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Special Issue "In honour of Jordan Grafman": Review

Studying the social mind: An updated summary of findings from the Vietnam Head Injury Study



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ABSTRACT

Lesion mapping studies allow us to evaluate the potential causal contribution of specific brain areas to human cognition and complement other cognitive neuroscience methods, as several authors have recently pointed out. Here, we present an updated summary of the findings from the Vietnam Head Injury Study (VHIS) focusing on the studies conducted over the last decade, that examined the social mind and its intricate neural and cognitive underpinnings. The VHIS is a prospective, long-term follow-up study of Vietnam veterans with penetrating traumatic brain injury (pTBI) and healthy controls (HC). The scope of the work is to present the studies from the latest phases (3 and 4) of the VHIS, 70 studies since 2011, when the Raymont et al. paper was published (Raymont et al., 2011). These studies have contributed to our understanding of human social cognition, including political and religious beliefs, theory of mind, but also executive functions, intelligence, and personality.

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Emotion regulation
 Executive functions
 Social cognition
 Intelligence
 Personality

This work finally discusses the usefulness of lesion mapping as an approach to understanding the functions of the human brain from basic science and clinical perspectives.

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1. Introduction

The question of how social cognition can be mapped to specific brain areas has been the focus of scientific attention for many years, specifically for its importance for better understanding how individuals navigate the social world and the underlying pathologies associated with a dysfunction of those neural systems. Among the different tools neuroscience can use to answer this question, lesion mapping studies can provide a particularly valuable insight thanks to their potential causal implications (Adolphs, 2016; Vaidya et al., 2019; Warren et al., 2014). Deficits in the social domain are a common problem following a TBI, especially following frontotemporal lesions and they have been largely described in the military population [see for example (Tellier et al., 1990; Walker & Seymour, 1961)].

The Vietnam Head Injury Study (VHIS) is a longitudinal study of American male combat veterans with focal penetrating traumatic brain injury (pTBI) and matched combat veterans without brain injury (Raymont et al., 2011). The VHIS began as a study of post-traumatic epilepsy by Dr. William Caveness at the National Institute of Neurological Disorders and Stroke shortly after the Vietnam War ended and has had 4 phases. Here we focus on studies conducted based on the Phase 3 and 4 evaluations, corresponding to 35 (Phase 3) and more than 40 (Phase 4) years post-injury. This work provides a summary of studies conducted and published since a prior review (Raymont et al., 2011). In particular, we focus on studies examining social cognition, including political and religious beliefs, theory of mind, executive functions, intelligence, and personality.

The study of patients with focal pTBI has made fundamental contributions to the cognitive and social neurosciences (Corkin, 2002; Marshall & Halligan, 1988; Newcombe & Russell, 1969; Teuber, 1975). Lesion mapping research establishes the necessity of any putative neural substrate for a given function. The lesion studies reviewed here complement the studies using functional neuroimaging and non-invasive brain stimulation and contribute to our understanding of the social brain of humans.

Comparing results across studies with closed traumatic brain injury (TBI) patients has been challenging, in part due to the inconsistency in data collection and coding procedures (Maas et al., 2010). In the VHIS, we have explored different components of the social and executive brain using a single dataset, in which multiple cognitive measures were drawn from the same group of patients with stable pTBI.

The goal of this paper is to summarize the latest findings from the Vietnam Head Injury Study (VHIS) and highlight their

impact on our understanding of human social cognition. It is important to note that while the VHIS is a unique data set given its size, length, and the richness of collected data, it is far from being the only source for understanding brain-behavior connection through brain lesions. While many other studies contributed to our understating of these topics, they will not be discussed in the current summary. Moreover, we would like to establish that this is not a review in the traditional form (i.e., it will not be following Prospero, Prisma, or Cochrane guidelines) but instead a summary of over a decade of work done by numerous scientists using one specific data set. For reading purposes see the Acronym Table (Table 1).

1.1. Penetrating traumatic brain injuries: working definition and statistics

TBI is one of the leading causes of disability the United States. Although pTBI is less common than closed TBI (rapid rotations, accelerations/decelerations, shaking of the brain within the skull, or impact to the skull itself, mostly resulting from motor vehicle accidents), it carries a worse prognosis. Most deaths from traumatic brain injury are due to firearm injuries. In the United States, approximately 20,000 gunshot injuries to the head occur annually.

Individuals suffering from pTBI present with focal brain lesions produced by objects that penetrate the skull and the dura frequently resulting from projectiles or knife wounds in civilians or blast-related shrapnel or missile injuries in military populations (Cristofori & Grafman, 2019). pTBI is considered by some to be the most severe of traumatic brain injuries (van Rein et al., 2019). Based on the speed of penetration, it can be classified into two categories: high-velocity penetration (such as injuries caused by bullets or shell fragments, from direct trauma or shockwave injury to surrounding brain tissue due to a stretch injury) and low-velocity penetration (such as injuries caused by a knife or other sharp objects, with direct trauma to brain tissue) (Alao & Waseem, 2020; Grafman & Salazar, 1987). PTBI may result in a cascade of pathological events, including local neural dysfunction and/or disruption of neural networks (Cristofori & Grafman, 2019). PTBI severity depends on the lesion location and the extent of brain volume loss (van Rein et al., 2019), as well as pre-injury intelligence (Raymont et al., 2011), parental socioeconomic status (Cohen-Zimmerman et al., 2019), and genetic predisposition (Weaver et al., 2014), among other factors.

Prognosis is generally poor in pTBI (Van Wyck and Grant, 2015). Approximately 70–90% of victims of pTBI die before arriving at the hospital, and 50% of those who survive to reach

Table 1 – Acronym table.

Acronym	Extended meaning
VHIS	Vietnam Head Injury Study
P1/P2/P3/P4	Phase1/Phase2/Phase3/Phase4
pTBI/TBI	Penetrating Traumatic Brain Injury/ Traumatic Brain Injury
HC	Healthy Controls
Neuroimaging	
CT	Computed Tomography (scan)
MRI	Magnetic Resonance Imaging (scan)
VLSM	Voxel-Based-Lesion-Symptom- Mapping (analysis)
ABLe	Analysis of Brain Lesions (software)
Disorders	
PTE	Post-traumatic epilepsy
PTSD	Post-Traumatic Stress Disorder
Cognitive functions	
EF	Executive Functions
WM	Working Memory
TOM	Theory of Mind
Neuropsychological tests/tasks	
AFQT	Armed Forces Qualification Test
WAIS	Wechsler Adult Intelligence Scale
DKEFS	Delis–Kaplan Executive Function System
EPSI	Everyday Problem-Solving Inventory
MSCEIT	Mayer, Salovey, Caruso Emotional Intelligence Test
NEO-PI	NEO Personality Inventory
IAT	Implicit Association Task
Brain regions	
AI	Anterior Insula
dIPFC	Dorsolateral Prefrontal Cortex
mPFC	Medial Prefrontal Cortex
rlPFC	Rostrolateral Prefrontal Cortex
PFC	Prefrontal Cortex
OFC	Orbitofrontal Cortex
IFG	Inferior Frontal Gyrus
MTG	Middle Temporal Gyrus
STC	Superior Temporal Cortex
iTC	Inferior Temporal Cortex
ipTC	Inferior Posterior Temporal Cortex
pSTS	Posterior Superior Temporal Sulcus
TPJ	Temporo Parietal Junction
iPC	Inferior Parietal Cortex
SMA	Supplementary Motor Area
ACC	Anterior Cingulate Cortex
dACC	Dorsal ACC
White matter tract	
ACR	Anterior Corona Radiata
PCR	Posterior Corona Radiata
SFOF	Superior Fronto-Occipital Fasciculus;
SLF	Superior Longitudinal Fasciculus
Genetics	
BDNF	Brain-Derived Neurotrophic Factor

the hospital die during resuscitation attempts in the emergency department (Joseph et al., 2014; Rosenfeld et al., 2015). Of the 333,169 US military TBI recorded between 2000 and 2015, 4,904 were classified as pTBI (DOD, 2015). Approximately 32,000–35,000 civilian deaths are attributed to pTBI every year, with firearm-related injuries being the leading cause of mortality in this group (Joseph et al., 2014; Zafonte et al., 2001).

Less than 20% of civilians who reach a trauma center will undergo a neurosurgical procedure (Aarabi et al., 2014). Approximately half of pTBIs involving firearms are suicides (Bizhan et al., 2015); these injuries have higher mortality due to the close ranges at which the firearm is discharged (Rosenfeld et al., 2015). In 2010, total healthcare costs attributed to TBI were reported by the Centers for Disease Control and Prevention as \$76.5 billion with severe TBI accounting for 90% of the cost (CDC, 2014). Survivors of pTBI are faced with enduring motor, cognitive, and social impairment (Raymont et al., 2011). In the cognitive domain, some of the most common and serious deficits are in the areas of attention, memory, and executive functioning. Social and emotional disorders can manifest as apathy, irritability, unawareness of deficit, impulsivity, anxiety, and depression.

1.2. Recent history of cognitive-neuroscience research with pTBI survivors

This work is an update of a previous review published by Raymont and collaborators over a decade ago (Raymont et al., 2011). While the previous review focused on phases 2 and 3 of the VHIS, this work focuses mainly on phases 3 and 4. For phase 3 we did not include studies previously reported in Raymont et al.'s review. While Raymont et al.'s review focused on the impact of epilepsy, motor disorders, fatigue, neuropsychological deficits, decision-making, and genetics on functional recovery, the present work will focus on the contribution of the VHIS to social cognitive neuroscience.

1.3. History of the Vietnam Head Injury Study (VHIS)

The VHIS is a longitudinal follow-up study of male combat veterans who served in the Vietnam War, most of whom suffered a combat-related pTBI. The study was initiated by William F. Caveness, a neurologist, Korean War veteran, and former chief of the Laboratory of Experimental Neurology at the National Institute of Neurological and Communicative Disorders and Stroke [for an in-depth history of the VHIS, see Raymont et al., 2011]. Caveness built the initial VHIS registry with medical record information of 2,000 men who initially survived a pTBI during the Vietnam War between 1967 and 1970, with a focus on post-traumatic epilepsy.

The first phase of the study (P1; 1967–1970) involved an extensive review of 1,221 military and Veterans Administration medical records from the 5-year post-injury period. In the second phase (P2; 1981–1984), 520 individuals from the initial registry, as well as 85 Vietnam veterans who did not suffer a brain injury, were invited to attend a week-long evaluation at the Walter Reed Army Medical Center in Washington D.C. The P2 evaluation was done partly in collaboration with the Red Cross, and included epilepsy, neurological, medical, and neurobehavioral evaluations as well as the collection of brain CT scans. In the third phase (P3; 2003–2006) of the study, the participants were invited to attend another evaluation at the National Naval Medical Center, Bethesda, MD. Veterans with ($n = 199$) and without ($n = 55$) pTBI underwent a broad evaluation which included neuropsychological assessments and structured psychological interviews as well as psychiatric and neurological examinations. Brain CT scans were acquired

again (since most of the participants had retained metal in their brain, MRI scans were not administered). The Analysis of Brain Lesions software [ABLE; (Makale et al., 2002; Solomon et al., 2007)] was used to calculate normalized lesion volumes as well as the percentage of specific brain regions involved, based on manually drawn lesion outlines [see (Raymont et al., 2008) for a detailed description of this process]. Lastly, blood was drawn to enable genetic hypothesis testing.

In the fourth and final phase of the VHIS (P4; 2008–2012), 169 participants (134 pTBI, 35 healthy controls, HC) and their caregivers (115 pTBI, 31 HC) attended the National Institute of Neurological Disorders and Stroke in Bethesda, MD, USA. Tests in this phase included cognitive, social, and behavioral assessments. Unique to this phase, the long-term effects of pTBI on patient–caregiver relations were also assessed. See Fig. 1 for pTBI lesions overlay.

In summary, the VHIS followed a group of male veterans (of differing sample size depending on the Phase), similar in age and education level, for approximately 50 years following combat-related, focal penetrating brain injury, mostly due to lower-velocity shrapnel penetration. Using the data from the different phases, in combination with pre-injury intelligence measures that were obtained upon enlistment in the Army, has allowed us to thoroughly evaluate the recovery of function following brain injury and to uncover the neuronal and genetic underpinnings of behavior, which we describe next.

2. Summary of results

2.1. Papers selection criteria

Below we summarize the results of the 70 VHIS papers published since the first review by Raymont et al. (2011). We included all the papers that used data from the VHIS and were published after the first review. No paper has been excluded.

The findings are grouped into sub-sections according to the target outcome measure. In each sub-section, the studies are reported chronologically. See Figs. 2–4, and Table 2 for a Summary of the results.

2.2. Intelligence

There are more studies focused on intelligence compared to any other ability reviewed in this paper. Our attention dedicated to this general cognitive ability is not surprising

considering its far-reaching implications: intelligence is related to educational achievement, employment prospects, wealth generation, career outcomes, and well-being. Moreover, the VHIS provides a unique setting to study intelligence in patients with brain lesions: this registry includes premorbid intelligence scores that were collected by the military upon enlistment using the Armed Forces Qualification Test [AFQT-7A, (Department of Defense, 1960)]. The AFQT was designed as a classification test, but its percentile total score is highly correlated with the full-scale IQ. The AFQT was administered again during the VHIS P2, P3, and P4 evaluations, allowing for direct comparison of pre- and post-injury performance, as well as changes in score over time. Moreover, during Phases 2–4, the Wechsler Adult Intelligence Scale [WAIS-III; (Wechsler, 1997a)] was administered, with scores in this test being highly correlated with AFQT scores (Grafman et al., 1988), supporting the use of AFQT scores as indicative of intelligence. A focused review of patient-based approaches to understanding intelligence including a detailed overview of related VHIS studies can be found in Cohen-Zimmerman et al. (2021). Here, we will briefly describe the main findings from studies on (1) general intelligence, (2) emotional intelligence, and (3) problem-solving and reasoning.

2.2.1. General intelligence

General intelligence, also known as *g* factor, refers to a general mental ability that, according to Spearman (1904), underpins different skills, such as verbal and spatial. This classical theory found support from neuroimaging data (Duncan et al., 2000; Prabhakaran et al., 1997) that defined the PFC as the key structure orchestrating general intelligence. Other studies, however, found other regions to be involved in this process such as the dorsolateral prefrontal cortex (dlPFC) and parietal cortex (Jung & Haier, 2007) supporting the idea that the *g* factor reflects the average or combined activity of many separate cognitive operations (Barbey & Sloman, 2007; Bartholomew et al., 2009).

The VHIS dataset provided an opportunity to test these two competing hypotheses (*g* factor as general mental ability processed by the PFC, or *g* factor as average of different mental abilities processed by larger network such as dlPFC and parietal cortex).

The general factor of intelligence, *g*, was found to activate a distributed frontoparietal network (Barbey et al., 2012), suggesting that intelligence integrates verbal, spatial, motor and executive processes. In fact, *g* nearly perfectly correlated with executive function (EF), as measured by selected WAIS-III and

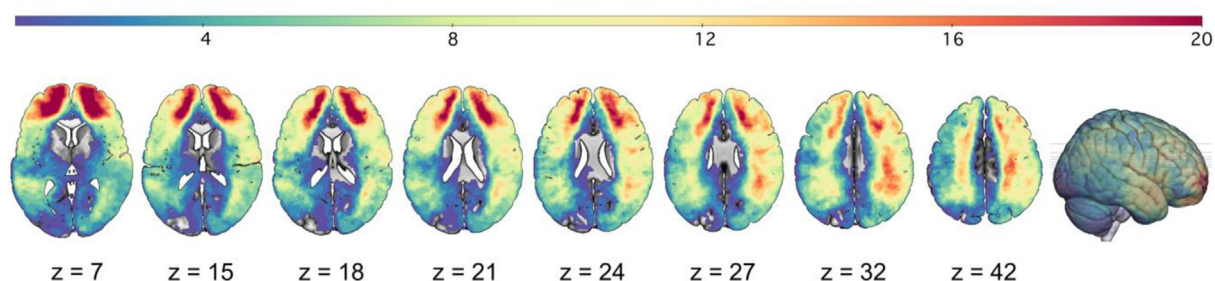


Fig. 1 – Lesion overlay demonstrating overlap in lesions across pTBI patients that had their CT scans collected as part of VHIS Phases 3 or 4. Values on bottom of the slices indicate the z coordinates (MNI).

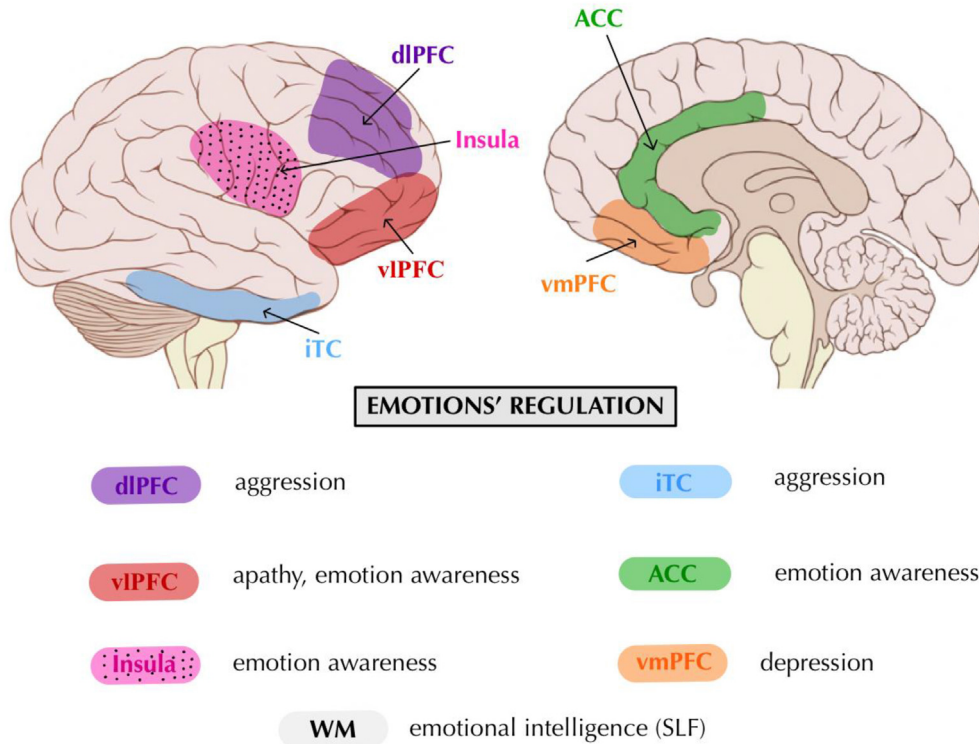


Fig. 2 – Brain areas and white matter tracts associated with different aspects of emotional regulation based on VHIS studies. dIPFC: dorsolateral prefrontal cortex, iTC: inferior temporal cortex, vIPFC, ventrolateral prefrontal cortex, ACC: anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, WM: white matter, SLF: superior longitudinal fasciculus (Brain image is adapted from work by Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist Creative Commons Attribution 2.5 License 2006).

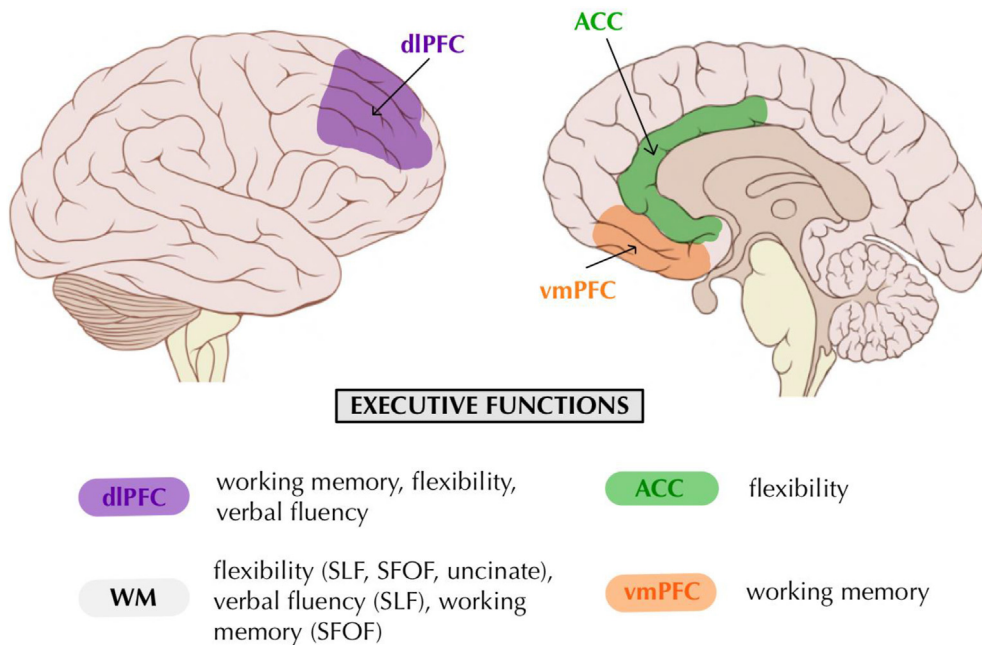


Fig. 3 – Brain areas and white matter tracts associated with different executive functions based on VHIS studies. dIPFC: dorsolateral prefrontal cortex, ACC: anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, WM: white matter, SLF: superior longitudinal fasciculus, SFOF, superior frontal occipital fasciculus (Brain image is adapted from work by Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist Creative Commons Attribution 2.5 License 2006).

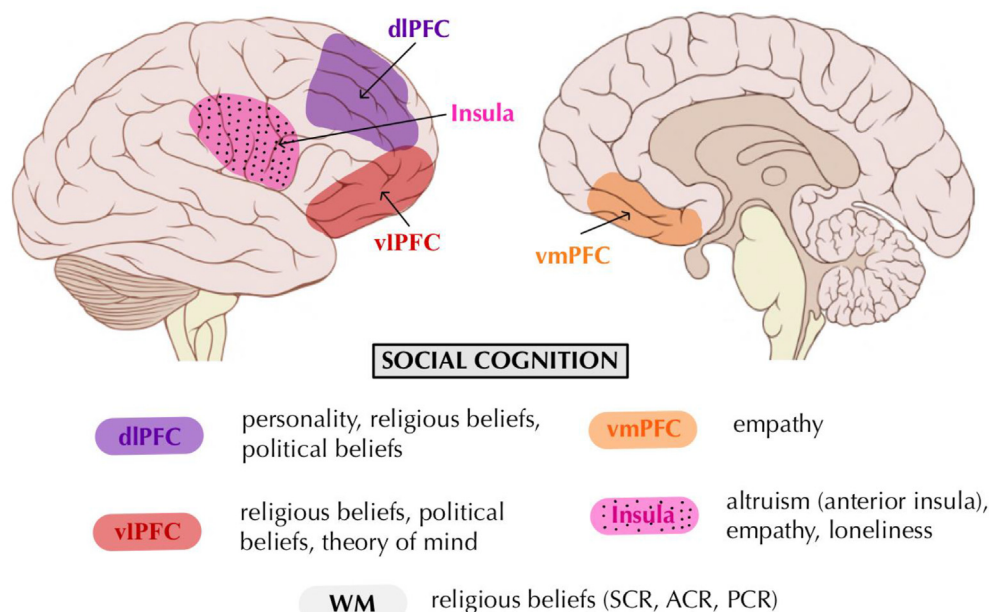


Fig. 4 – Brain areas and white matter tracts associated with different social cognition functions based on VHIS studies. dlPFC: dorsolateral prefrontal cortex, vmPFC: ventromedial prefrontal cortex, WM: white matter, SCR, superior corona radiata, ACR, anterior corona radiata, PCR, posterior corona radiata (Brain image is adapted from work by Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist Creative Commons Attribution 2.5 License 2006).

the Delis–Kaplan Executive Function System (D-KEFS) tests. In particular, dlPFC lesions resulted in lower IQ scores, which represent a rough estimate of the *g* factor. The effect of pTBI on IQ outcomes is mediated by the Val66Met single nucleotide polymorphism (SNP). Although there were no differences in intelligence scores between the Val/Val and Val/Met genotype groups before pTBI, the Val/Met group had better-preserved intelligence than the Val/Val group post injury (Barbey, Colom, Paul, & Grafman, 2014). Other variations of the brain-derived neurotrophic factor (BDNF) gene, namely the rs7124442 and rs1519480 SNPs, accounted for 5% of the variance in AFQT scores independent of other significant predictors (Rostami et al., 2011), further contributing to the recovery of intelligence post-pTBI.

More recently, changes in AFQT across all four study phases were investigated (Cohen-Zimmerman et al., 2018), revealing that, while exacerbated intellectual decline following pTBI occurred when the veterans were between their mid-30s to their early 60s (between P2 and P3), there was no evidence of subsequent accelerated cognitive decline later in life (between P3 and P4). These findings mirror what has been recently observed in other populations, where the effects of midlife vascular change are most predictive of later dementia (Gottesman et al., 2017). A more recent paper on the VHIS sample showed that childhood socioeconomic status (determined by parental occupational status and education) can also play a role in predicting both pre- and post-injury intelligence scores, accounting for 4.3–9.2% of the variance in intelligence across the study phases (Cohen-Zimmerman et al., 2019).

These results suggest that intelligence, genetics, and socio-economical status may play a role in recovery of function

following a TBI, and these factors should be considered when planning/charting individualized therapies.

2.2.2. Fluid intelligence and reasoning

Fluid intelligence refers to the ability to reason and solve new problems independently of previously acquired knowledge. Fluid intelligence represents a crucial component of the Cattell-Carroll intelligence framework (Carroll, 1997). Together with crystallized intelligence, memory, and speed processing, fluid intelligence constitutes a set of broad cognitive abilities, more specific than general intelligence. Previous neuroimaging studies (Gray et al., 2003) found that fluid intelligence is mediated by brain regions that support attentional and executive control, including subregions of the prefrontal cortex. The generalized factor of fluid intelligence (g_f , measured using the matrix reasoning, block design, and picture completion subtests of the WAIS-III) appears dependent upon a fronto-parietal network localized in the right hemisphere, supporting its association with executive functions (Barbey, Colom, Paul, Chau, et al., 2014).

The related concept of reasoning was also addressed in several studies. Two studies administered a similar test, in which participants were tasked with determining whether certain syllogisms were logical, with some containing neutral and others containing emotional content. Lesions to the orbital and polar prefrontal cortex (PFC) were associated with deficits in emotional content reasoning (Goel et al., 2017). A double dissociation was found between these frontal cortices and the parietal lobes with respect to emotional versus neutral content reasoning, with parietal lobe lesions resulting in greater impairment of neutral content reasoning (Eimontaite et al., 2018).

Table 2 – Key findings from the past nine years of VHS research. This table serves as a visual summary of the latest VHS findings regarding associations between lesion location and behavioral outcome. While lesion studies can guide us toward a potential causal association between brain area and associated behavior, it is important to note that these associations are dynamic and that other studies might have completed this network with other regions.

Affected function	Lesion site
Emotion regulation & social cognition	
<i>Emotion's awareness</i>	
Impairment in facial emotion recognition	mPFC, ACC, left insula and temporal areas
Recognizing unpleasant emotions	PFC
Recognizing pleasant emotions	PFC and left temporal cortex
Alexithymia	Anterior insula
Simultaneous non-emotional language	Inferior frontal gyrus
<i>Implicit bias</i>	
Social bias	PFC
<i>Theory of mind</i>	
Affective theory of mind	Left vmPFC
Cognitive theory of mind	Right dlPFC
<i>Empathy</i>	
Lower empathy	Posterior temporal lobes, vlPFC and insula
<i>Altruism</i>	
Altruistic attitudes	Anterior insula
Increased donations	Dorsomedial parietal cortex
Decreased donations	Right PSTS and middle temporal gyri
Increased altruistic punishments	dmPFC
Decreased altruistic punishments	Right perisylvian and left temporo-insular cortex
Atypical third-party punishment (TPP)	dmPFC, vmPFC, and dlPFC and right intraparietal
Association of TPP/concept formation	Left PFC
Association of TPP/altruism	Right dlPFC and SMA
<i>Aggression</i>	
Implicit aggression	dlPFC and ipTC
<i>Apathy</i>	
Increased apathy	vmPFC
<i>Loneliness</i>	
Less perceived loneliness	Right anterior insula and right PFC
<i>Political, & religious beliefs</i>	
Abnormal social behavior and thinking	vmPFC
Lower radicalism	vmPFC
More mystical experiences	dlPFC and middle/STC
Religious fundamentalism	vmPFC and dlPFC
Stronger relationship with God	Right vmPFC
Stronger connection to God	Right OBF
Executive functions	
<i>Working memory</i>	
Deficits in coordination of working memory maintenance, manipulation, and monitoring processes	medial OFC
Manipulating representations in working memory (letter-number sequencing) and in reasoning (arithmetic)	dlPFC
Manipulating verbal and spatial knowledge in working memory (letter-number sequencing; spatial span backwards)	Left dlPFC
Verbal and spatial reasoning (arithmetic; matrix reasoning)	Right dlPFC
Lower monitoring working memory performance	Right vlPFC, right IPC, and right MTG
Lower manipulating working memory	Left angular gyrus, left superior parietal cortex, left superior temporal gyrus, right dlPFC and right SFOF
Lower verbal/numeric working memory	Left angular gyrus, left superior parietal cortex, left superior temporal gyrus, right dlPFC, right SFOF, and right superior parietal cortex
Lower spatial working memory	Right dlPFC, right superior parietal cortex, and right SFOF
<i>Inhibition and cognitive flexibility</i>	
Relationship between general intelligence and EF	Left PFC, left dlPFC, ACC, inferior and superior parietal lobe, superior longitudinal/arcuate fasciculus, SFOF and uncinate fasciculus
Fluid intelligence and working memory	Right ipC, right dlPFC, right SFOF, right superior parietal cortex
<i>Recovery of executive functions</i>	
Verbal fluency impairment	PFC and SLF

Table 2 – (continued)

Affected function	Lesion site
Intelligence	
<i>General intelligence</i>	Fronto-parietal network including dlPFC
<i>Emotional intelligence</i>	Fronto-temporo-parietal network and SLF
Generalized factor of fluid intelligence	Right fronto-parietal network
Deficits in emotional content reasoning	OFC and parietal cortex
Deficits in neutral content reasoning	OFC and parietal cortex
Impaired transitive inference reasoning	Parietal cortex
Poorer abstract reasoning skills	Left lateral PFC
Social problem solving	Fronto-parietal network
Psychiatric related	
<i>Anxiety</i>	
Increased anxiety	Left middle, inferior and superior temporal lobe, hippocampus, fusiform regions, inferior occipital lobe, parahippocampus, amygdala, insula, dlPFC
Depressive symptoms	
Increased anhedonia	Right vlPF
Increased crying	Right vlPF
Decreased suicide	Left lateral PFC
Personality	
Higher neuroticism	dlPFC
Lower self-discipline	dlPFC
Lower conscientiousness	dlPFC
Increased Machiavellianism	Left dlPFC

Another study evaluated transitive inference reasoning that requires the examination and comparison of a given number of relational pairs to understand group hierarchy. This complex cognitive ability was significantly impaired in patients with parietal cortex lesions compared to the right lateral PFC lesion group and healthy controls (Waechter et al., 2013).

2.2.3. Emotional intelligence

The neural architecture of emotional intelligence was explored in two VHIS studies. By analyzing the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) scores, obtained in P3 of the VHIS, both studies revealed that emotional intelligence is associated with a core network of frontal, parietal, and temporal structures that also mediate social and executive processes (Barbey, Colom, Paul, & Grafman, 2014; Operskalski et al., 2015).

First, emotional intelligence was associated with a left-lateralized network comprised of the extrastriate region within the posterior temporal cortex, posterior superior temporal sulcus, temporoparietal junction, orbitofrontal cortex, and the superior longitudinal fasciculus (SLF) that connects the frontal and parietal cortices. Emotional intelligence was also found to share anatomical substrates with the left perisylvian language network, indicating that it relies on systems utilized for crystallized intelligence, i.e., intelligence based on learning and past experiences (Barbey, Colom, Paul, Chau, et al., 2014). Next, separate facets of emotional intelligence (i.e., perceiving, using, and managing emotions) were shown to be supported by distinct brain regions within the frontal, temporal, and parietal cortices (Operskalski et al., 2015). These results were confirmed in subsequent studies, where at the structural level, emotional intelligence was found to be positively correlated with gray matter volume in the insula and prefrontal areas (Killgore et al., 2012; Tan et al., 2014).

Taken together, these studies support an integrative framework for understanding the cognitive and neural architectures of executive, social and emotional processes.

2.3. Emotions regulation

2.3.1. Emotions recognition & awareness

Being able to experience and recognize emotions in ourselves and others is crucial for human survival. Emotions, together with cognition, help individuals interact with others and integrate into society (Brooks, 2011; Cosmides & Tooby, 2000; Ekman & Davidson, 1994; Lerner & Arsenio, 2000; Nummenmaa et al., 2012). Therefore, impaired emotions processing presents an additional impediment to recovery from pTBI.

The ability to understand the emotions of another person is a fundamental social skill that can be impaired in individuals suffering from pTBI. Dal Monte et al. used the Facial Expression of Emotion test to assess the recognition and naming of basic emotions conveyed by facial expressions (Ekman & Friesen, 1976). The findings revealed that individuals with pTBI performed worse than normal controls in recognizing unpleasant emotions. Voxel-based lesion-symptom mapping (VLSM) analysis showed that their impairment in facial emotion recognition was due to damage in a bilateral fronto-temporo-limbic network, including the mPFC, anterior cingulate cortex, left insula, and temporal areas. More specifically, poor recognition of unpleasant emotions was associated with damage to the bilateral anterior regions of the PFC, whereas failure to recognize pleasant emotions stemmed from damage to the bilateral posterior PFC and left temporal regions. These findings add empirical evidence to the conclusion that the ability to read pleasant and unpleasant emotions in other people's faces is a complex process that not

only involves a common network encompassing the bilateral fronto-temporo-limbic lobes, but also relies on distinct brain regions depending on the faces' positive or negative emotional valence.

Another line of VHIS studies investigated the neurocognitive underpinnings of alexithymia (Hogeveen & Grafman, 2021). Alexithymia is a clinical condition characterized by impaired awareness of one's emotional states. Alexithymia has profound effects on individuals' mental health and social interactions. Recent computational models suggest that impaired anterior insula functioning may contribute to alexithymia (Quattrocki & Friston, 2014; Seth, 2013). In a recent VHIS paper, Hogeveen, Bird, et al. (2016) aimed to identify the neurocognitive impairment(s) that lead to alexithymia. Using the Toronto Alexithymia Scale [TAS-20; (Bagby et al., 1994)], the researchers indexed the alexithymia levels to understand whether alexithymia can be acquired after damage to the anterior insula. First, the results showed that patients with >15% damage to the anterior insula had higher alexithymia levels relative to all other groups (patients with <15% damage to the anterior insula, patients with no damage to the anterior insula, and healthy controls). Second, a multiple linear regression model indicated that greater anterior insula damage predicted increased alexithymia after controlling for the other regressors (anterior cingulate cortex, ACC damage; total lesion volume). Taken together, these findings suggest that prominent anterior insula damage results in increased alexithymia, providing additional evidence that this region supports emotional awareness.

Given that alexithymia is associated with poorer regulation of one's emotions, decreased treatment response, and increased burden on caregivers, a subsequent study investigated the relationship between alexithymia and language (Hobson et al., 2018). While clinically important, the etiology of alexithymia is still a matter of debate, with several authors arguing for multiple "routes" to the impaired understanding of one's own emotions, which may warrant grouping alexithymia into distinct subtypes. While previous studies supported the role of impaired interoception (perceiving bodily states) in the development of alexithymia, Hobson et al.'s study assessed whether acquired language impairment following pTBI and damage to language regions may predict alexithymia. Neuropsychological testing revealed that poor performance on a non-emotional language task, such as object naming, was associated with alexithymia, specifically with difficulty identifying one's own emotions. Both region-of-interest and whole-brain lesion analyses revealed that damage to the language areas in the inferior frontal gyrus was associated with the presence of both language impairment and alexithymia. These findings are consistent with the framework for acquired alexithymia that incorporates both interoceptive (Gu et al., 2013) and linguistic processes (Hobson et al., 2018), and supports the idea that brain injury may result in alexithymia via impairment in more basic processes, as well as the language processes involved in the expression of the condition.

2.3.2. Aggression

Increased aggression is common after TBI, and may persist after cognitive recovery (Tateno et al., 2003). Maladaptive

aggression and violence are associated with dysfunction of the prefrontal and temporal cortices (Forbes & Grafman, 2010; Seidenwurm et al., 1997; Yang & Raine, 2009), but such dysfunctional behaviors are typically measured by explicit scales and clinical history. However, it is well known that items on explicit scales, that probe sensitive topics—such as aggressive thoughts and behaviors,—may not reveal true tendencies. Before our study, only one behavioral study had investigated implicit attitudes toward aggression. This evidence suggested that explicit measures of violence are not as sensitive as the implicit measures in predicting aggression related to criminal activity (Banse et al., 2015; N. S. Gray et al., 2003). For example, psychopathic murderers (compared to non-psychopathic murderers) showed a more positive implicit attitude toward aggression (N. S. Gray et al., 2003).

To address the potential bias in self-reports, Cristofori and colleagues (Cristofori, Zhong, et al., 2016) investigated the neural basis of implicit attitudes toward aggression using a modified version of the Implicit Association Task [IAT; (Greenwald et al., 1998)]. This study found a more positive implicit attitude toward aggression among individuals with lesions to the dlPFC and inferior posterior temporal cortex (ipTC). Furthermore, executive functions were involved in regulating implicit attitudes toward violence and aggression. These findings highlight the role played by dlPFC and ipTC in modulating implicit attitudes towards violence and demonstrate the crucial involvement of these areas in the pathogenesis of aggressive behavior, alongside the vmPFC that had previously been reported to mediate explicit aggression (Blair, 2010; Chester et al., 2017; Grafman et al., 1996). The dlPFC has a key role in downregulating behaviors (Koechlin et al., 2003), and our results are consistent with this hypothesis. In fact, we found that damage to the dlPFC is associated with a more positive implicit attitude toward aggression. These results suggest that interventions aimed at increasing cognitive control, for instance, using cognitive behavioral therapies, could reduce aggressive behavior (Landenberger & Lipsey, 2005).

2.3.3. Apathy

Another common deficit observed after TBI is apathy. Apathy consists of reduced goal-directed behavior and is common after lesions to the vmPFC or with temporal lobes (see e.g., (Klüver & Bucy, 1939; Lilly et al., 1983)). Human and non-human primate studies indicate that the vmPFC plays a crucial role in stimulus valuation, that is, computation of the subjective reward value of a stimulus (Padoa-Schioppa & Assad, 2006; Rangel & Clithero, 2014). Recently, Hogeveen, Hauner, et al. (2016) investigated whether the association between vmPFC damage and increased apathy is driven by impaired valuation. An auction task was used to measure valuation, and apathy was assessed via the ratings of patients' day-to-day behavior provided by their caregivers. VLSM analysis confirmed that the vmPFC was associated with impaired valuation and that patients with damage to this region demonstrated increased apathy relative to patients with lesions in the dmPFC and other brain regions, as well as compared to healthy controls. In addition, the association between vmPFC damage and apathy was mediated by impaired valuation, with no effect as a function of dmPFC

damage. With respect to valuation, previous studies have speculated that, in addition to stimulus valuation, vmPFC codes for the level of confidence in decision processes (De Martino et al., 2013; Kepecs et al., 2008). It would thus be reasonable to hypothesize that patients with vmPFC lesions exhibit apathy due, at least partially, to a lack of confidence in their stimulus valuations. The task used in the VHIS study did not allow us to disentangle stimulus valuation from decision confidence. Therefore, future studies should clarify the distinct contributions of both variables and their interaction in guiding goal-directed behavior. With respect to apathy, goal-directed behavior requires the contribution of several neurocognitive abilities, and damage to brain regions beyond the vmPFC might be associated with apathy (Arnould et al., 2013; Levy & Dubois, 2006). Future work will thus be needed to clarify other potential causes of apathy in patients with TBI. Providing evidence that damage to the vmPFC valuation system is one possible cause of apathy, the presented study can provide insights into designing targeted interventions for reducing apathy in TBI patients with lesions to the vmPFC. Previous research has identified other brain regions (e.g., dlPFC) as critical for moderating valuation processes together with the vmPFC (Hare et al., 2009; Kirk et al., 2011). For TBI patients, interventions that indirectly manipulate vmPFC activity (TMS, or tDCS) might help and regularize stimulus evaluation processing. Based on the present study, such work has the potential to ease goal-directed behavior and improve long-term functional outcomes. Taken together, these results point to the valuation-based mechanism underlying the relationship between vmPFC integrity and apathy, bridging the findings from the clinical literature and neuroeconomics research.

2.4. Executive function

Executive function (EF) impairments following TBI are a common finding that significantly complicates patients' lives. EFs are multifaceted and include cognitive flexibility, speed of processing, planning, reasoning, working memory, inhibitory control, and problem-solvings (Andrés, 2003). EFs are intimately related to the PFC. But the PFC is not exclusively involved in EFs, nor are EFs the product of only the PFC. Multiple cortical and subcortical regions connected to the PFC have been found to form extended executive neural networks (Andrés, 2003; Champod & Petrides, 2007; Collette et al., 2006) contributing to various aspects of EF. Moreover, more recently, even the cerebellum has been reported to have a role in EFs (Beuriat, Cristofori, et al., 2022). CT imaging and cognitive testing conducted in Phases 3 and 4 of the VHIS have allowed us to explore and specify the role of some of these cortical and subcortical regions in the networks that mediate EFs, as well as their role in the recovery of function after pTBI.

2.4.1. Working memory

Among all EFs, working memory (WM) is perhaps one of the most studied. WM is a complex function that involves different cognitive operations (maintenance, manipulation, and monitoring), that can be performed on information in different modalities (verbal and spatial). Maintenance refers to the temporary online retention of information in WM and is

measured by simple retention tasks (e.g., the digit-span forward task). Manipulating items in WM refers to the rearrangement and transformation of representations for goal-directed behavior and is measured by active retention tasks (e.g., the letter-number sequencing task). Monitoring serves to update novel information, focusing on task-relevant items, and eliminating irrelevant ones. The joint maintenance, manipulation, and monitoring of items in WM are probed by executive control tasks that draw upon multiple components of working memory (e.g., the n-back task).

In a study exploring the role of the orbitofrontal cortex (OFC) in WM, Barbey et al. (2011) reported several main findings: 1) medial OFC lesions were associated with reliable deficits in executive control functions underlying the joint maintenance, manipulation, and monitoring of information in WM, particularly at high levels of cognitive load; 2) medial OFC lesions were not associated with pervasive deficits on tests of WM maintenance or manipulation; 3) medial OFC lesions were not associated with reliable deficits on tests of verbal or spatial reasoning; 4) lateral OFC lesions did not cause significant impairments in WM functions. Together, these results indicate that the neural architecture of the medial OFC is computationally necessary for the coordination of WM maintenance, manipulation, and monitoring processes (Barbey et al., 2011). In a related study, this time exploring the dorsolateral PFC (dlPFC), Barbey et al. reported several main findings: 1) unilateral dlPFC is not necessary for WM maintenance, monitoring, or for tasks that measure WM performance under high cognitive load; 2) the dlPFC is important for manipulating representations in WM (letter-number sequencing) and in reasoning (arithmetic); 3) the left dlPFC is necessary for manipulating verbal and spatial knowledge in WM (letter-number sequencing; spatial span backwards), while the right dlPFC is critical for verbal and spatial reasoning (arithmetic; matrix reasoning). Together, these results indicate that the dlPFC mediates specific processes for manipulating cognitive representations (in the verbal and spatial domain) and therefore supports a domain-general model of the functional organization of the dlPFC (Barbey, Koenigs, et al., 2013). The same authors then used whole-brain VLSM analysis to explore brain networks supporting different subtypes of WM (Barbey, Colom, Paul, & Grafman, 2014). They identified other key brain regions in addition to the ones reported above. Impaired monitoring of WM was associated with damage to the right ventrolateral PFC (vlPFC), right inferior parietal cortex, and right middle temporal gyrus. Moreover, impaired manipulation of stimuli in WM was associated with damage to the left angular gyrus, left superior parietal cortex, left superior temporal gyrus, right dlPFC, and the right superior fronto-occipital fasciculus. Finally, lower verbal/numeric working memory performance was associated with damage to the left angular gyrus, left superior parietal cortex, left superior temporal gyrus, right dlPFC, right superior fronto-occipital fasciculus, and parietal cortex. Poorer spatial WM performance was associated with damage to the right dlPFC, right superior parietal cortex, and right superior fronto-occipital fasciculus.

To summarize, medial (but not lateral) OFC is crucial for maintenance, manipulation, and monitoring WM processes, while dlPFC is devoted to manipulating verbal and spatial

information in WM. While bilateral OFC is involved in different aspects of WM, other brain regions play a specific role in the monitoring of information (such as right vlPFC, right inferior parietal, and right middle temporal gyrus) or in manipulating information (left angular gyrus, left superior temporal cortex, left parietal cortex, right dlPFC, right superior fronto-occipital fasciculus, and right superior parietal cortex). These data are in accordance with models in neuroscience that consider WM to be at least partially supported by the frontoparietal cortex, included in the default mode network, a system mediating cognitive control, among other functions (D'Esposito et al., 1995; Murphy et al., 2020; Palva et al., 2010; Pessoa et al., 2002).

2.4.2. Inhibition & cognitive flexibility

One of the special features of the VHIS is that the participants were administered many neuropsychological tests so that investigators could not only study each function separately but also investigate how these different functions might be related to one another and whether they are supported by separate or distinctive neural networks. Barbey et al. studied the relationship between general intelligence and EFs (Barbey et al., 2012). They showed that EFs shared a distributed network of brain regions with general intelligence. This network was localized in the left hemisphere and included frontal (lateral frontopolar cortex, anterior PFC, dlPFC, anterior cingulate/medial PFC) and parietal cortices (inferior and superior parietal lobe) and white matter fiber tracts (superior longitudinal/arcuate fasciculus, superior fronto-occipital fasciculus, and uncinate fasciculus) that connected these areas into a coordinated system. Their analysis also identified cortical areas that were specific to each high-level domain. Given this unique connectivity pattern and specialization in a wide variety of high-level processes, the authors provided strong evidence that the fronto-parietal network can function as a source of integration and top-down control in the brain (Barbey et al., 2012). In another study, the same authors examined the relationship between fluid intelligence and WM (Barbey, Colom, et al., 2013). They reported that these two aspects of cognition shared a common anatomical substrate in the right hemisphere, that included the right inferior parietal cortex, right dlPFC, right superior fronto-occipital fasciculus, and parietal cortex. None of the left hemisphere regions associated with WM performance were found to be associated with fluid intelligence.

2.4.3. Recovery from EF deficits

Cristofori et al. focused on the recovery of executive functions and on the role of white matter pathways in this process in particular (Cristofori et al., 2015). They confirmed that both gray and white matter lesions can lead to impairment of EFs. But more interestingly, they provided strong evidence that the relative contribution of white and gray matter depends on the property of the EF tasks. Although both lesions to the PFC and to the superior longitudinal fasciculus (SLF) impaired performance on the Verbal Fluency test, the white-matter (SLF) lesions predicted the functional outcome better than the gray matter (PFC) lesions (Cristofori et al., 2015).

More recently, Beuriat et al., 2020 (Beuriat et al., 2020) investigated whether the cerebellum plays a critical or supportive role in executive processes in adults. There have been

multiple reports of EF deficits in patients with cerebellar lesions [for a review see (Strick et al., 2009)]. Beuriat et al. hypothesized that EF deficits would be milder in patients with lesions limited to the cerebellum compared to cases of brain damage involving not only the cerebellum but also cerebral cortical areas. Results showed that participants with cerebellar lesions which extended to the cerebral cortex performed similarly to controls on the EF tests but were significantly impaired on the WM. When the authors examined a sub-group of participants with large cerebellar lesions but minimal lesions in the cerebral cortex, they found that those patients performed similarly to the healthy controls on WM. Thus, the cerebellum may not be critical for EFs in adults, but could play a supportive role characterized by its computing of the motor requirements when EF processing is required.

EFs appear to rely on a specialized but significantly interconnected fronto-parietal network. Also, white matter damage may further hinder EF recovery by altering and degrading signal transmission between cortical areas within the functional network. The cerebellum appears to play a supporting role in EF by mediating the motor planning.

2.5. Social cognition

Social cognition/neuroscience research has emerged over the past 30 years to play an important role in helping us understand the brain bases of human social behavior. Particularly in Phases 3–4, we have studied aspects of social behavior ranging from implicit bias to religious belief. Below we describe those studies.

2.5.1. Implicit Bias

Researchers studying social cognition face several biases that could confound their results, such as social desirability bias. An effective way to overcome this kind of bias is to study social cognition using implicit techniques. The IAT (Greenwald et al., 1998) is one of the most common implicit tasks, used to investigate social attitudes, without relying on explicit questionnaires or tasks [see for instance (Knutson et al., 2007; Luo et al., 2006; Milne & Grafman, 2001; Schiller et al., 2016)]. Studies using the IAT have suggested that the vmPFC plays a crucial role in regulating implicit biases. For instance, patients with lesions to the vmPFC did not show any gender stereotyping (Milne & Grafman, 2001).

During P3, a study explored the relationship between genes, lesions, and implicit social biases (Forbes et al., 2012). The gene under investigation was the brain-derived neurotrophic factor (BDNF) known for its role in regulating synaptic connections (Huang & Reichardt, 2001), neural growth (Binder & Scharfman, 2004; Leibrock et al., 1989), and synaptic plasticity (Lu, 2003; McAllister et al., 1995). Forbes et al. (2012) found that pTBI patients and controls demonstrated comparable levels of implicit bias, but whereas the propensity towards implicit bias in the Met/Val patient group was proportional to the extent of the OFC lesion, OFC lesion size had no effect on the implicit bias in the Val/Val group. When the tendency to explicit bias was assessed in the patient sample, BDNF genotype was found to show a significant interaction with the dlPFC lesion size. Notably, the OFC lesion size and BDNF genotype did not modulate explicit bias; the

dlPFC lesion size and BDNF genotype did not modulate implicit bias (nor did other medial or lateral regions). These findings suggest that the genetic predisposition affects implicit bias via PFC plasticity following TBI, and that plasticity within specific PFC regions regulates the type and degree of implicit bias that individuals might have. These findings emphasize the importance of understanding the interaction between genetic predispositions and neural substrates critical for regulating behavior, as well as identifying the processes for maintaining and inhibiting negative perceptions of others. Nevertheless, it is important to note that the data regarding genetics and TBI is not consistent, and any finding reported here should be treated with caution.

2.5.2. Theory of mind

The ability to infer what others think or feel, known as “Theory of Mind” (ToM), is a central function of social cognition. Five VHIS studies investigated the neural underpinnings of ToM using different behavioral tasks administered during P3 of the VHIS. The first study (Leopold et al., 2012) focused on the ability to infer what other people are feeling (i.e., affective ToM) rather than what they are thinking (i.e., cognitive ToM). In this study, left lesions in the vmPFC were found to be associated with impaired affective ToM (measured by a task that requires detection of social faux pas), but not with cognitive ToM (measured via a second-order false belief task). The second study (Dal Monte et al., 2014) continued the investigation of the neural underpinnings of affective ToM, this time focusing on the ability to attribute mental states to others by looking at images of their eyes [Reading the Mind in the Eyes test; (Baron-Cohen et al., 2001)]. A VLSM analysis revealed that the left inferior frontal gyrus (IFG) mediated this affective ToM ability. More recently, Cohen-Zimmerman et al. (2021) focused on the cognitive ToM ability of mental state attribution. Using both VLSM and quantitative methods to measure the impact of a lesion on white matter disconnections, this study demonstrated that patients with lesions in the right dlPFC compared to controls presented with lower ToM performance, while patients with lesions to the temporoparietal junction (TPJ; reportedly, a key hub in the ToM network) performed no different than controls.

Another lesion study showed that the cerebellum played a prominent role in ToM (Beuriat, Cohen-Zimmerman, et al., 2022; Beuriat, Cristofori, et al., 2022). Specifically, left cerebellar damage (Crus 1 and lobule VI) altered cognitive ToM processing. Additional analyses revealed that the disconnection of the left thalamic projection and the left frontostriatal fasciculus was related to poor cognitive ToM processing. This study was the first to reveal direct causal neural evidence of cerebellar involvement in cognitive ToM. It supports the idea that social cognition relies on a complex neural network that includes the cerebellum. In addition, it presents evidence that the neural networks underpinning the different types of ToM can be distinguished.

Taken together, these studies provided much-needed patient-based data investigating the neural underpinnings of ToM. Moreover, the findings support the proposed distinction between neural networks which are involved in processing affective versus cognitive mental states, with the vmPFC being involved specifically in affective ToM tasks, while a larger

frontal network including the dlPFC and cerebellum are involved in cognitive ToM tasks.

2.5.3. Altruism

P4 investigators sought to identify the neural networks involved in reward and reinforcement by studying altruistic attitudes, donations, and punishments. One study was designed to explore the brain regions necessary for everyday altruistic attitudes and to investigate the influence of empathy and alexithymia on altruism (Chau et al., 2018). This study revealed that injury to the anterior insula (AI), but not the ACC nor the vmPFC, and increased alexithymia, were negatively correlated with resource-costly altruistic attitudes. It also found that the effect of AI lesions was moderated by alexithymia, but not by empathy. These findings support the importance of affective processing in altruism.

Moll et al. (2018) had used functional neuroimaging to show the relevance of brain structures concerned with reward and social bonding for altruistic decision-making. In a more recent lesion study, the relationship between altruistic donations versus punishments and cortical structures was investigated (Moll et al., 2018). This study did not reveal significant correlations between lesions and altruism. VLSM analyses revealed that bilateral lesions of the dorsomedial parietal cortex were associated with increased donations, whereas in the participants who experienced injury to the right posterior superior temporal sulcus and middle temporal gyri donations were decreased. Moreover, lesions of the right perisylvian and left temporo-insular cortex were correlated with a lower tendency towards altruistic punishments. On the other hand, greater propensity for altruistic punishments was seen in those with bilateral dmPFC lesions. The study found no association between altruistic decisions and personality changes after trauma. Another VHIS study found altruism to be associated with lesions in the right dlPFC (Glass et al., 2016). In this study, impartial third-party punishment was the primary targeted outcome. VLSM analysis revealed that patients with a propensity for atypical third-party punishment suffered lesions in the core regions involved in mentalizing (dmPFC and vmPFC) and executive function (bilateral dlPFC and right intraparietal sulcus). These processes contribute to evaluating the legal responsibility and selecting the appropriate punishment. Altruism and concept formation predicted 39% of the variance in atypical third-party punishment in participants with pTBI. Third-party punishment was associated EF in individuals with lesions in the left PFC and was correlated with altruism in individuals with lesions in the right dlPFC extending into the supplementary motor area (Glass et al., 2016). These findings have clinical implications, as early-onset PFC damage can result in symptoms that resemble psychopathy in individuals that otherwise have normal cognitive abilities (Koenigs et al., 2011). These findings may also inform the legal system about the cognitive and social features of psychopathy to promote the adoption of judicial practices that improve the outcomes of rehabilitation and reduce recidivism in criminals.

2.5.4. Empathy

One of the necessary prerequisites for effective social interactions is empathy. Empathy enables us to perceive and

share the affective experiences of others (Singer & Lamm, 2009). Two main components characterize empathy: the *cognitive* one is the ability to represent and understand another individual's mental state or perspective (e.g., mentalizing or theory of mind); the *emotional* one is the ability to recognize and share another's emotional state, to distinguish between one's own and other's feelings, and to regulate emotion successfully (Decety, 2010; Decety & Jackson, 2004; Rankin et al., 2005; Shamay-Tsoory et al., 2009). Neuroimaging studies indicated that a number of brain structures, including the medial and lateral frontal regions, the posterior temporal lobe, and the insula support empathy (Decety & Lamm, 2006; Hein & Singer, 2008; Hynes et al., 2006; Jabbi et al., 2007; Rankin et al., 2005; Shamay-Tsoory et al., 2009). Previous to the VHIS study on empathy, no large-scale lesion studies have investigated the neural basis of emotional empathy. Empathy was assessed via the Balanced Emotional Empathy Scale [BEES; (Mehrabian, 1996)], a 30-item self-reported questionnaire (15 items worded positively such as "I very much enjoy and feel uplifted by happy endings"; and 15 items worded negatively such as "I cannot feel much sorrow for those who are responsible for their own misery"), on a 9-point agreement–disagreement scale. Evidence from P3 revealed that damage to the left and right posterior temporal lobes, vlPFC, and insula led to decreased empathy (Driscoll et al., 2012). This finding contributed to identifying key regions within the distributed network of brain areas that are involved in emotional empathy.

These findings provided further insight into the neural architecture of emotional empathy. Further research should focus on the distinct role of the regions processing emotional empathy, and how they interact. A better understanding of emotional empathy network modulations could help to better understand empathic disorders in different psychiatric and neurological populations.

2.5.5. Loneliness

Among the persistent psychosocial impacts of TBI is social isolation, which can present challenges to the quality of life after injury (Morton & Wehman, 1995). Previous studies indicated that individuals with TBI experience a reduced social support network and loss of social contact (Hoofien et al., 2001; Lezak & O'Brien, 1988), and this problem of social isolation can persist for years after injury. Recently, Cristofori and collaborators (Cristofori et al., 2019) performed VLSM analyses to investigate the potential causal effect of brain lesions on self-reported loneliness [UCLA Loneliness Scale; (Russell, 1996)]. They found that individuals with selective lesions to the right AI and right PFC were less likely to report loneliness compared to patients with selective lesions to the posterior cortex and the controls. Therefore, it appears that lesions to key regions involved in the processing of social pain (Cristofori et al., 2013; Eisenberger & Lieberman, 2004) act to lower the perception of loneliness. Moreover, self-reported loneliness was positively associated with executive dysfunction, apathy, disinhibition, and lower life satisfaction. This piece of knowledge is crucial since it indicates that lesions to regions of the social pain network (such as the anterior insula and PFC) could lessen the ability of individuals with TBI to perceive social isolation. Therefore, special attention should be given to this category of TBI patients, to prevent social isolation and

the subsequent cascade of negative cognitive and emotional effects.

2.5.6. Social problem-solving

Another aspect of social behavior is social problem-solving which refers to the ability to solve problems encountered in everyday social life (Dimitrov et al., 1996). This ecological approach to studying problem-solving focuses on social, emotional, and contextual factors involved during the process (Artistico et al., 2010; Diehl et al., 1995; Mienaltowski, 2011). According to this approach, the ability to solve a problem is modulated by different factors such as if the problem reflects situations faced in daily life, if the problem is meaningful or salient to the individual, how the individual integrates social and emotional information to guide effective behavior, and how adaptive a specific solution is given.

Patients with focal TBI provide a unique opportunity to study the neural mechanisms of social problem-solving, supporting the potential causal contribution of specific brain structures to a given behavior. Before the analysis using the VHIS dataset, the neural basis of social problem-solving was not assessed using lesion methods.

We studied social problem-solving by administering the Everyday Problem Solving Inventory (EPSI; (Cornelius & Caspi, 1987)) and we investigated how social problem-solving related to a broad spectrum of psychological variables, including psychometric intelligence [Wechsler Adult Intelligence Scale, WAIS (Wechsler, 1997b)]; emotional intelligence [Mayer, Salovey, Caruso Emotional Intelligence Test; MSCEIT (Mayer et al., 2008)], and personality traits [Neuroticism–Extroversion–Openness Personality Inventory, NEO-PI (Costa & McCrae, 2008)]. The advantage of this study was to conduct a holistic assessment of social problem-solving that examined the contributions of executive, social and emotional information, and personality traits. In fact, the role of personality traits, such as extraversion, agreeableness, and conscientiousness, in predicting an individual's ability to manage and resolve conflict in social problem-solving contexts was unexplored before. Social problem-solving appeared represented in a distributed fronto-parietal network. Consistent with this finding, other cognitive functions localized in this network, including working memory, processing speed, and emotional intelligence, were able to reliably predict EPSI scores (Barbey, Colom, Paul, Chau, et al., 2014).

2.5.7. Political & religious beliefs

We and others have described the importance of the human prefrontal cortex for social beliefs. In the next section, we will examine this association in more detail by targeting specific social belief systems like political and religious beliefs, two forms of belief that have played extraordinarily significant roles in the development of human social expression. Humans acquire all sorts of beliefs, and these beliefs (moral, political, and religious) shape their character and influence daily decision-making (Cristofori & Grafman, 2017).

The vmPFC plays a crucial role in evaluation processing, and patients with lesions involving the vmPFC have displayed abnormal social behavior and thinking (Mah et al., 2004). Cristofori et al. (2015) examined whether the vmPFC also modulates how individuals express political beliefs. Patients

with pTBI were tested on the Political Belief Task (Zamboni et al., 2009). This task involved rating 75 statements expressing political beliefs concerned with welfare, economy, political involvement, civil rights, war, and security. Participants rated each statement according to their level of agreement. The statement set could be reduced to three dimensions underlying political beliefs: radicalism (whether a statement was radical or moderate), individualism (whether a statement better reflected individual or societal concerns), and conservatism (whether a statement reflected conservative or liberal ideology). VLSM analysis found that patients with vmPFC lesions tended to score statements as less radical than healthy controls. Further, the authors divided the patients into three groups according to lesion location, namely, vmPFC, dlPFC, and parietal cortex, with the latter area chosen as the control lesion site. They found that the vmPFC, but not the dlPFC, group assigned lower radicalism scores to statements compared with the parietal and healthy control groups. These findings emphasize the pivotal role of the vmPFC in appropriately evaluating political beliefs and suggest that vmPFC lesions may lead to patients underestimating how radical certain social behaviors are.

Another kind of belief system that profoundly affects people's lives is religion. Religious beliefs emerged in conjunction with moral beliefs and motivate political, economic, and legal beliefs. Religious beliefs are often concerned with the existence of supernatural agents and phenomena that are difficult to assess in the laboratory. In the first study on mystical experience (subjectively believed encounters with a supernatural world), Cristofori, Bulbulia, et al. (2016) investigated pTBI patients and healthy volunteers. VLSM analysis showed that lesions to the frontal and temporal brain regions were associated with greater mystical experiences. Such regions included the dlPFC and middle/superior temporal cortex (TC). In a confirmatory group analysis, the researchers found that the dlPFC lesion group demonstrated increased mysticism. Notably, longitudinal analysis of pre-injury data (correlating with general intelligence and EF task performance) ruled out the potential confounding of the results by individual differences. These findings support previous reports linking EF to mystical experiences, and suggest that EF (particularly those aspects of EF that depend upon the dlPFC) contributes to the down-regulation of mystical experiences.

Mystical experiences diverge from religious beliefs, in the sense that someone can experience a mystical phenomenon even without prior religious beliefs. Previous research has identified the vmPFC as an area critical to representing religious beliefs (Asp et al., 2012). However, the means by which the vmPFC enables religious beliefs until recently remained uncertain. Zhong et al. (2017) hypothesized that the vmPFC represents diverse religious beliefs and that a vmPFC lesion would be associated with religious fundamentalism, or the narrowing of religious beliefs. To test this prediction, the authors assessed religious adherence with a widely-used Religious Fundamentalism Scale (Altemeyer & Hunsberger, 1992). The results showed that participants with dlPFC and vmPFC lesions expressed similar fundamentalist beliefs and that the effect of a dlPFC lesion on fundamentalism was significantly mediated by decreased cognitive flexibility and openness. These findings indicate that flexible and adaptive religious

commitment relies on the dlPFC, whereas the vmPFC could be potentially more involved in representing traditional and fundamental religious beliefs.

In monotheistic religions, religious beliefs also encompass the particular relationship an individual has with God. Individuals that demonstrate a strong personal relationship with God have been shown to exhibit an enhanced sense of control over their lives (Jackson & Coursey, 1988). A recent VLSM study by Cohen-Zimmerman et al. (2020) found that damage to the right vmPFC was associated with a stronger self-reported personal relationship with God, and that patients with damage to this region reported a greater sense of control compared to patients with damage to the posterior cortex, as well as to healthy controls. Moreover, the association between the vmPFC damage and a greater sense of control was mediated by a stronger personal relationship with God.

More recently, Cristofori et al. (2021) investigated the neural interplay between empathy and religious beliefs. Extending previous observations that the ToM network is recruited during prayer (Boyer, 2003, 2008), the authors found that pTBI patients with vmPFC damage reported higher scores on the God Image Inventory items probing their personal relationship with God (Lawrence, 1997), even when they were not praying. They also found that vmPFC and posterior superior temporal gyrus/temporo-parietal junction (pSTS/TPJ) lesions, mediated by the strength of the personal relationship with God, promoted more empathetic responses to others. These findings call for greater attention to the mechanisms by which religious cognition may modulate empathetic responses to others.

The neural underpinnings of religiosity were also studied in relation to attachment style. A VHIS study that focused on the association between the attachment style that people develop in infancy and the relationship with God (Cohen-Zimmerman et al., under review) found that individuals with secure attachment style exhibited a close connection to God regardless of brain damage. Moreover, a VLSM analysis showed that damage to the right OFC was associated with a stronger connection to God in individuals with secure, but not in those with non-secure attachment style.

In summary, the lesion studies of beliefs, that we described above, identify a network of brain regions involved in the production of political and religious cognition, including the dlPFC and vmPFC, as well as more posterior regions, such as the superior temporal cortex and pSTS/TPJ (default mode network), primarily in the right hemisphere. In addition, they clarified the functional relationship between social beliefs and executive control, emotional regulation, the rigidity of ideological commitments, as well as other aspects of social cognition. Such studies pave the way to better understanding these complex and unique human social phenomena. In addition, given the impact of the beliefs in our decision, understanding how beliefs are modulated following a TBI could help in targeting interventions to promote recovery.

2.6. Psychiatric symptoms

In addition to probing the impact of TBI on different aspects of cognition, the VHIS also investigated the effects of pTBI on anxiety and other mood disorders. TBI is generally considered to be a risk factor for psychiatric disorders (Gualtieri & Cox,

1991; Silver et al., 2001), especially related to anxiety (Hart et al., 2014; van Reekum et al., 1996). A better understanding of the psychiatric disorders related to TBI is crucial since it could lead to a better functional outcome for patients, and to a better understanding of the neural underpinning of these disorders. Individuals with brain lesions in cortical and limbic areas of the left hemisphere (including the middle, inferior, and superior temporal lobe, the hippocampus, and fusiform regions, along with the inferior occipital lobe, parahippocampus, amygdala, and insula) showed increased anxiety (Knutson et al., 2013).

Koenigs et al. (Koenigs et al., 2008; Koenigs & Grafman, 2009) reported that the amygdala and medial PFC were particularly relevant for post-traumatic stress disorder (PTSD), as lesions to these regions were associated with a significantly lower occurrence of PTSD compared to lesions to other brain areas. Fatty-acid amide hydrolase (FAAH) activity is associated with the extinction of aversive memories (Lutz, 2007) and arousal (Dlugos et al., 2010), two key components of PTSD. (Pardini et al., 2012) found that rs2295633, an SNP in the FAAH gene, modulates PTSD risks in participants with intact vmPFC. Also, the presence of the C allele (wild-type) of this SNP was correlated with more frequent recollections of traumatic events, including early childhood traumas.

Anhedonia is defined as a loss of pleasure usually associated with a reward and can be separated into consummatory anhedonia (deficits in the hedonic responses to rewards) and motivational anhedonia (decreased motivation to pursue rewards) (Pardini et al., 2020; Treadway & Zald, 2011) found that injury to the right vlPFC—which is involved in motivational aspects of reward—was correlated with anhedonia and more crying.

Horror combat experiences, which often result in PTSD, can predispose people to suicidal ideation and attempted suicide (Paradiso et al., 2016). Numerous studies reported an increase in suicidal thoughts after TBI (Bahraini et al., 2013; Mackelprang et al., 2014; Pardini et al., 2020) found that lesions to the left rIPFC can mitigate suicidal ideas independent of depression, PTSD, and global functioning. In another pTBI study (Paradiso et al., 2016), found that those who endorsed suicidal thoughts showed poorer emotional processing, were deployed to Vietnam at a younger age, and had lower education. These veterans also reported more negative experiences in social interactions after returning to the US. These findings suggest that the patients' distress may be at least partially mitigated by improving their coping styles, as well as emotional intelligence and competence.

A more recent study by Fremont et al. (2022) focused on the relationship between different types of repetitive behaviors (obsessions, compulsions, and tics) and cortico-striato-thalamo-cortical circuits. The authors found that the left dlPFC lesions were associated with a higher prevalence of compulsions, whereas lesions to the basal ganglia were associated with more frequent occurrence of tics.

Psychiatric disorders can hinder the recovery of function and decrease the quality of life, with the rIPFC and the dlPFC contributing to PTSD and obsessive-compulsive behaviors respectively. Moreover, genetics can influence the expression of these psychiatric disorders, as evidenced by the FAAH gene modulating PTSD risks in participants with intact vmPFC.

These studies provide information crucial for the development of individualized treatments (e.g., non-invasive brain stimulation) for patients, whose psychiatric disorders result from the concomitance of stressful events and neural lesions.

In the next section, we will focus on other aspects that can crucially impact recovery, such as personality traits, or caregiver burden.

2.7. Personality

Personality disorders, such as impulsivity or aggressiveness, and/or personality changes have often been associated with TBI to PFC (Cristofori, Zhong, et al., 2016; Grafman et al., 1996; Moley et al., 2022). The TBI model also offers an excellent opportunity to study the neural basis of personality constructs. Even though several studies have advanced the understanding of the physiological basis of individuality, consistent with a psychological constructionist approach [i.e., the theoretical perspective which argues that neural regions support the basic psychological functions underlying an extensive range of mental states (e.g., (Lindquist et al., 2012)], fewer studies have investigated whether the expression of different, independent dimensions of personality might rely on a shared neural network (Omura et al., 2005).

In two VHIS studies, damage to the dlPFC was found to impact personality traits. Forbes et al. (2014) used data collected in P3 to investigate neuroticism and conscientiousness, two of personality traits. This study found that bilateral dlPFC damage resulted in higher levels of anxiety and neuroticism and lower levels of self-discipline and conscientiousness, as measured by the NEO Personality Inventory (NEO-PI (Costa & McCrae, 2008)). More recently, (Cohen-Zimmerman et al., 2017) investigated the neural underpinnings of Machiavellianism, a personality trait marked by the use of manipulation and deception to achieve power, status, or wealth. In this study, data collected in P4 of the VHIS showed that damage to the left dlPFC resulted in increased Machiavellianism as measured by the Mach IV test (Christie & Geis, 1970). These studies provide direct evidence for the claim that frontal lesions may result in specific types of personality changes.

Achieving a better understanding of the personality changes that an individual with TBI could encounter may help develop more individualized therapy protocols. In line with this idea, specific brain lesions to the PFC might exacerbate certain personality traits such as anxiety and neuroticism, and may make individuals less inclined to comply with therapy/interventions.

2.8. Caregiver burden

Caregivers play a vital role in the healthcare system. For instance, caregivers in the US account for 30 billion hours of care/work and \$522 billion in healthcare costs yearly (Chari et al., 2015). Long periods of caregiving can induce negative consequences such as anxiety, depression, somatic symptoms, fatigue, sleep disorders, reduced marital satisfaction, social isolation, financial difficulties, and, more generally, decreased quality of life (Brickell et al., 2020). As a result of all these physical, emotional, social, and financial limitations associated with caregiving for a relative, the caregiver may

feel a burden (Zarit et al., 1986). Caregiver burden is associated with increased suicide, depression, anxiety, and lower quality of life in caregivers (Adelman et al., 2014; Lai et al., 2019). As discussed above, many TBI survivors face cognitive, neuro-behavioral, physical and social challenges that can affect the family unit, especially the primary caregiver.

In P4 of the VHIS, caregivers of participants with pTBI, who sustained their injury 40 years earlier, as well as caregivers of healthy Vietnam combat veterans (who served as controls), were studied (Guevara et al., 2016). In the VHIS dataset, caregivers' burden information was collected via the Zarit Burden Interview (Zarit et al., 1986). The Zarit Burden Interview is one of the most commonly used instruments to assess caregiving burden in clinical and research settings; it consists of 22 items probing different aspects of caregiver burden (e.g., financial limitation, lack of time, emotions, and feelings).

Our data allowed us to answer two specific research questions, namely (1) if patients' lesion location would modulate caregiver burden, and (2) if post-traumatic epilepsy [since epilepsy is a serious and continuing problem following TBI (Salazar & Grafman, 2015; Walker et al., 2015)] associated with TBI would increase caregiver burden.

Results showed that caregivers of participants with pTBI felt significantly more burden than caregivers of the controls. Also, caregivers of pTBI patients with lesions in the left dlPFC and dorsal anterior cingulate cortex (dACC) perceived a higher burden than caregivers of participants with lesions in other parts of the brain. Participants with lesions in these areas revealed impairments of behavior and cognition related to the dysexecutive syndrome, presenting with deficits in executive control, decision-making, monitoring of performance, and error detection, indicating that such deficits place a higher burden on caregivers.

Jabbarinejad et al. studied the caregivers of pTBI patients with post-traumatic epilepsy (PTE) (Jabbarinejad et al., 2021). They assessed caregivers' burden at 15, 45 and 50 years after the patients' pTBI. At all three periods time points, caregivers of PTE patients felt significantly more burden than caregivers of pTBI patients without epilepsy and caregivers of HC. Caregiver distress was associated with pTBI patients' cognitive decline, apathy, disinhibition, older age at epilepsy onset, and role limitation due to physical problems. In addition, patient disinhibition, emotional distress, and the patients' role limitation due to physical problems predicted greater caregiver burden. This kind of evidence can have important clinical implications. Clinicians should pay greater attention to caregivers of patients with lesions to the dlPFC and dACC, and associated post-traumatic epilepsy.

These studies highlight the need to incorporate caregiver assessment during the patient's clinical visits to improve the targeting and quality of social interventions post-TBI.

3. Discussion

3.1. Significance of the VHIS in general, and of phases 3 and 4 in particular

The data collected in the VHIS during P1 and P2 was instrumental in establishing specialized TBI units in military and

Veterans Administration hospitals. In addition, this body of research assisted many of the combat veterans who participated in the VHIS in meaningful ways, specifically by helping them obtain specialized medical care when they returned home. This benefit continued to be available through P3 and P4. From a research perspective, many of our later studies are crucial for a better understanding of recovery of function and brain plasticity.

We highlighted the importance of social cognition in our more recent studies. Social cognitive impairments can last a lifetime, and they need to be addressed by rehabilitation intervention programs by assisting brain injury patients to better re-integrate into society and their functional role at work. Such rehabilitation is particularly important, given the fact that social cognition deficits are less tolerated in our society compared to memory or language deficits. Our research suggests that social cognitive deficits represent one of the best predictors of long-term outcomes of brain injury.

The lesion studies reviewed here highlight a network of lesioned areas overlapping within the prefrontal cortex, which, in association with the posterior temporal lobe and the underlying white matter tracts, appear to critically regulate emotions, executive functions, and different aspects of social cognition, such as beliefs and social behaviors.

We remind the reader that there is a large literature corpus on each topic treated in this summary that has not been addressed. It is important to note that this manuscript aims to summarize the contribution of the VHIS to our current understanding of brain-behavior connection. While we acknowledge that other case studies-including Phineas Gage or H.M.- have made important contributions to the field, they fall outside the scope of this paper.

3.2. Improvements in lesion mapping

In recent collaborations (Ferguson et al., 2022; Jiang et al., 2022; Joutsa et al., 2022), we have contributed data from the VHIS to validate and exploit lesion network mapping strategies. The VHIS dataset could be further explored by performing multi-variate VLSM analysis, considering white and gray matter lesions in the same statistical models, and using AI methods, such as supervised/unsupervised machine learning, to analyze the data in a more efficient way. These complex models could consider the role of all the possible variables (lesion site and size, genetics, cognition, socio-economic status, caregivers, and social circle presence, etc.) on long-term recovery and to produce a more personalized description of individual cases. The VHIS is, of course, limited in significant ways by including the male-only sample, the use of CT scans instead of MRI (due to the metal retained in the brains of our participants), and the sample size, which, although considerable in some respects, is much smaller than samples collected as part of multicenter studies conducted today (albeit with less detailed evaluations).

3.3. How do these findings contribute to our overall understanding of the functions of the human brain?

The VHIS dataset provides a number of advantages for studying the potential causal relationship between the brain

anatomy and its functions. The participants include a homogeneous group of male Vietnam veterans that were healthy before the injury and the age- and education-matched control group consisting of Vietnam veterans that returned from the war without a brain injury and were healthy at the time of their evaluations. Additionally, preinjury intelligence scores are available for almost all the participants. Results from the VHIS have suggested that pTBI carries a high risk of life-long cognitive, emotional, and social impairments, providing a strong argument that such patients would benefit from long-term medical follow-up and rehabilitation interventions.

The VHIS was able to probe the long-term clinical, neuropsychological, and genetic variables only in subsets of the original P1 cohort, and we may well have had differing results if we had been able to examine the entire sample at all phases of the study. Besides a core clinical evaluation, each phase of the VHIS aimed to address emerging issues within cognitive and social neuroscience, neurology, and psychiatry. For instance, the need for an improved assessment of the extent of participants' brain lesions in P3 led to the development of the ABL software (Makale et al., 2002), which characterized lesions in terms of their volume and their intersection with regions from an anatomical atlas. The identification of white matter tracts (Mori et al., 2008) was later added, allowing for correlations between behavioral deficits and gray and white matter lesions.

As noted above, the results of the VHIS P2 evaluation led to the creation of the Defense and Veterans Head Injury Program (DVHIP, later morphed into the Defense and Veterans Brain Injury Program), as well as the establishment of TBI units and programs at major military and VA Hospitals. Until the creation of the DVHIP, there had been no US national systematic program providing TBI-specific management and rehabilitation support within the VA and military medical programs (Salazar et al., 2000). The DVHIP was created as a clinical program focused on treatment, rehabilitation, and care management. It had the support of the United States Department of Defense, the Department of Veteran Affairs, the Brain Injury Association, and the International Brain Injury Association. The main objectives of the program now are to guarantee that military and veteran TBI patients receive standardized TBI-specific neurobehavioral evaluations, treatment, and follow-up, while at the same time helping to define optimal acute and chronic care for victims of TBI nationwide, as well as conducting rehabilitation and clinical treatment trials (Raymont et al., 2011). Thus, not only has the VHIS been vital in its contribution to our understanding of the functions of the human brain, it gave birth to programs that facilitated the early identification of TBI in military personnel and substantially improved their long-term management – a worthy legacy of Dr. Caveness's original vision. Of course, none of these advances would have occurred without the selfless contribution of the VHIS participants studied over the last 40 years. We are forever grateful to them. The value of new longitudinal studies that include both clinical and experimental tasks and updated technologies for a better understanding of the functions of the human brain and the treatment of its disorders is undeniable. Improving on past studies, including the VHIS, requires a thorough understanding of how to set up such a study, bonding with the

participants, and a dedicated and knowledgeable team of clinicians and investigators.

3.4. Open questions

Lesion studies have been essential to many core theories in cognitive and behavioral neuroscience. Human lesion mapping studies have unique inferential strengths that are different from temporary manipulations (such as TMS/tDCS) or correlative measures of neural activity (such as fMRI, PET, EEG, MEG). Lesion mapping can contribute to an improved understanding of the extent of neuronal plasticity after brain damage and whether this plasticity is alike between different brain areas or whether some areas are more plastic than others. In addition, it remains to be seen whether genetic analyses can contribute to individualized therapy and maximize long-term recovery.

Lesions in humans typically affect both gray and white matter. Another avenue of research concerns the possibility of integrating white and gray matter volume loss in a single statistical model that suitably attributes variance to damage within brain regions or their connections to better understand the effects of the lesion on behavior.

Usually, we accomplish lesion tracing based on the decision of one or a few raters. Automated tools for lesion analysis are already available but they are impractical when structural neuroimaging presents major distortions or artifacts, or small deep lesions that can be difficult to detect. Developing better tools for segmenting and registering the extent of white and gray matter lesion damage in humans with TBI will be crucial to improve the accuracy of lesion mapping approaches.

Besides introducing modern modeling techniques and experimental tasks into future longitudinal studies of TBI, the use of state-of-the-art ecological tasks will be an option. Such data will include capturing internet behavior and data, cell-phone and digital watch probes, and recording participants' real-life behavior. While these latter techniques can appear quite invasive, there will assuredly be methods that will insure confidentiality regarding this form of data collection.

3.5. Limitation of the VHIS

Although lesion-mapping studies are fundamental in determining the relationship between brain structure and behavior, the studies reviewed here must be considered in the context of a few limitations. First, we were only able to study male Vietnam War veterans (even today, there are very few females experiencing pTBI in the military), and hence the results cannot be generalized to the general population (i.e., including females and younger populations as well as civilian closed TBI). In addition, the VHIS used CT scans rather than MRI (and not functional imaging) due to the presence of metallic fragments in the brain. While the VHIS participants had focal lesions, it is highly likely that the damage was not restricted to the area of the penetration. Lesions are likely to have affected tissue proximal to the lesion area and interfere with communications between proximal and distal brain areas. It is difficult to estimate the effects of the injury on brain connectivity without investigating the underlying activity of networks and tracts that may have become non-

functional. While methods such as fMRI and DTI could not be used in this sample (due to the presence of metal fragments for many of the study participants), the findings that arise for the VHIS were since corroborated by studies that did use DTI and fMRI in their methods [e.g., (Padmanabhan et al., 2019)]. Moreover, this data set was recently analyzed using methods looking at damage to white matter tracts (Cohen-Zimmerman et al., 2021; Cristofori, Bulbulia, et al., 2016; Cristofori et al., 2015), and using lesion network mapping techniques (Ferguson et al., 2019; Padmanabhan et al., 2019) which further strengthens the impact of the findings.

In addition, even though our cohort of patients is concerned with focal TBI, we cannot exclude that some of them also experienced blast-related injuries. The effects of pTBI can be accompanied by, or even potentiated by blast injury (Taber et al., 2006). Blast injuries can result in white matter changes, which have been linked to complex neurobehavioral syndromes including autism to schizophrenia. Unfortunately, blast-related injury often fails to show focal lesions in structural MRI (Graner et al., 2013). Functional neuroimaging can provide more useful information, but as mentioned above the VHIS cohort could not undergo functional MRI due to the presence of metal fragments. Surely, it would be interesting for further research to compare blast injury to closed and penetrating injury.

We understand that various biological processes have differing rates of recovery after brain injury and may resolve differently. Our studies simply do not have the fine-grained evaluations for each of the noted brain systems to make claims about their time-constrained responses to the original pTBI.

Testing the association between brain lesion and cognitive dysfunction in each voxel involves several individual tests and requires statistical correction for multiple comparisons. Most VHIS studies addressed this issue by applying the standard False Discovery Rate (FDR)- a method that quantifies the proportion of above-threshold results that can be expected to be false positives. An alternative way to address this issue would be to use a voxel-level family-wise error rate (FWER), a method that takes into account the probability of making one or more false positive errors among the entire set of tests. Voxel-level FWER does not align with VLSM interpretation, which never depends on a single voxel. The misalignment between standard FWER correction and VLSM interpretation makes standard voxel-level FWER correction conservative: if no inferences are made based on a single voxel, then a single false positive voxel cannot be responsible for an invalid inference about lesion-symptom relations. Due to these limitations, researchers (Mirman et al., 2018) have recently proposed to use continuous permutation-based FWER correction method to strengthen VLSM results and reduce error risk.

Another limitation relies on the fact that the AFQT scale was the only pre-injury cognitive measure available in our cohort of participants. Even if the AFQT is highly correlated with IQ, the AFQT is a narrow measure of a limited set of abilities that should not be equated with the intellectual processes measured by individually administered IQ tests [see (Roberts et al., 2000)].

We must highlight that the results summarized by this work complement neuroimaging and other patients' studies,

and do not provide an exhaustive list of all brain areas that can be involved in complex behaviors, emotion regulation, and beliefs. One of our dataset's prominent limitations is that our patients were all males drawn from a specific military population. However, recent studies in stroke patients of both genders drawn from the civilian population (Fox, 2018) provide support to the claim that these results can be generalized to a broader population. The VHIS findings replicate [for instance, see (Ferguson et al., 2022; Joutsa et al., 2022)] other similar studies of brain-injured patients with different etiologies using MRI scans. In addition, we have recently added Bayesian analyses to complement the frequentist analyses we have relied upon in the past to further validate our findings.

3.6. Lessons from the VHIS

The last decade of investigation using the VHIS dataset has continued to contribute to the scientific knowledge about a vast range of human abilities involving the social mind, such as emotion regulation, executive functions, and social cognition. The advantage of studying the social mind having such a well-controlled dataset, that not only has pre-injury data but also an appropriate matched control group is unique. As well-established lesion studies provide casual inference from structure to function, however, these later studies went beyond the simple structure-function relationship and looked at modeling social behavior including white matter pathways, genetics, and other cognitive functions that can influence the expression of a particular social behavior. In addition, these data provide unique information on caregivers' burden and the extent to which this burden may play a role in recovery and plasticity. Taken together, the knowledge acquired in the VHIS also has important implications in the clinical setting, for targeting individualized therapies following brain injury to minimize the deficits throughout life, and therefore reduce caregiver (and societal) burden. A final lesson from the VHIS was that adding new research for each phase of the VHIS in conjunction with a selected number of repeatable tests allowed the study to continue to make scientific contributions that retain their relevance over time.

CRediT authorship contribution statement

Irene Cristofori: Writing – review & editing, Writing – original draft, Conceptualization. **Shira Cohen-Zimmerman:** Writing – review & editing, Writing – original draft. **Frank Krueger:** Writing – review & editing, Conceptualization. **Roxana Jabbarinejad:** Writing – original draft. **Ekaterina Delikishkina:** Writing – review & editing. **Barry Gordon:** Writing – review & editing. **Pierre-Aurélien Beuriat:** Writing – original draft. **Jordan Grafman:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors have no conflict of interests to declare.

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