in social settings (Bzdok et al., 2012; Salazar Kämpf et al., 2023; Wheatley et al., 2007).

Cognition and affect are essential behavioural domains, each representing distinct but interacting processes. Further, they each offer important insights into human individual behavioural variability. In sum, cognition includes attention, memory, reasoning and problem-solving. It is linked to information processing and goal-directed responses. Affect includes emotional states, responses and regulation, and is driven by reflexive, spontaneous responses. However, despite these distinctions, cognition and affect interact dynamically. Emotional states can bias decision-making, while cognitive appraisal can influence and regulate emotion processing. Furthermore, they are both influenced by internal and external stimuli (Langner et al., 2018; Pessoa, 2008). In my dissertation I aim to investigate these concepts both separately as well as their overlap.

3.2 Brain–Behaviour Relationships

To investigate the human brain and to link structure and function to behaviour, a lot of different neuroimaging modalities have evolved. The prerogatives of being non-invasive and in-vivo have been crucial for behavioural neuroscience. In my research I primarily focused on structural and functional MRI, while further using multivariate analyses comprised of heritability analyses and machine learning prediction.

3.2.1 Structural MRI - grey matter structure

Structural MRI captures the anatomy in a static, high-resolution image of the brain, while fMRI measures brain activity over time. Structural MRI takes advantage of the different densities of water content in the brain tissues. This is translated into images, where the different tissues and structures of the brain, such as grey and white matter, and cerebrospinal fluid can be distinguished. In my research I focused on grey matter structure. Grey matter can be found in the central nervous system, hence the spinal cord and the brain. It consists of neuronal cell bodies, dendrites, unmyelinated axons, astrocytes, oligodendrocytes, microglia and blood vessels. It plays a central role in sensory perception, motor control, and higher-order cognitive functions.

3.2.1.1 Cortical thickness and subcortical volume

Cortical thickness refers to the distance in millimetres between the white matter and the pial surface. The distance typically ranges between 1 and 4.5 millimetres (Fischl & Dale, 2000; Palomero-Gallagher & Zilles, 2019). Even though measuring the grey matter cortical thickness sounds simple, it is no small feat, since the pial surface is difficult to detect in standard MRI. Hence, (Fischl & Dale, 2000) developed with FreeSurfer an algorithm to estimate the grey and white matter boundary. This boundary representation is then deformed, with specific constrains, outward until the pial surface. From there, the distance to the white matter border at any point results in the cortical thickness (Fischl & Dale, 2000). This procedure requires both T_1 and T_2 weighted images to accurately map the grey matter as well as distinguish the pial surface from dura and blood vessels (Glasser et al., 2013).

Further, subcortical structures are neural formations in the basal brain, that have been shown integral in motor function, memory, and emotional and cognitive processing. They include deep grey matter structures and nuclei such as the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens area, and ventral diencephalon. Similarly to cortical thickness, estimating the difference in tissue densities between subcortical structures and surrounding white matter, boundaries can be drawn and the subcortical volume can be calculated. Since the subcortical structures are integral in several behavioural processes, it is important to include them analogously to cortical thickness in brain–behaviour analyses.

3.2.1.2 Surface area

Surface area, understandably, refers to the surface of the cerebral cortex. It is intrinsically related to the cortical folding (gyrification). Therefore, most of the surface is hidden in the sulci (Chauhan et al., 2021), making it challenging to map out. Similar to cortical thickness and subcortical volume, the computation of surface area requires sophisticated processes. To automate and improve the delineation of the cortical surface, (Glasser et al., 2013) further enhanced the widely-used FreeSurfer pipeline for the Human Connectome Project (HCP) dataset (Fischl, 2012) used here. Both T_1- and T_2-weighted images are used to clearly define the white matter and pial surfaces and thereby the cortical ribbon. Following this ribbon, triangles are formed and summed to create a grid or mesh. This mesh transforms the cerebral cortex into a 2D sheet. This sheet can then be aligned to different spaces, such as the MNI surface space, to further allow for comparison between subjects.

Importantly, surface area is a morphological feature distinct from cortical thickness. It has been suggested that cortical thickness and surface area evolutionary developed independently (Geschwind & Rakic, 2013), are influenced by different genetic and environmental factors (Panizzon et al., 2009), and develop differently and independently across the lifespan (Fjell et al., 2015; Hogstrom et al., 2013). Cortical thickness reflects neuronal density and dendritic arborization within a cortical column, while cortical surface area reflects the horizontal expansion of the cortical sheet and number of cortical columns. Therefore, it is important to look at them separately (instead of using cortical volume), as well as looking at them both, in order to understand the individual neural influences.

3.2.2 Functional MRI - functional connectivity

While structural MRI captures static images of the brain's anatomy by acquiring each brain slice once, functional MRI (fMRI) measures brain activity over time by repeatedly scanning the whole brain. fMRI is based on the effect, that active brain regions have increased metabolic demand, consuming more oxygen, resulting in an increased blood flow into the specific region. This vascular response results in a shift in the ratio of oxygenated to deoxygenated haemoglobin, producing the so-called Blood Oxygen Level Dependent (BOLD) contrast, which can be detected by the MRI scanner as changes in signal intensity. This alteration in regional blood oxygenation, the hemodynamic response, is observed over several seconds, with peaks at 3–5 seconds after a stimulus (Hillman, 2014).

To reliably capture these dynamics and acquire high-quality fMRI images, it is important to scan the brain with a repetition time shorter than the width of the hemodynamic response function. Additionally, shorter repetition time also improves artefact removal through e.g. physiological noise or head movement. Therefore, in the HCP high-resolution data with a repetition time of 0.72 seconds was acquired (Glasser et al., 2016). Further, spatial resolution is critical for accurately localizing BOLD signals and distinguishing between anatomical compartments such as grey matter, white matter, and CSF. Therefore, by acquiring functional data at 2 mm isotropic resolution, this further enables a precise location of the BOLD signal onto the cortex (Glasser et al., 2013, 2016). Despite significant technical differences between structural and functional imaging, acquired fMRI data can only be processed and analysed precisely by projecting the functional signals onto the structural surface reconstruction, providing an anatomically informed framework for analyses.

3.2.2.1 Resting-state and task-based FC

While the BOLD contrast is considered a proxy for neuronal activation, functional connectivity (FC) identifies correlations of activity between multiple regions of the brain. FC refers to the temporal (statistic) correlation of signal fluctuations between spatially distant regions, revealing distinct brain regions functioning in accordance, reflecting the functional integration of brain regions.

Since the brain is constantly active, the interactions between brain regions can be measured in the absence of tasks, hence during rest (resting-state FC), or during the performance of specific tasks (task-based FC). Resting-state FC captures BOLD signal fluctuations that occur in the absence of explicit tasks. It captures the intrinsic network structure of the brain, which have been shown to be stable and reproducible over time (Biswal et al., 1995). Commonly observed networks include the default mode network, frontoparietal network, dorsal attention network, and salience network (Biswal et al., 1995; Yeo et al., 2011). Resting-state FC is suggested to reveal baseline or "trait-like" properties of brain organization (Finn et al., 2015).

Task-based FC assesses connectivity patterns of functional coupling between brain regions in response to specific cognitive, emotional, or sensory tasks performed in the scanner. Task-based FC reflects context- or state-dependent networks, by task-evoked modulation of functional connectivity through increased coupling. While resting-state and task-based FC share common network architectures, task-based FC shows altered functional coupling in response to task demands (Cole et al., 2014; Shine et al., 2016).

Particularly resting-state fMRI (rs-fMRI) has gained popularity in recent years, due to its convenient application. It can be assessed quickly and easily for all parties involved. The low level of compliance simplifies measurement, making it especially popular in clinical populations, while additionally reducing costs. This lead to a high focus of research on resting state fMRI. As mentioned above, while there seems to be an overlap between resting-state and task-based activation, and even structural morphology, some resting-state fMRI research reveals rather low brain–behaviour relationships. However, both resting-state and task-based FC patterns are unique and can therefore be used to research inter-individual differences. Therefore, in my dissertation I compare and investigate different "states" (resting-state and different task-states) and their effect on predictability of individual behaviour.

FC can be assessed with seed-based correlation analysis or data-driven methods, such as independent component analysis (ICA) or graph-theoretical approaches. While each of these methods have their specific uses and advantages, data-driven methods pose the difficulty of interpretability, while also often being data-set specific. Thus, in my dissertation, I used seed-based correlation analysis. By using *a priori* regions of interest (ROIs), or seeds, it can be assumed, that the selected regions activate during certain tasks. *A priori* ROIs can be defined in a multitude of ways. Here, I defined specialised networks based on activation likelihood estimation (ALE) meta-analyses, and further used a data-driven approach, by delineating networks using general linear modelling (GLM) reflecting brain activation in the large HCP data sample during the tasks of interest. However, the question is whether it has to be exactly the task network that is related to a specific behaviour or whether interactions within other networks are also associated with behaviour.

3.2.3 Neural correlates of cognition and affect

While cognition is multifaceted, a consistent set of brain regions have been identified quite early due to lesion studies: the prefrontal and parietal cortices (Damasio et al., 1996; Rosenbaum et al., 2005; Scoville & Milner, 1957; Stuss et al., 2001). Damage to these regions lead to impaired executive functions. Then, Haier and colleagues showed a correlation between intelligence and grey matter volume in frontal, temporal, parietal, and occipital regions using voxel based morphometry (Haier et al., 2004), which has been supported in functional studies as well. In a large meta-analysis Basten et al. found supporting evidence of brain activation in the lateral prefrontal cortex, the medial frontal cortex, as well as the parietal and temporal cortex in intelligence. More specifically, they found the inferior frontal sulcus and gyrus, middle frontal and temporal gyrus, superior parietal lobule, and the pre-supplementary motor area to be consistently activated during tasks associated with cognition (Basten et al., 2015). Other meta-analyses focussing on working memory found, in addition to some of the aforementioned regions, the thalamus and basal ganglia to be involved (Rottschy et al., 2012).

A similar trajectory can be seen in how we came to understand which brain regions are critical for trait affect. Early lesion studies highlighted the importance of the amygdala, ventromedial prefrontal cortex (vmPFC), and insula in emotion processing and regulation, emotional experience, and decision-making involving affective valence (Adolphs et al., 1995, 1996; Bechara et al., 1999; Calder et al., 2000; Damasio et al., 1994). However, also frontal, temporal and parietal brain regions, as well as the anterior cingulate cortex, have been shown to be involved (Barbey et al., 2014; Hornak et al., 2003). The lesion-based evidence is also supported by structural und functional studies (Lindquist et al., 2012; Schmaal et al., 2017), which further found the prefrontal cortex, the thalamus and the periaqueducal grey to be involved (Kober et al., 2008; Lindquist et al., 2012). In particular relevant for emotion processing (or emotional face processing) are the already mentioned amygdala and insula. However, further active regions found in the limbic areas include the parahippocampal gyrus and the posterior cingulate cortex, and in the temporoparietal areas the parietal lobule and the middle temporal gyrus. Further involved are visual areas, such as the fusiform and lingual gyrus, the medial frontal gyrus, the putamen and the cerebellum (Fusar-Poli et al., 2009; Müller et al., 2018).

In sum, key brain regions in cognition are covered mainly by the multiple-demand and the cognitive control network. The multiple demand network includes the (posterior-medial) frontal cortex, insula, intraparietal sulcus, and inferior frontal sulcus. The cognitive control network includes the anterior cingulate cortex/pre-supplementary motor area, dorsolateral prefrontal cortex, inferior frontal junction, and posterior parietal cortex. In affect, the limbic system, including in particular the amygdala, with extensions to the prefrontal cortex, cingulate gyrus, thalamus, and hippocampus, have been associated. These regions have been mainly based on lesion studies and group effect between task conditions. They therefore show, that these regions are consistently involved in these processes. However, to what extent they are associated with individual behavior is incompletely understood.

3.3 Influencing Factors on Brain–Behaviour Relationships

One of the main goals in behavioural neuroscience is to understand how the human brain works and how individual variability is driven. Several approaches can be applied to try to elucidate this quest: heritability analyses can help explain how much of individual variability in brain structure or function is influenced by genes. Prediction can help us move beyond group averages. Finally, multivariate and multimodal analyses tie all modalities together and try to approach the brain as it is: an interconnected system.

3.3.1 Heritability

Heritability is a statistical estimate explaining what proportion of the variation in a given trait in a population is due to genetic variation. The variance (V) of a phenotype (P) within a population is composed of genotypic (G) and environmental (E) variance. Narrow-sense heritability (h^2), calculable with twin studies, refers to the proportion of phenotypic variance that is attributable to additive genetic variance V(A), and is estimated as $h^2 = V(A) / V(P)$ (Bruell, 1970; Nes & Roysamb, 2015). Research of genetic influences provides insights into the biological basis and possible influences in both healthy and diseased people. It helps us further understand the biological (genetic) constrains, while empowering us with the knowledge about potential environmental influence. This pertains to both the brain, as well as behavioural traits.

Thanks to heritability analyses based on twin studies, it has been analysed, that the majority of the human brain morphology is highly heritable (Jansen et al., 2015), but also, individually both cortical thickness and surface area revealed to be highly heritable in humans (Panizzon et al., 2009). Further, behavioural traits are heritable. Ranking at the top is cognition, which has been shown to be highly heritable (Krapohl et al., 2014; Plomin & Deary, 2015). In contrast, since affective traits are much more elusive and a clear delineation still of debate (Desmet, 2018; Gross, 2015), the research of heritability in these traits is much less consistent. Nevertheless, affective traits have been identified as heritable to some extent (Bouchard & Loehlin, 2001; Lykken & Tellegen, 1996), while some diseases associated with affective disorders show high heritability (Fernandez-Pujals et al., 2015; Kendall et al., 2021). Further, cognitive empathy or social cognition has also been shown to be heritable (Warrier et al., 2018).

Therefore, in the first study, I not only investigate the phenotypic association between cognition, affect and local brain anatomy, but also investigate the shared brain basis between cognition and trait affect and their genetic correlation. This enables me to investigate heritability as an influencing factor on brain–behaviour relationships in cognition and affect.

3.3.2 Prediction

For the most time, and laid out in the previous section, neuroscience relied on very specified lesion patients or large samples to establish brain–behaviour relationships. Through new insights this locationist approach is being challenged by the constructionist approach, which suggests an interaction between brain functional networks, instead of one specific location to be responsible for a specified function (Lindquist et al., 2012). In addition, we now have more (brain) data available, including large densely sampled datasets, such as the Human Connectome Project. Prediction with machine learning allows us to go beyond conventional statistics and make use of the large, complex and high-dimensional datasets. While conventional statistical approaches help us understand relationships between variables, they often rely on simplifying assumptions—such as independence, linearity, and low dimensionality—that may not reflect the true complexity of brain–behaviour relationships.

In contrast, predictive modelling and machine learning are able to handle high-dimensional, complex, and often nonlinear data, enabling the analysis and identification of distributed patterns across the brain that are informative at the level of individual behaviour. Therefore, the application of prediction in neuroscience offers the potential to further knowledge and the development of brain-based biomarkers for personalized medicine to inform diagnosis, prognosis, and intervention strategies on an individual level.

However, statistics allow an interpretable hypothesis driven approach to brain–behaviour relationships, while machine learning functions largely within a "black box". While the ability to handle complex data and potentially discover patterns with machine learning is a major strength, the models often lack interpretability, making it difficult to infer the underlying biological mechanisms driving the observed patterns.

Therefore, in my dissertation, I applied statistical models to achieve an interpretable and reduced feature space of brain data before applying different machine learning algorithms. Instead of relying on whole-brain data—and therefore omit biological interpretability—I yielded functional networks through different approaches: 1) Meta-analyses of networks activated through specific tasks, and 2) Definition of networks from high-powered and diversified task-fMRI studies. I then computed the functional connectivity within these networks based on different task states and analysed their predictability with regards to corresponding behaviour. By comparing FC derived from resting-state and task-based fMRI, and applying predictive modelling techniques, I can assess whether FC from behaviourally related states (e.g. FC from WM predicting WM) offer better predictive power than unrelated states (e.g. FC from WM predicting EMO).

This integrated approach allows not only to identify associations between brain regions and behaviour (statistical analysis), but also to determine whether these associations are genetically influenced (heritability analysis) and whether they are informative for predicting individual differences in behaviour (predictive modelling).

3.4 Aim of the studies

One main goal of neuroscience is to understand and gain deeper insights into brain function and organisation and to link it to behaviour. Many studies investigated how experience and behaviour is linked to brain structure and function, and also how much influence can be attributed to our genetic makeup. While there are many converging studies investigating cognition, there are inconclusive findings for affect, as well as their interplay. Further, little is known about how behavioural domains are subject to different influencing factors of inter-individual differences of the brain. In particular, how overlapping genetic influences exhibit in brain structure, and which influence different functional task states drive predictability of individual behaviour.

Therefore, the first study focused on identifying a shared behavioural basis across cognition and affect and examined whether this convergence is mirrored in local brain structure. Here, I focused on structural morphometry such as cortical thickness, surface area, and subcortical volume. Finally, by analysing the heritability, I investigate if cognition and affect have shared genetic effects within behaviour and in brain morphology.

In the second study I move from structural anatomy to functional brain networks. Here, I investigate if individual differences in cognition (represented by working memory), emotion, and social cognition can be predicted from potential patters of FC. By comparing the predictability of FC derived from resting-state and task-based fMRI in different *a priori* networks, I can assess the influencing factor of task state and network specificity on brain–behaviour relationships. Further, by using *a priori* defined networks based on meta-analyses and large samples, I aim to improve interpretability of machine learning models.

With this dissertation I aim to investigate how inter-individual differences in cognitive and socio-affective processes are related to structural brain anatomy and functional connectivity. Further, I assess phenotypic and morphological heritability, as well as the predictability of task states and network specificity as influencing factors of brain variability.

4 Study 1

Behavioral, anatomical and heritable convergence of affect and cognition in superior frontal cortex

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Own contributions	Conception and design of study Implementation, reviewing and adapting analysis code Statistical data analysis Interpretation of results Preparing figures Writing paper Total contribution 70 %

5 Study 2

Network and State Specificity in Connectivity-Based Predictions of Individual Behavior

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Own contributions	Conception and design of study Implementation, reviewing and adapting analysis code Statistical data analysis Interpretation of results Preparing figures Writing paper Total contribution 85 %

6 Summary and general discussion

With this dissertation I aimed to investigate how inter-individual differences in cognitive and socio-affective processes are related to structural brain anatomy and functional connectivity and how heritability and task state impact brain–behaviour relationships as influencing factors. First, I investigated the phenotypic and morphological association of cognition and affect in the brain, as well as their shared genetic variance. I then assessed the predictability of task states and network specificity.

With my first study I was able to show phenotypic relationships with both affect and cognition and brain structure in the left superior frontal cortex. Decomposing the phenotypic correlations into genetic and environmental components showed that the associations were accounted for by shared genetic effects between the traits. Yet, my second study revealed that individual behaviour can only moderately be explained by network interactions. The results indicate that interactions within *a priori* networks are less predictive than global effects. However, a slight benefit of predictions based on FC from task versus resting state was observed for performance in the cognitive domain, indicating state specificity.

6.1 Cognition and affect – integrated dimensions

Intelligence or cognition is a very well-studied and delineated concept. Reliable measures have been developed (Akshoomoff et al., 2013; Heaton et al., 2014), capturing different aspects of cognition such as fluid reasoning and crystallized knowledge, including executive function, working memory, processing speed, attention, episodic memory, and language. In the first study, I used these measures to analyse crystallised and fluid intelligence, assessed with the National Institute of Health (NIH) toolbox for Assessment of Neurological and Behavioral Function® (neuroscienceblueprint.nih.gov). This measurement has been shown to capture interindividual differences reliably (Akshoomoff et al., 2013; Gershon et al., 2013). However, in the second study, to investigate the influence of task states, I used the cognitive process of working memory, which in this dataset was assessed with a 2-back task. Unfortunately, the simplicity of the task leads to a ceiling effect, where many participants solve the task successfully, leading to a low variance. This has been, however, mitigated by introducing reaction time into an inverse efficiency score. Nevertheless, the moderate predictability of task states could be related to the low variance within both the cognitive score, as well as a within the task states.

Emotion or affect has gained scientific attention later and has seen struggles being investigated due to the elusive nature (Barrett, 2012; Lindquist et al., 2012). However, emotion and trait affect influence what we notice, learn (Mather & Sutherland, 2011; Tyng et al., 2017), remember (Cahill & McGaugh, 1998; Mather & Sutherland, 2011) and even how we decide (Bechara et al., 2000). Several tests have been developed to assess emotion and affect. In the first study, self-reports were used to capture trait affect from the Emotion Battery of the NIH Toolbox (Pilkonis et al., 2013; Salsman et al., 2013, 2014). For the second study an emotional face matching task was performed, which has been developed and tested to reliably activate the amygdala. However, only little variance of individual emotion processing abilities is captured. This has been, again, mitigated by introducing reaction time into an inverse efficiency score. Nevertheless, it would be interesting to see a similar study setup to investigate state and network specificity, however with different, more complex tasks.

Despite cognition and affect being seen as separate constructs for a long time and therefore being studied separately, an integration is inevitable. This can be seen with the word "emotional intelligence", the ability to use and regulate emotions. But also with social cognition or theory of mind, which has been investigated in the second study, showing a combination of both emotional interpretation and social inference.

While cognitive functions have traditionally been attributed to higher-order cortical regions—such as the lateral and medial prefrontal, temporal, and parietal cortices—affective processes have historically been associated with evolutionarily older, subcortical structures, including the amygdala, basal ganglia, and hypothalamus. However, as outlined above, recent research increasingly investigates the integration of affect and cognition across both cortical and subcortical systems, challenging the historical dichotomy between emotional and cognitive brain networks. In line with that, both my studies showed on the one hand a convergence phenotypically, as well as in the superior frontal gyrus (study 1), as well as no network-specificity and only moderate state-specificity for cognition (study 2), suggesting potential overlapping networks and functions.

6.1.1 Brain morphology and heritability (study 1)

The modular approach on cognition and affect has already been challenged by several researchers such as (Barrett et al., 2011; Lindquist et al., 2012; Pessoa, 2008), arguing, that cognition and emotion are deeply intertwined in both brain and behaviour. In this dissertation, by using anatomic data and twin modelling, I build on this by demonstrating that cognitive and affective traits are not only theoretically connected, but phenotypically and genetically associated, pointing toward a shared neural infrastructure in the superior frontal gyrus. This convergence underlines previous findings (Barrett & Satpute, 2013), while furthering this integration through heritability modelling, showing a shared phenotypic and genetic association with cortical thickness in the left superior frontal cortex. This convergence indicates the prefrontal cortex as not just essential for cognitive function, but a hub where emotional and cognitive traits are co-constructed. The discovery of a brain region simultaneously relating to cognitive and affective traits, while further driving these associations genetically, strongly indicates that cognition and emotion are integrated within the brain. Therefore, this biologically stable marker has further implications for understanding trait-level vulnerabilities, also in mental health.

6.1.2 Functional connectivity and predictability of task states (study 2)

The finding of a shared phenotypic and genetic association between cognition and trait affect in the superior frontal cortex is rooted in quantifiable structural morphology providing trait-level and heritability insights. In a next step, I put a stronger focus on the effects of state and the relationship to brain function, in contrast to brain structure. Thus, these results led me to develop the research of cognition and emotion into a more dynamic approach, by complementing it with functional connectivity in resting-state und task-based fMRI.

Unlike structural markers, functional connectivity reflects state-dependent and network-based dynamics. Therefore, in my second study I explored whether functional connectivity could predict inter-individual differences within cognition (represented through WM), and emotion, complemented with social cognition. Moving from structural morphology and heritability to functional connectivity and machine learning prediction, allowed me to investigate the influence of state on brain–behaviour relationships.

Here, I found that, overall, FC patterns showed limited ability to predict individual behavioural performance. The predictive power was modest, though comparable to other studies applying a similar approach (Dubois et al., 2018; Greene et al., 2018; Ooi et al., 2022). However, slightly better predictions were achieved using task-based FC compared to resting-state FC, particularly in the working memory domain, which extend results from previous studies, showing that FC from task-based fMRI carry more behaviourally relevant and individual information (Finn et al., 2015; Finn & Bandettini, 2021; Greene et al., 2018). Despite the modest predictive power, the stronger prediction performance of task-based compared to resting-state FC supports the idea that contextual activation enhances signal relevance by being more reflective of individual differences. While in my study this was only observed for working memory, it stands to investigate, whether an improvement could be seen within a larger sample (through increase of statistical power) or with different task capturing the emotion domain (through capturing more emotional variance).

6.1.3 Complementary results

With these two studies I investigated how the behavioural and brain morphometric data provide trait-level and heritable foundations, revealing a stable hub of convergence between cognition and affect in the superior frontal cortex. Further, I approached functional connectivity with machine learning predictions offering insights into large-scale patterns in cognitive and emotional functioning. Here, task-based connectivity yielded better prediction performance (compared to resting-state FC, in working memory prediction) implying the importance of state and network interactions within interindividual variation. However, no significant difference in prediction performance between the different domains could be observed, which could potentially indicate individual variability similarities in FC of cognitive and socio-affective processing.

Encompassing both studies, I applied several analyses, leveraging the power of multimodal integration. With the analyses on both structural and functional data I offer complimentary insights. While the analysed structure in combination with the heritability analysis reveals stable traits and genetic boundaries within which one can change and develop, functional analysis reveals how a person behaves and feels in the moment. Therefore, my results show that cognition and affect are both stable and flexible within our behaviour, as well as our brain, revealing insights important for our understand within the layered inter-individual brain–behaviour relationships. With this dissertation I present the results of a genetically driven overlap between cognition and affect in the superior frontal cortex, while the influence of state showed moderate predictability only in cognition but none for the socio-affective domain. This is in line with the latest research endeavours and important for future individualised neuroscience. In sum, by examining structure and function and investigating different influencing factors of brain–behaviour relationships one gets a more nuanced picture about the integration of cognition and affect in the human brain.

6.2 Limitations and opportunities

Despite the faceted and broad approach, there are some limitations to be acknowledged. First, both studies used the openly available Human Connectome Project. Openly available large datasets such as the HCP used here, or the Adolescent Brain Cognitive Development Study (ABCD), and the UK Biobank are tremendously valuable and have transformed and furthered research in neuroscience. They play an important role in the standardization of protocols and data collection, and in the promotion of reproducibility through transparency, replicability and validation of findings. Further, the varied data sampling within these datasets allows for the multimodal analysis of complex research questions as done here. Importantly, the large sample sizes increase statistical power, through which robust correlations (study 1) and the application machine learning models (study 2) are only possible.

While the HCP is a densely sampled dataset enabling the research of complex research questions, it also shows only a small fraction of the population: the age range is between 22 and 37 years, with all healthy subjects from the USA, with a slightly higher IQ than the population average. While this sample was chosen consciously in an effort to establish potential brain–behaviour relationships within a healthy and constrained sample, it anyhow constrains the results to only a section of the population. For both studies it would be beneficial to repeat the analyses in different samples in order to test for generalisability. However, these very specific research questions addressed in this dissertation could for now unfortunately only be answered with the HCP dataset, as they allow for twin-based heritability testing (study 1), and further offer a wide variety of in- and out-of-scanner tests and questionnaires allowing for the analysis and comparison of FC predictability between different behaviour performances (study 2). Yet, the extensive testing comes at the cost of potentially rather superficial and short tasks. This includes the tasks performed in the scanner as well as outside. Most of the task developed for fMRI induce a robust activation of targeted brain areas instead of allowing for strong interindividual variability. Further, tasks performed both inside and outside the scanner are often optimized for stable group-average effects. In both studies this needs to be factored into the interpretation of the findings.

Furthermore, the widespread use of these datasets increases the risk of false positive findings. Since numerous researchers are conducting a multitude of independent analyses within these datasets, statistically significant results may arise by chance. Publication bias adds to this problem, as positive findings are more likely to be published, skewing the literature towards overstated effects. Therefore, it was especially important to me to publish the results of the second paper as transparently as possible, without overstating the findings and acknowledging the moderate prediction performance.

As mentioned above, it would be valuable to test the generalisability of these findings using independent samples. Since there are so far no suitable large openly available datasets, it could be interesting to test the findings in smaller datasets, as well as in harmonised data from several smaller datasets. Such a data pool could also be used to inform synthetic data. Synthetic data could offer an exciting opportunity to train machine learning models, especially in areas where there is notoriously insufficient data (J. Wang et al., 2023), such as rare diseases, diseases with difficulties to be scanned in an MRI scanner, or areas where data privacy protection is an issue (Vaden et al., 2020).

Further, it is important to mention that although multimodal analyses are highly promising, technical nuances and methodological limitations, and therefore meaningful interpretation, depends on having (or inquiring) domain-specific expertise. This has been especially evident in the work on the second paper applying machine learning for behavioural performance prediction based on FC. Several landmark papers used oversimplified assessments of prediction performance, painting a more optimistic picture of the achievements. For my publication it was therefore important to offer a critical and transparent assessment of the findings.

Moreover, potential avenues to develop these findings presented here, despite the multimodal approach within the papers, are manifold. Within the first paper the research focus between brain–behaviour relationships and the genetic drivers, could be extended to investigate the heritability of functional task activation and connectivity. Based on studies performed in the same dataset, it would be expected to be in line with our current findings and show that not only brain structure, but also FC is heritable (Colclough et al., 2017; Ge et al., 2017). However, a potential convergence between cognition and affect and FC has not been investigated. Furthermore, in the second paper, only FC was used to predict behavioural performance. While one of the goals of the second paper—to improve interpretability of machine learning features—would be hindered, it would nevertheless be interesting to see if a combination between structural and functional data or even genetic or EEG data could improve prediction performance. Finally, since the network used in the second paper were based on *a priori* defined delineations, future work could adopt and compare different individualised parcellations (such as different approaches developed by (Beckmann et al., 2005; Kong et al., 2019; Mueller et al., 2013; D. Wang et al., 2015)). Within the scope of my research, I have applied the approach by (Kong et al., 2019). However, preliminary results revealed only a marginal improvement in prediction performance for the specific networks and behavioural targets. Therefore, I assume that even individualised *a priori* defined networks may not significantly improve prediction performance and therefore interpretability of relevant features. Instead, machine-learning appropriate *post-hoc* analyses of whole-brain FC predictions (Tian & Zalesky, 2021) might offer greater potential to identify biologically relevant features.

6.3 Relevance and impact

The research and investigation of cognition and affect is not only of theoretical interest, but is essential in everyone’s daily life, as well as fundamental in different mental disorders. Many cognitive and neural processes are expected to operate in similar ways in both healthy individuals and those with neurological or psychiatric disorders. With my dissertation, using a healthy and constrained sample, I aimed to apply different analyses to contribute new insights for precision neuroscience, by providing a deeper understanding of the interplay between cognition and affect, and individual variability in brain and behaviour.

Therefore, in line with previous studies showing structural association with cognition and emotion in the superior frontal cortex (Engen & Anderson, 2018; Okon-Singer et al., 2015), I extend these findings in study 1 by providing evidence for shared genetic effects between the traits. It therefore reinforces the importance of integrated theories (Barrett, 2012; Pessoa, 2008) and provides a basis for investigating shared risk factors in mental health disorders. Further, study 2 extended the already extensive research of task-based FC compared to resting-state FC comparison for behavioural prediction within the cognitive domain (e.g. (Avery et al., 2020; Greene et al., 2018; Jiang et al., 2020)), by the socio-affective domain. Although the prediction performance was moderate, an additional important contribution was the transparent acknowledgment and reporting of these limitations. Moreover, the undetected differences in prediction performance between unrelated FC and behavioural score (e.g. prediction of working memory score from FC yielded from emotion recognition task), might also suggest that cognitive and emotional processes are interconnected at the neural level to allow for clearly separable predictive patterns.

Finally, in order to improve interpretability of machine learning features, I defined *a priori* networks based on meta-analyses and from large individual task-fMRI studies. Therefore, I computed GLM for all tasks, and further conducted three separate meta-analyses for working-memory (n-back task), emotion recognition and social cognition. These meta-analytically defined networks are openly available via the ANIMA-database (Reid et al., 2016); https://anima.fz-juelich.de/studies/Kraljevic_NetStateSpec_2024).

6.4 Conclusion

In sum, with my dissertation I provide an integrative model of how cognition and affect relate to the human brain. By combining insights from structural anatomy, heritability modelling, and functional connectivity-based prediction, my results reveal that these traditionally distinct domains share common neural substrates, while also being dynamically shaped through context-sensitive activation and connectivity.

The identification of the superior frontal cortex as a heritable anatomical hub for both cognitive and affective traits emphasizes the stability of this integration at the trait level. In contrast, the moderate, yet comparable, predictability of task-based FC shows the influence of brain state and network dynamics in shaping individual behaviour, while also promoting a transparent and critical assessment of multi-modal analyses.

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