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Insulin and disorders of behavioural flexibility

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ABSTRACT

Behavioural inflexibility is a symptom of neuropsychiatric and neurodegenerative disorders such as Obsessive-Compulsive Disorder, Autism Spectrum Disorder and Alzheimer's Disease, encompassing the maintenance of a behaviour even when no longer appropriate. Recent evidence suggests that insulin signalling has roles apart from its regulation of peripheral metabolism and mediates behaviourally-relevant central nervous system (CNS) functions including behavioural flexibility. Indeed, insulin resistance is reported to generate anxious, perseverative phenotypes in animal models, with the Type 2 diabetes medication metformin proving to be beneficial for disorders including Alzheimer's Disease. Structural and functional neuroimaging studies of Type 2 diabetes patients have highlighted aberrant connectivity in regions governing salience detection, attention, inhibition and memory. As currently available therapeutic strategies feature high rates of resistance, there is an urgent need to better understand the complex aetiology of behaviour and develop improved therapeutics. In this review, we explore the circuitry underlying behavioural flexibility, changes in Type 2 diabetes, the role of insulin in CNS outcomes and mechanisms of insulin involvement across disorders of behavioural inflexibility.

1. Introduction

Behavioural processes are key to an organism's response to the environment and to each other. These behavioural processes are often conditioned either by reward or punishment and involve changes to learning, memory, attention and behavioural flexibility. Behavioural flexibility, or the adaptive change of behaviour in response to changing environmental contingencies, is compromised in numerous disorders, including those that emerge in early life such as Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and Tourette's Syndrome; those that emerge in adolescence, including schizophrenia and mood disorders; and those in later life including dementias. While many of these conditions share flexibility deficits, the treatment of flexibility as a discrete feature in its own right is a challenge, owing to the heterogeneous nature, severity and patterns of comorbid symptoms. Treatment options rely heavily on non-pharmacological therapies such as Cognitive-Behavioural Therapy (CBT), which aims to attenuate symptoms by altering the thoughts and responses to triggers. Pharmacotherapy includes Selective Serotonin Reuptake Inhibitors (SSRIs) but up to half of all patients fail to respond requiring new treatment approaches. Furthermore, the long lag time of three to six weeks before a behavioural change is elicited with SSRIs,

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leads to poor rates of treatment maintenance and low adherence. The aetiology of behavioural inflexibility is poorly understood, with factors including genetics, environment and specific life stressors all involved. Diagnostic criteria are based upon presentation. Diagnostic strategies differ drastically across disorders of behavioural inflexibility, owing to its various presentations. For example, the main diagnostic strategies for ASD are the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Observational Diagnostic Schedule (ADOS), which capture a child's early developmental history, social and communicative functioning. On the other hand, the Yale-Brown Obsessive-Compulsive Scale (YBOCS) is a semi-structured interview that is commonly utilised for OCD diagnosis and instead aims to capture the severity of intrusive, obsessive thought patterns and compulsions. Behavioural changes in animals can be identified using tasks such as reversal learning, attention set shifting, and radial arm mazes. In humans, the CANTAB (Cambridge Neurophysiological Test Automated Battery) tests, a standard in cognitive research can also assess behavioural flexibility using tasks incorporating discrimination reversal (switching reward-response associations) and extra-intra dimensional set shifting (attention and cognitive flexibility). Learning and memory impairments utilising the CANTAB have been observed in patients with ASD (Spatial Span (visuospatial working memory), Spatial Working Memory, Stockings of Cambridge (spatial planning and working memory), and Intradimensional/Extradimensional Shift Test) (Chen et al., 2016), in addition to reduced sensitivity to outcome devaluation in OCD (Pattern Recognition Memory (matching information input to already-stored memory), Paired Associates Learning (inter-stimuli associations) and Intra-Extra Dimensional Set Shift (attention shifting)) (Gottwald et al., 2018).

The generation of reliable rodent models to encompass inflexibility disorders remains a challenge due to the relative heterogeneity of symptom presentation. As such, not all 'compulsive' or 'behaviourally rigid' animal models have the same phenotypic type of behavioural inflexibility, and it is unknown whether the same molecular mechanisms subserve these different types of behavioural inflexibility. Genetic knockout rodent models aim to encompass specific symptom types, for example *Integrin beta3* knockout mice show an autistic phenotype with reduced preference for social novelty and increased grooming behaviour (Crawley, 2012), while both the serotonin transporter *5-HT2C* knockout and SLITRK5 knockout mouse models of OCD show increased repetitive, habitual behaviours (Chou-Green et al., 2003). Pharmacological induction of behavioural inflexibility can be initiated prenatally by both valproic acid and the immunostimulant polyinosinic:polycytidylic acid (poly IC), while administration of the dopamine receptor D2/D3 agonist quinpirole in adulthood incudes compulsive checking behaviour

Table 1
Summary of compulsivity-associated regions; their role, structural and functional changes in OCD and ASD.

Region	CSTC Circuit	Role	Changes in OCD, ASD	
			Structural	Functional
Orbitofrontal cortex	Ventral-motivational circuit (Stein et al., 2019).	Assesses the value of reward and motivational value of a stimulus (Graybiel and Rauch, 2000).	Smaller in OCD (Heuvel et al., 2022) Increased cortical thickness in ASD (Van Rooij et al., 2018)	Increased activation in OCD patients vs controls (Thorsen et al., 2018). Altered functional connectivity across ages (Long et al., 2016)
Dorsal Anterior Cingulate Cortex	Frontolimbic, dorsal-cognitive circuits	Value-based decision making (Fatahi et al., 2018). Roles in linking reward and error in decision making in reversal learning paradigms (Chudasama et al., 2013). Cognitive conflict, decision making and fear extinction (Milad and Rauch, 2012)	Smaller in OCD (McGovern and Sheth, 2017) . Increased cortical thickness in ASD (Jiao et al., 2010) (Van Rooij et al., 2018)	Increased activation in OCD patients (Thorsen et al., 2018) (Rotge et al., 2008) Reduced activation (Ameis and Szatmari, 2012) Reduced functional connectivity (Long et al., 2016)
Midcingulate Cortex	Frontolimbic, dorsal-cognitive circuits	Goal-directed action (Holroyd et al., 2018).	No data Increased cortical thickness in ASD (Hyde et al., 2010) (Van Rooij et al., 2018)	Decreased neuron size (Uppal et al., 2014) Reduced activation (Ameis and Szatmari, 2012)
Amygdala	Frontolimbic circuit (Stein et al., 2019)	Fear extinction (Sun et al., 2019)	Asymmetry across hemispheres (Szeszko et al., 2004) Reduced size (Szeszko et al., 1999) Smaller in ASD (Van Rooij et al., 2018)	Increased activation in OCD patients (Rotge et al., 2008) Altered connectivity (Heuvel et al., 2022) Reduced activation (Ameis and Szatmari, 2012)
Nucleus Accumbens	Ventral-motivational circuit (Stein et al., 2019).	Forms stimulus-reward relationships (Day and Carelli, 2007).	Larger in OCD (Heuvel et al., 2022) Smaller in ASD (Van Rooij et al., 2018)	Reduced activity (Wu et al., 2021) Reduced functional connectivity in ASD to regions including cingulate cortex, dorsal striatum and thalamus (Polk and Ikuta, 2022)
Dorsomedial striatum (encompassing caudate and putamen	Dorsal cognitive and ventral cognitive circuits	Attention (Rubia et al., 2011) Fear, reward conditioned associations (Strata, 2015)	Altered volume in OCD patients (Heuvel et al., 2022) Smaller in ASD (Van Rooij et al., 2018)	Reduced activity (Lipton et al., 2019) Reduced activation during socialisation (Delmonte et al., 2012)
Hippocampus	Extra-CSTC	Role in formation of episodic memory. Connections with amygdala facilitate emotional context to memory. Memory formation Spatial memory Approach-avoidance conflict	Smaller in OCD (Heuvel et al., 2022) Volume changes associated with symptom severity (Reess et al., 2018) (Boedhoe et al., 2017a) Asymmetrical in children with low-functioning ASD (Schumann et al., 2004), reduced size associated with symptom severity (Van Rooij et al., 2018)	Increased activation in OCD patients (Rotge et al., 2008). Reduced connectivity between hippocampus ad fronto-parietal network in memory retrieval (Cooper et al., 2017)
Cerebellum	Extra-CSTC	Cerebellum in inhibition, lesions in cerebellar vermis cause dysregulated executive function (Miquel et al., 2019)	Larger in OCD (Heuvel et al., 2022) Larger in ASD (Sparks et al., 2002)	Altered connectivity to cerebellum and cingulate in OCD (Zhang et al., 2019b) Reduced connectivity to frontal, motor cortex and striatum (Crippa et al., 2016)

(Szechtman et al., 1998).

Both structural and functional MRI studies have shed light on parallel, partially segregated cortico-striatal-thalamo-cortical (CSTC) loops (Parmar and Sarkar, 2016; Vahabzadeh and McDougle, 2014)) which mediate different behavioural, cognitive and sensorimotor processes, the dysregulation of which mediates abnormal cortical excitation patterns and compulsive behavioural phenotypes (Stein et al., 2019). Table 1 below illustrates structural and functional changes in CSTC circuit regions in both ASD and OCD. Beyond these CSTC loops, both the hippocampus and the cerebellum have a role in behavioural inflexibility. The hippocampus has roles in episodic memory, can denote emotional contexts to memory and enable approach-avoidance conflict, encompassing the weighing up of pros and cons of a decision. Indeed, this region has connections to CSTC regions including the nucleus accumbens (reward and addiction behaviours) orbital area (valuation and decision-making) and anterior cingulate cortex (adaptive switching). The cerebellum is a region that has gained attention for its roles in compulsive behaviour in recent years (Xing et al., 2020) and is implicated in learning (Fullana et al., 2018) and habit formation (Miquel et al., 2019). Neuroimaging studies reflect this CSTC involvement across OCD (Rasgon et al., 2017), (Xu et al., 2019; Zhang et al., 2019a), ASD (He et al., 2021), Depression and Parkinson's Disease (which commonly occurs with comorbid addiction/reward-related impairments) (Vriend et al., 2014). Additionally, this circuitry regulates synaptic plasticity changes (Song et al., 2017) and neurotransmitter imbalance, such as reward and motivation-related dopamine (Iino et al., 2020). Additionally, anxiety plays a role in the generation of compulsive symptoms. In OCD, anxiety is deemed the driving force behind the need to complete various repetitive compulsion behaviours, while in ASD, deviation from routine may generate anxiety in the individual, warranting inflexible behavioural patterns. Tourette's Syndrome, while typically presenting in the form of physical tics and repetitive movements, may also be aggravated when the individual is anxious and is often comorbid with OCD. Studies of brain regions involving anxiety predominantly encompass the hypothalamus, hypothalamic-pituitary-adrenal axis, amygdala, with reciprocal projections with the anterior cingulate cortex and hippocampus, governing fear-memory links (Anon, 2021) and regions of the mPFC (Calhoon and Tye, 2015).

Recently, aberrant insulin signalling has been proposed as a key mechanism behind behavioural inflexibility (van de Vondervoort et al., 2016, 2019). Insulin is a hormone synthesised in pancreatic beta cells, and regulates metabolic processes including new lipid production and glucose uptake. Insulin resistance is a feature of Type II Diabetes and involves an insensitivity of target receptors to insulin. Networks resulting from genome-wide association study (GWAS) examining OCD have identified insulin signalling as the most enriched network underlying OCD symptomology, with many associated genes implicated in neuronal dendritic spine formation (van de Vondervoort et al., 2016). According to In situ hybridisation data on the Human protein Atlas, most brain regions express the insulin receptor (INSR) and Insulin-like growth factor-1 receptor (IGF1R). Insulin reportedly can regulate brain function and shows links with cognitive dysfunction in Alzheimer's Disease, coined "Diabetes Type 3". Interestingly, insulin was utilised as an early therapeutic for psychiatric disease in the early 20th century (James, 1992). Insulin is capable of crossing the blood-brain barrier. Additionally, evidence suggests that insulin is also locally secreted in brain (Gray et al., 2014), with mRNA reported in striatum, thalamus, frontal cortex, hippocampus and brainstem in mice of various ages (Mehran et al., 2012a). Insulin resistance is reported to affect processes including synaptogenesis (Chiu et al., 2008; van de Vondervoort et al., 2016; Lee et al., 2011), myelination (Mozell and McMorris, 1991), aggregate accumulation (Han et al., 2016; Jolivalt et al., 2008)) and neurotransmitter homeostasis (Stouffer et al., 2015a). Insulin-Growth Factor 1 and 2 (IGF-1 and IGF-2), molecules of similar structure to insulin, also engage with similar processes. Indeed, the IGF-1 receptor and Insulin receptor are highly homologous, despite having varying tissue expression patterns. While insulin signalling primarily mediates metabolism, IGF-1 mediates growth and proliferation signalling (Cai et al., 2017). However, both insulin and IGF-1 can bind to each other's receptors as agonists. Animal models of insulin resistance further support the importance of insulin in the brain, with the TALLYHO/JngJ mouse model of Type 2 Diabetes (T2D) demonstrating compulsive behaviours and increased anxiety (van de Vondervoort et al., 2019). Additionally, T2D patients reportedly demonstrate increased obsessive-compulsive symptomology (Kontoangelos et al., 2013).

This review will be structured into four main parts. The first will discuss current knowledge of the aetiology of behavioural rigidity. The second will discuss insulin signalling in brain and T2D-associated structural and functional changes. The third section will examine specific brain processes governed by insulin. The final section will explore the input of insulin signalling into various disorders in which rigidity is a feature, i.e. Obsessive-Compulsive Disorder, Addiction, Anorexia nervosa, binge eating, Alzheimer's Disease and Parkinson's Disease.

2. Circuitry in rigidity disorders

2.1. Cognitive-affective dysfunction

Behavioural flexibility falls under the broader umbrella of executive functions, which are processes needed to regulate goal-directed behaviour. These processes include appropriate valuation of a stimulus, inhibition of nonrewarding responses, switching behavioural strategy, appropriate allocation of attention and working memory.

2.2. Valuation of a stimulus

Stimulus valuation is necessary to allocate an appropriate rewarding value to a stimulus or environment, with overvaluation a common feature of unhealthy or maladaptive behaviours. Previous human functional neuroimaging studies identified the midcingulo-insular network comprising the dorsal anterior cingulate cortex, orbital frontoinsular cortex and subcortical structures including the amygdala and thalamus (Seeley et al., 2007; Uddin et al., 2019). Kable and Glimcher (2007) studied neural correlates of immediate vs delayed reward (Kable and Glimcher, 2007). They identified activation of the ventral striatum, medial prefrontal cortex and posterior cingulate cortex across subjects, with the most impulsive participants showing a steep decline in activation as delay time increases. This indicates that these regions govern both the subjective value placed on a reward, and also the time at which the reward will be received.

2.3. Inhibition of nonrewarding responses

Shifting responses to adapt to environment requires the inhibition of a previous response. There are conflicting reports regarding the deficit in inhibition amongst patients of compulsivity. Indeed, OCD patients appear to show medium effect size (Shin et al., 2013), whereas a meta-analysis of studies in ASD patients showed more concrete impairment in response inhibition (Hlavatá et al., 2018). Alzheimer's Disease is associated with significant impairments in controlled inhibition (Amieva et al., 2004). Consistent with the human imaging studies, impaired ability to inhibit responding to the previously-rewarded but no-longer-correct stimulus (perseverative errors) has been observed in a rodent model of ASD in which cerebellar dysfunction is present (Dickson et al., 2010).

2.4. Switch behavioural strategy

The ability to effectively switch between behaviours depending on changes in environmental reward-salience is essential for adaptability, and is captured in the reversal learning task. *In vivo* recordings of the orbitofrontal cortex (OFC), dorsal medial striatum (DMS) and dorsal

lateral striatum during shifting reveal altered neuronal firing rates in the caudate and orbitofrontal cortex between goal-directed and habit-based actions (Germal and Costa, 2013). Neuronal monitoring in head-fixed mice demonstrated that neurons in the mouse OFC respond saliently and transiently to rule switches during reversal learning, a task measuring the effectiveness at which mice can shift from a non-rewarding to rewarding response (Banerjee et al., 2020). The dorsomedial striatum is thought to dynamically interact with multiple prefrontal subregions that generate new strategies to facilitate behavioural flexibility, with inactivation impairing the ability of the mouse to maintain a new choice pattern (Ragozzino, 2007). The ventral striatum governs reward sensitivity, with reduced reversal learning ability following ablation of orbitofrontal-nucleus accumbens projections (Groman et al., 2019). Temporal lobe epileptic patients, with hippocampal atrophy, demonstrate an impaired ability to anticipate stimuli in reversal learning compared to healthy controls (Vilà-Balló et al., 2017). Patients with cerebellar lesions also exhibit normal acquisition of stimulus contingencies, however impaired reversal learning (Thoma et al., 2008).

2.5. Attention

Another necessary process for affective shifting between tasks is attention, a cognitive process in which the brain dedicates sensory resources to relevant stimuli. However, this process is context dependent, and is influenced by factors including memory, reward motivation and anxiety (Bissonette et al., 2013). Evidence suggests that compulsivity may result from dysfunctional selective attention. For example, children with ASD are more likely to be influenced by visual distractors (Poole et al., 2018) and OCD is characterised by an atypical allocation of attention to normally unattended stimuli (Levy, 2018). Those with ADHD are reported to be more likely to develop addiction later in life (Davis et al., 2015). Attention can be split into two distinct processes: top-down for goal-directed stimuli and bottom-up for unexpected stimuli. The former (dorsal attention network; DAN) employs use of the intraparietal cortex and superior frontal cortex, the latter (ventral attention network; VAN) involves the temporoparietal cortex and inferior frontal cortex (Corbetta and Shulman, 2002). Hence, attention issues may arise from a hypoactive top-down DAN or hyperactive bottom-up VAN, or a mix of both. The attentional set-shifting task in rodents, which measures the ability to transition between cognitive attentional sets, is reported to require activity of the medial prefrontal cortex (mPFC) (Bissonette et al., 2013), which receives projections from hippocampus, and projects to orbitofrontal cortex, ACC, striatum, amygdala, mediodorsal thalamus and ventral tegmental area (Vertes, RP., 2006).

2.6. Working memory

Adapting behaviour is also dependent on working memory, both in our ability to update our current knowledge in a situational context and in our conditioned associations to reward-based or aversive stimuli. Working memory is a temporary, short-term memory system required for decision making and reasoning. The employment of previous information contributes to our ability to predict the future and make decisions. A task that reflects the ability to update information and simulates real-life decision making is the Iowa Gambling Task. This requires participants to select cards from four decks, with various weights of advantageousness and disadvantageousness, associated with small rewards and punishments respectively. Patients with hippocampal damage do not develop a preference for either set, suggesting that patients maintain only a momentary response to the outcome, and do not maintain or update choice-outcome relations (Gutbrod et al., 2006). The hippocampus interacts with other regions implicated in flexible decision-making, including the prefrontal cortex (PFC) (Simons and Spiers, 2003) and amygdala (Pikkarainen et al., 1998). One study showed, via optogenetic stimulation, that the central amygdala (CeA) sends robust inhibitory projections to the lateral substantia nigra (SNL) that contribute to appetitive and aversive learning in mice (Steinberg et al., 2020). This is associated with habitual behaviours, in which motor responses are produced without regard for the outcome (Lingawi and Balleine, 2012). The basolateral amygdala (BLA) on the other hand projects to the nucleus accumbens (NAc) to implement instrumental behaviour for conditioned reinforcement, with deep brain stimulation in the NAc a successful treatment for disorders of compulsivity including OCD (Everitt et al., 1991). Information about pleasant and aversive stimuli converge at the amygdala from regions including the prefrontal cortex and hippocampus, potentially influencing amygdala response to information including memories and expectations (Belova et al., 2007).

To summarise, behavioural flexibility in the face of a changing environment is dependent on the interaction of numerous processes; the appropriate assignment of value to a stimulus, the inhibition of a previously, but no longer-rewarding behaviour, the ability to switch from one behaviour to another, the ability to focus and refocus attention, and finally the integrity of our short-term working memory. Dysregulation of these mechanisms may generate errors in decision making and maladaptive behaviour.

3. Insulin signalling in the brain

Diabetes mellitus is a disorder characterised either by impaired insulin synthesis (Type 1) or insulin resistance at the level of receptors (Type 2). First-line treatments involve insulin injection in the former, and medication to decrease insulin resistance, e.g. metformin, in the latter. Type 2 diabetes as a result of impaired insulin signalling is associated with impairments in working memory and cognitive functioning (Backeström et al., 2021). Insulin is a peptide hormone synthesised in β cells of the pancreas in response to physiological triggers, predominantly peripheral glucose levels. Despite the decades-long assertion of the brain as an insulin-insensitive organ, both the insulin receptor and IGF-1 receptor are widely expressed across human brain regions including the cerebellum, frontal cortex, hippocampus and caudate (Anon, 2020a, 2020a). The bulk of brain insulin is derived from the pancreas and transported across the blood-brain barrier (Banks et al., 2012), however insulin mRNA has also been identified in brain tissue indicating localised transcription takes place, including in hypothalamus, hippocampus (Mehran et al., 2012b; Steen et al., 2005)), olfactory bulb (Kuwabara et al., 2011), striatum, thalamus and pyramidal neurons of the cortex (Dorn et al., 1982). Insulin appears to be derived in neurons but not in astrocytes, with no insulin gene expression reported in astrocyte cultures (Devaskarss et al., 1994). Depolarisation of neurons yields release of insulin from the synaptic terminal, suggesting that it may possess neurotransmitter-like properties (Clarke et al., 1986; Wei et al., 1990)). There is a scarcity of literature examining insulin production and secretion from microglia and oligodendrocytes, however activated microglia were found to secrete IGF-1 in the hippocampus of mouse models of Alzheimer's Disease (Myhre et al., 2019). Insulin signalling in brain is also reported to regulate metabolism in peripheral tissues, with suppression of hepatic glucose production, lipolysis in adipose tissue, hepatic catabolism of branched-chain amino acids and hepatic triglyceride secretion reported to occur independently from plasma insulin levels (Arnold et al., 2018).

The two predominant cascades induced by insulin are the AKT and MAPK pathways. The former is particularly relevant for T2D as this mediates the recruitment of the glucose transporter GLUT4 for glucose cellular uptake in muscle and adipose cells. The AKT pathway is also responsible for the phosphorylation of multiple downstream targets including mTOR and GSK-3 implicated in neural development, synapse formation, neurite branching (Takei and Nawa, 2014), axonal guidance, migration and tau accumulation (Salcedo-Tello et al., 2011). MAPK regulates synaptic plasticity (Giachello et al., 2010) and inflammation (Brown et al., 2015). Insulin growth factors are structural homologs of

insulin and share common signalling cascades, with the key difference between the two in their different affinities for common receptor targets. IGF1 binds IGF1R and it may also bind the IR/IGF1R receptor hybrid. Insulin binds to the insulin receptor and also the IR/IGF1R hybrid. In order to successfully bind to their receptors, insulin and IGF interact with insulin growth factor binding proteins 1–7. These are shown to play roles in myelination and plasticity during crucial periods of neonatal brain development (Bunn et al., 2005). These pathways are summarised in Fig. 1. The kinase protein AMPK is important in the regulation of insulin signalling, and functions to suppress hepatic glucose synthesis and increases insulin sensitivity in low adenosine diphosphate (ADP) conditions. The T2D drug metformin activates AMPK activity, and by yet not fully defined mechanisms, optimises insulin use by cells (Ruderman et al., 2013).

3.1. Type 2 diabetes and the brain

3.1.1. Structural changes

MRI studies of adolescents with T2D have identified reduced grey matter volume in the hippocampus, dorsal striatum, amygdala and thalamus, left insular lobe, left nucleus accumbens area, right hippocampus, putamen and amygdala compared to age matched controls (Nouwen et al., 2017; Chen et al., 2013b)). In middle age, glycaemic control is an important factor that has been linked to the degree of atrophy in brain (Gold et al., 2007). This multivariate regression analysis found that HbA1c, a measurement of glycosylated haemoglobin, was the only significant predictor of hippocampal atrophy in individuals with T2D. Interestingly obesity, a common feature of T2D, was a significant predictor of smaller volume of the hippocampus, anterior cingulate gyrus, frontal lobes and thalamus (Raji et al., 2010), possibly due to input from associated low-grade inflammation (Miller and Spencer, 2014). Patients also demonstrate increased neuroinflammation (Rom et al., 2019), in addition to vascular changes (Kooistra et al., 2013; Zeng et al., 2016)). Comparison of white matter tracts revealed an increase in mean diffusivity in patients with T2D which, in turn, was related to worse memory performance and slower information processing speed (Reijmer et al., 2013). Overall, T2D is implicated with significant reductions in the cerebral grey:white matter volume, detrimental to cognition.

3.1.2. Functional changes

An rs-fMRI study of T2D patients showed reduced functional connectivity between the hippocampus and numerous regions including the anterior cingulate cortex, inferior parietal and medial temporal lobes (Zhou et al., 2010). Diffusion tenor image (DTI) analysis showed that the right inferior frontal gyrus presented increased nodal degree; the left post central gyrus presented decreased local efficiency; the right hippocampus and the superior pole of the right temporal lobe exhibited decreased global and local efficiency respectively; the left pallidum and the right amygdala presented decreased global efficiency (Zhang et al., 2019c). These represent regions implicated in memory and emotion-memory associations. Experiments by the Utrecht Diabetic Encephalopathy Study investigated associations between T2D and total cerebral blood flow (CBF) in a cross-sectional study of 98 patients and 47 control participants. In this sample, total CBF – as measured by blood flow within the internal carotid and basilar arteries – was significantly diminished in patients (Tiehuis et al., 2008). However, when the values were corrected for brain volume there was no significant difference in cerebral blood flow between patients and controls. Across all participants, lower CBF was associated with poorer performance on cognitive tests (independent of white matter pathology and infarcts), but this association was independent of diabetes status. Based on these findings, the authors concluded that total CBF was likely not the underlying cause of cognitive impairment in patients but may be a contributing factor. Cerebral blood flow is also positively associated with impaired glucose tolerance in regions included orbitofrontal cortex, superior temporal gyrus and the inferior parietal lobule (Thambisetty et al., 2013). In addition to cerebrovascular changes, in patients with prediabetes or T2D, higher insulin resistance was associated with reductions in glucose metabolism in regions including posterior cingulate cortex, precuneus, temporal lobes and regions of prefrontal cortex (Baker et al., 2011). This study also conducted a separate scan as participants completed a memory-encoding task. Healthy participants displayed the predicted increase in activation in regions associated with memory encoding, including medial cingulate, frontal and temporal cortices. Qualitatively, those participants with prediabetes/T2D had a more widespread pattern of activation extending into putamen, cerebellum and thalamic regions. Based on this pattern of diffuse activation, the authors draw parallels to changes in cerebral metabolism that are commonly seen in AD,

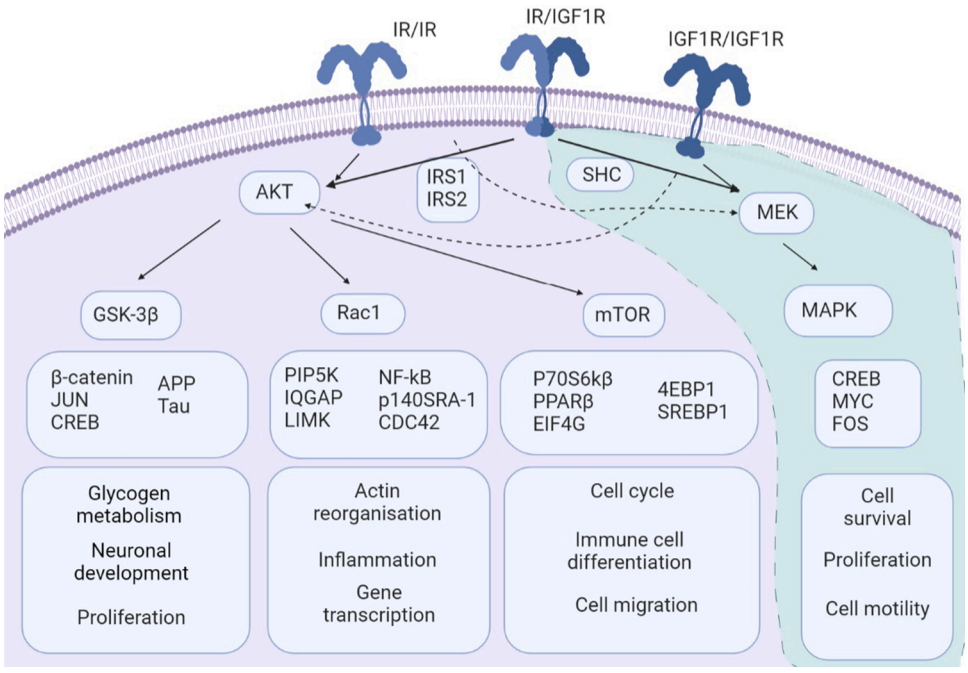

Fig. 1. Insulin/IGF1 signalling pathways. Insulin binds the insulin receptor homodimer (IR/IR) and IGF-1 binds the IGF-1 receptor homodimer (IGF1R/IGF1R), and both bind the IR/IGF1R heterodimer. Downstream signalling mechanisms govern metabolic processes including glycogen metabolism, inflammatory and immune processes and processes concerning cell survival and activity (GSK-3β: Glycogen synthase kinase 3-beta; mTOR: mammalian target of rapamycin; MAPK: mitogen activated protein kinase). Created with Biorender.com.

involving frontal, temporal-parietal and cingulate regions. In summary, connectivity and activation states across memory and emotion-associated brain regions are impacted by T2D.

3.1.3. Association with cognitive dysfunction

While insulin receptors are expressed throughout the brain including the hippocampus, cerebral cortex and cerebellum, evidence of insulin synthesis in brain is patchy and while regulation of insulin secretion and action in the periphery is well documented, whether the same mechanisms are also involved in any local brain regulation of insulin action is not known. The molecular landscape by van de Vondervoort et al. (2016) reported enrichment of the insulin signalling pathway amongst OCD-associated genes and also highlighted the voltage-gated potassium channel KCNQ1, with a role in insulin secretion regulation in pancreas, as a significantly associated gene. A recent study by Bralten et al. (2020) utilised GWAS, polygenic-risk score-based analysis and gene-set analysis to examine genetic overlap between T2D and OCD. This showed shared genetic etiology between the insulin-linked gene set and symmetry/ordering/counting behaviour, with gene-set analyses reporting influence of genes including brain-derived neurotrophic factor (BDNF), associated with neuroplasticity, DCC for axonal growth and SLIT3 in axonal guidance, however no single gene from the total gene set reached significance. Research suggests a link between T2D and the development of cognitive changes, and is associated with disorders including ADHD (Chen et al., 2013a), Anorexia Nervosa (Watson et al., 2019) and ASD (Stern, 2011) in addition to cognitive decline, with many patients reported to show impaired information processing speeds, attention and executive functioning over time (Van Den Berg et al., 2010). A systematic review of these studies examined cross-sectional and longitudinal effects of T2D on cognition (Van den Berg et al., 2009). Across studies, the most common finding was impairment in processing speed (63% of studies), followed by attention (50%), memory (44%), and cognitive flexibility (38%), especially with older age. Interestingly, blood levels of glycosylated hemoglobin (HbA1c), a proxy for diabetes severity, correlates positively with OCD symptoms (Kontoangelos et al., 2013). Indeed, patients are reported to exhibit brain changes to varying extents, including reduced cerebral volume and atrophy (Roberts et al., 2014) and white matter abnormalities (Xiong et al., 2016), oxidative stress and mitochondrial dysfunction (Kleinridders et al., 2015), neuroinflammation (Rom et al., 2019), neurotransmitter imbalance (Datusalia and Sharma, 2014), aggregate accumulation (Platt et al., 2016) and vascular damage (Kooistra et al., 2013; Zeng et al., 2016). Previous investigations into the cognitive phenotype of the TALLYHO/JngJ model of T2D show decreased spontaneous alternation and repetitive entries into arms of a maze compared to control counterparts (van de Vondervoort et al., 2019). A study by Kleinridders (2015) established a mouse model of brain-specific insulin resistance, which exhibited increased anxious and depressive behaviours compared to controls, in addition to abnormal mitochondrial activity, aberrant dopamine balance and evidence of protein aggregate accumulation (Kleinridders et al., 2015). Overall, evidence from recent years is mounting to indicate that periphery or brain-derived insulin impacts neurophysiological processes, with associations between T2D and a variety of cognitive, neurodevelopmental and neurodegenerative disorders.

Table 2
Comparison of functional changes in compulsivity-associated brain regions in Obsessive-Compulsive Disorder (OCD), Autism Spectrum Disorder (ASD) and Type 2 diabetes.

Region	Functional changes		
	OCD	Autism	Type 2 diabetes
Orbitofrontal cortex	Increased activation in OCD patients vs controls (Thorsen et al., 2018).	Altered functional connectivity across ages (Long et al., 2016)	Reduced activation (Sun et al., 2017)
Dorsal Anterior Cingulate Cortex	Increased activation in OCD patients (Thorsen et al., 2018) (Rotge et al., 2008)	Reduced activation (Ameis and Szatmari, 2012) Reduced functional connectivity (Long et al., 2016)	Reduced activation (Sun et al., 2017)
Midcingulate Cortex	Decreased neuron size (Uppal et al., 2014)	Reduced activation (Ameis and Szatmari, 2012)	No data
Amygdala	Increased activation in OCD patients (Rotge et al., 2008) Altered connectivity (Heuvel et al., 2022)	Reduced activation (Ameis and Szatmari, 2012)	Right amygdala shows decreased global efficiency (Zhang et al., 2019c)
Nucleus Accumbens	Reduced activity (Wu et al., 2021)	Reduced functional connectivity in ASD to regions including cingulate cortex, dorsal striatum and thalamus (Polk and Ikuta, 2022)	No data
Dorsomedial striatum (encompassing caudate and putamen	Reduced activity (Lipton et al., 2019)	Reduced activation during socialisation (Delmonte et al., 2012)	Decreased activation (Antal et al., 2022)
Hippocampus	Increased activation in OCD patients (Rotge et al., 2008).	Reduced connectivity between hippocampus ad fronto-parietal network in memory retrieval (Cooper et al., 2017)	Reduced connectivity with regions including anterior cingulate cortex, inferior parietal and medial temporal lobes (Zhou et al., 2010)
Cerebellum	Altered connectivity to cerebellum and cingulate in OCD (Zhang et al., 2019b)	Reduced connectivity to frontal, motor cortex and striatum (Crippa et al., 2016)	Reduced frontal cortex – cerebellum connectivity (Zhang et al., 2020)

3.2. Metformin and cognitive function

Identifying the physiological aspects of T2D that contribute to cognitive decline is essential in determining a therapeutic strategy. This could be a range of possible factors, including obesity and lipid levels, hyperglycaemia, or insulin resistance. The T2D drug metformin is capable of crossing the BBB (Gantois et al., 2019) and is known for its ability to normalise blood glucose, which it achieves via mechanisms including inhibiting hepatic gluconeogenesis, decreasing intestinal glucose absorption, increasing peripheral glucose uptake and improving insulin sensitivity (DeFronzo and Goodman, 1995). Metformin is reported to reduce insulin-resistance-associated increases in reactive oxygen species (ROS)elicited through mitochondrial dysfunction, implicating it in an anti-inflammatory role (Ruegsegger et al., 2019). Metformin also inhibits NF-KB phosphorylation and reduces C-reactive protein (CRP; an inflammatory marker) levels in serum (Song-Nan and Wang, 2009). When administered to 18-month old healthy mice, metformin elicited reduced microglial activation, enhanced autophagy in the hippocampus and reduced proinflammatory cytokines, in addition to improved cognition (Kodali et al., 2021). Metformin is capable of restoring normal endothelial function in high fat-fed rodents (Sena et al., 2011), and promotes nitric oxide (NO) synthesis via AMPK (Davis et al.,

2006), mediating vasodilation. This is an important process in transcytosis of compounds from blood, including insulin. Metformin is also reported to prevent amyloid deposition in APP/PS1 mice, reduced hippocampal neuronal loss and improved spatial memory (Ou et al., 2018). Whether or not it does this via an insulin-mediated change is undetermined in this study, however metformin has separately been found to induce Insulin-degrading enzyme expression, a key factor in amyloid beta breakdown (Lu et al., 2020). Additionally, metformin is reportedly capable of inducing alternative splicing in a selection of genes, including exon 11 of the insulin receptor INSR, causing greater inclusion and a possible therapeutic mechanism in the insulin resistance-associated disorder Myotonic Dystrophy which also demonstrates aspects of behavioural inflexibility (Laustriat et al., 2015). Metformin may have benefits not only on T2D but also associated cognitive dysfunction via multiple mechanisms including its ability to alter splice variation of insulin target receptors and action on AMPK signalling.

4. Insulin regulation of neurophysiological mechanisms

4.1. Glucose uptake and energy

Glucose is utilised for adenosine triphosphate (ATP) production via the tricarboxylic acid (TCA) cycle, with impaired ATP synthesis in patients suffering with cognitive dysfunction in Alzheimer's Disease (Butterfield and Halliwell, 2019), ASD (Rossignol and Frye, 2012) and Depression (Bansal and Kuhad, 2016). Glucose is transported across the cell membrane via glucose transporters, some of which are insulin-independent (GLUT1, 2, 3, 5) and insulin-dependent (GLUT4, 8). GLUT4 is the principal insulin-regulated glucose transporter located mainly in the neuronal cell bodies and proximal dendrites at the synaptic level in the cortex, amygdala, hippocampus, hypothalamus, and cerebellum (Jurcovicova, 2014). Some GLUT4 immunoreactivity has been also observed in endothelial cells of microvessels. It is intracellularly present on the membranes of transport vesicles, Golgi apparatus, and rough endoplasmic reticulum. Grillo et al. (2009) demonstrated GLUT4 translocation is dependent upon PI3K/AKT signalling and could be inhibited by PI3 kinase inhibitor. GLUT4 shows the heaviest immunoreactivity in the hippocampus, with chronic GLUT4 blockade impairing long-term memory, and reducing BDNF expression (Pearson-Leary and McNay, 2016). An interesting study described that, during upregulated neuronal activity, GLUT4 was translocated to the synapse, providing glycolytic support in response to activation of AMPK (Ashrafi et al., 2017). In diabetic rats, GLUT4 translocation was reduced in the hippocampus, hypothesised as a possible contributor to memory impairments (Winocur et al., 2005). Brain-specific GLUT4 knockout mice show reduced glucose uptake in the hypothalamus, hippocampus, cerebellum, nucleus tractus solitarus and cortex (Reno et al., 2017). GLUT8 is expressed in several brain areas, predominantly hippocampus and amygdala, with expression also in cortex and hypothalamus. The expression of GLUT8 is principally neuronal (Reagan et al., 2002). It is hypothesised that GLUT8 may catalyze the transport of glucose after the glycolysation process of proteins from rough endoplasmic reticulum to cytosol for reuse (Piroli et al., 2002). In this way glucose can be recycled to provide cells with energy. Diabetic rats with hyperglycaemia and hypoinsulinemia showed reduced GLUT8, an effect that is exacerbated in the presence of stress (Piroli et al., 2004; Piroli et al., 2002)), suggesting that insulin might regulate glucose recycling. More recently, GLUT8 knockout mice showed ADHD-like hyperactivity (Schmidt et al., 2008). In summary, insulin regulates GLUT4 and GLUT8-mediated glucose uptake for metabolic support, which may influence cognitive processes and neuronal growth.

4.2. Atrophy

Insulin signalling promotes cell viability (Schubert et al., 2004), with application to neurons undergoing oxygen or glucose deprivation shown to elicit neuroprotective effects (Mielke and Wang, 2005). This is proposed to occur via PI3-K signalling, indeed the neuroprotective effect of insulin following serum-deprivation-induced apoptosis of cells reversed following addition of the selective PI3K inhibitors wortmannin or LY294002 (Ryu and Ko, 1999). Insulin addition to 1–Methyl-4–phenyl pyridinium (MPP^+) Parkinson's Disease model cells induced pro-survival PI3K/Akt/GSK-3 signalling (Ramalingam and Kim, 2016). Insulin also inhibits cytochrome c-mediated apoptosis (Sanderson et al., 2013; Jiang and Wang, 2004)). Insulin also promotes NO-mediated vasodilation, hence promoting oxygen and glucose perfusion of tissues, with impairments contributing to atrophy (Arnold et al., 2018). Indeed, experiments by the Utrecht Diabetic Encephalopathy Study identified reduced cerebral blood flow in T2D patients that corresponded with reduced cerebral volume (Tiehuis et al., 2008). Such volumetric changes are characteristic across psychiatric and cognitive disorders. A recent study by Cauda et al. (2018) generated a co-atrophy network based on grey matter decreases across ASD, OCD and schizophrenia. Here, they identified alterations predominantly in insulo-frontal, insulo-insular, insulo-hippocampal and frontoparietal nodes. Atrophy in Alzheimer's Disease involves a number of unique networks; medial-temporal atrophy with a dramatic effect on memory and language function, parieto-occipital atrophy with poor executive function and attention and diffuse cortical atrophy with a decline in visuospatial functioning (Ten Kate et al., 2018). Interestingly, this atrophy appeared before the full onset of symptoms, and were predictive of the trajectory of symptoms. Depression is characterised by inflexibility in switching between emotions, and is characterised by significantly reduced volume in the putamen, pallidum, thalamus and hippocampus, while amygdala volume in those with comorbid anxiety was increased (Espinoza Oyarce et al., 2020). Taken together, insulin promotes cell viability via mechanisms including inhibition of mitochondrial-mediated apoptosis and oxygen perfusion of tissue, with atrophy a signature feature of some cognitive and mood disorders.

4.3. Synaptogenesis

Insulin and IGF1 receptors are present on presynaptic axon terminals and on postsynaptic densities of dendrites (Arnold et al., 2018), in addition to soma of Purkinje cells (Garcia-Segura et al., 1997), and are essential for normal dendritic growth (Cheng et al., 2003), synaptogenesis (Chiu et al., 2008; Popken et al., 2004) and for the regulation of synaptic plasticity (Van Der Heide et al., 2005; Sherrard and Bower, 2003). This is mediated via various downstream targets including mTORC1, GSK3β, and the FoxO family of transcription factors. mTORC1-mediated protein synthesis is important for synaptic plasticity (Stoica et al., 2011). Blockade of insulin signalling, specifically the PI3K-AKT-mTOR cascade yielded both a significant reduction in dendritic spines and diminished excitatory postsynaptic currents (Lee et al., 2011; Lee et al., 2005)). GSK3β regulates multiple aspects of neuronal functioning, including neural progenitor cell proliferation, neuronal polarity, and neuroplasticity (Salcedo-Tello et al., 2011). Insulin is hypothesised to mediate Long-term potentiation: Long-term depression balance via regulating GSK-3β, a protein previously associated with many neurological disorders, via PI3K/AKT signalling (Van Der Heide et al., 2005; Phane Peineau et al., 2007). GSK3β can also phosphorylate tau protein, a process involved in the pathogenesis of Alzheimer disease (AD). Insulin stimulates phosphorylation of GSK3β, and this reduces its enzymatic activity. Brain-specific knockout of IRS-2 results in decreased GSK3β activity and increased tau phosphorylation (Schubert et al., 2003) . FoxOs mediate the inhibitory action of insulin or insulin-like growth factor on key functions involved in cell metabolism, growth, differentiation, oxidative stress, senescence, autophagy and aging (Lee and Dong, 2017), with FOXO1 regulating mTOR signalling required for synaptogenesis (Southgate et al., 2007). FOXOs also regulate microtubule stability in neurons (Nechipurenko and Broihier, 2012). Insulin/IGF-1 signalling also activates the MAPK/ERK signalling, which

phosphorylates synapsin protein required for appropriate synaptic vesicle release during neurotransmission (Giachello et al., 2010). The KCNQ1 voltage-gated potassium channel has roles in the regulation of insulin release in pancreas and interacts with the ASD-associated anchoring protein AKAP9 (Yamagata et al., 2011). The molecular landscape of OCD reports enrichment for signalling cascades implicated in postsynaptic dendritic formation, a process central to synaptogenesis and plasticity (van de Vondervoort et al., 2016), with mutations in associated genes identified in OCD mouse models and patients (Song et al., 2017). Synaptic dysfunction is hypothesised as a major mechanism of ASD, with multiple studies having revealed that mutations in genes like *NRXN, NLGN*, *SHANK*, *TSC1/2*, *FMR1*, and *MECP2* converge on common cellular pathways that intersect at synapses (Guang et al., 2018). These genes encode cell adhesion molecules, scaffolding proteins and proteins involved in synaptic transcription, protein synthesis and degradation, affecting various aspects of synapses including synapse formation and elimination, synaptic transmission and plasticity. In addition to dendritic expression, components of insulin receptor signalling were found at high concentrations at the postsynaptic membrane in the hippocampus, cerebral cortex and cerebellum of cultured rodent neurons, suggesting a role in long-term potentiation and depression (Abbott et al., 1999; Van Der Heide et al., 2005)). The higher rate of cognitive decline amongst T2D patients, in addition to reported reduced brain volume support this hypothesis of insulin involvement in brain connectivity and neuron growth (Roy et al., 2020; Roberts et al., 2014). Insulin-associated signalling in synaptogenesis is shown in Fig. 2 (adapted from van de Vondervoort et al. (2016).

4.4. Neurotransmitter balance

4.4.1. Dopamine

Dopamine is a key neurotransmitter previously associated with motivational behaviour and Pavlovian conditioning (Saunders et al., 2018). In particular, the mesolimbic projection from the ventral-tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc) is significant in disorders including depression and addiction (Xu et al., 2020). Dopamine binds to dopaminergic receptors D_{1-5}. Its significance in OCD symptomology is clear in clinical studies of deep brain stimulation of the nucleus accumbens (a dopamine terminal region) which offers symptomatic relief and the development of the dopamine based subchronic quinpirole mouse model of compulsive behaviour, following repeated administration of the D2/D3 agonist quinpirole (D_2 $IC_{50} = 0.15$; D_3 $IC_{50} = 5.6$) (Zaworski et al., 1999; Haluk and Floresco, 2009). The D_2 receptor family is the main target receptor of antipsychotic drug action, has the highest affinity for dopamine and is expressed in nucleus accumbens, cerebellum, cerebral cortex, hippocampus and caudate to mediate spine enlargement and plasticity via downstream MAPK and AKT signalling, in addition to discrimination learning (Iino et al., 2020).

In a brain-specific insulin resistant mouse model, insulin was shown to negatively regulate expression of the monoamine oxidases MAO-A and MAO-B, responsible for dopamine degradation, in neuronal and glial cultures (Kleinridders et al., 2015). This study interestingly demonstrated elevated MAO-A/B expression and increased dopamine turnover in striatal regions, alongside increased anxious and depressive behaviour compared to controls. This was rescued by administration of the irreversible MAO-A/B inhibitor phenelzine. Insulin also promotes expression of the membrane-bound dopamine transporter DAT via PI3K signalling, increasing overall dopamine neuronal uptake (Carvelli et al., 2002). *Ex vivo* experiments showed that insulin indirectly promotes dopamine release in the striatum via binding to cholinergic neuron insulin receptors, yielding release of acetylcholine and activation of dopaminergic transmission via nAChRs (Stouffer et al., 2015a). Insulin receptors in astrocytes are also associated with exocytosis of ATP and dopamine release via purinergic signalling in the NAc (Cai et al., 2018). In addition to dopaminergic consequences of insulin receptor signalling, insulin resistance-associated elevated blood sugar is reported to induce hypoxia in brain, to which dopaminergic neurons are reported as highly sensitive (Mercuri et al., 1994). Indeed, T2D is a reported risk factor for the development of Parkinson's Disease, characterised by the deterioration of dopaminergic neurons (Pagano et al., 2018).

Research is still emerging about insulin's role in behavioural

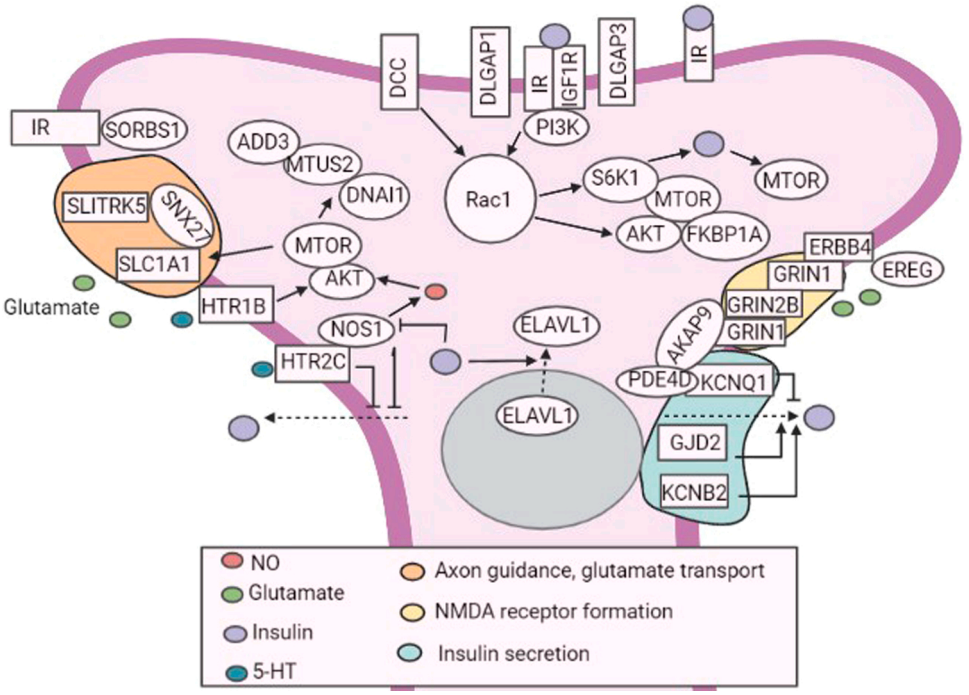

Fig. 2. Dendrite-associated cascades. Insulin is implicated predominantly in cytoskeleton formation and plasticity. Insulin also has roles in axon guidance, glutamate transport and NMDA receptor formation, with associated proteins and signalling shown (IR: Insulin receptor; IGF1R: Insulin-like growth factor 1 receptor). Created with Biorender.com.

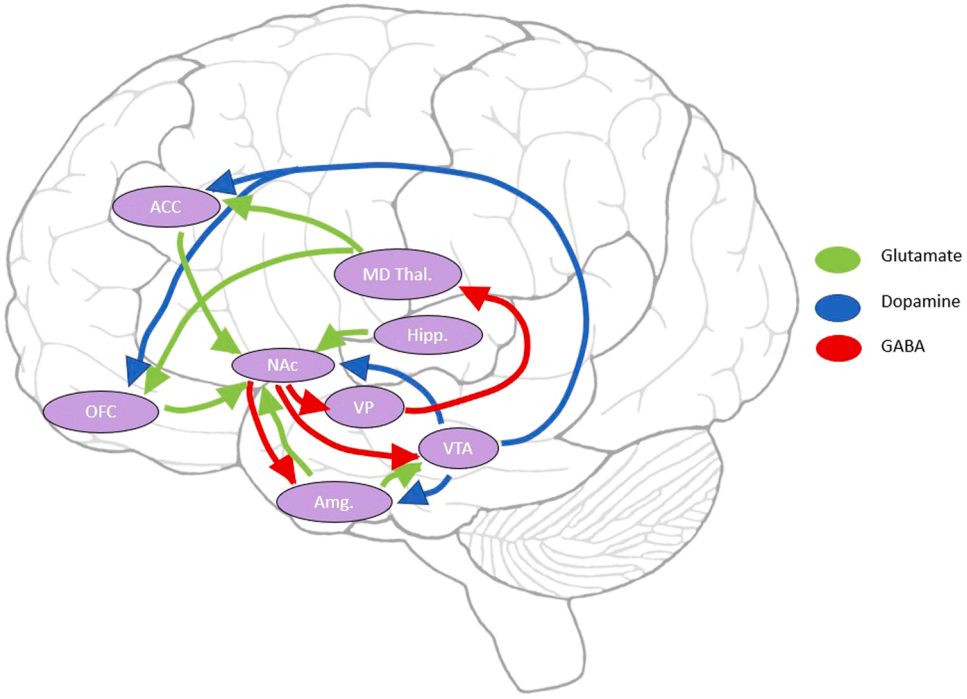

Fig. 3. Key projections and neurotransmitters implicated in reward and addictive/compulsive behaviours. ACC, Anterior cingulate cortex; OFC, Orbitofrontal cortex; NAc, Nucleus accumbens; VP, Ventral Pallidum; Amg, Amygdala; VTA, Ventral Tegmental Area; Hipp., Hippocampus; MD Thal., Mediodorsal Thalamus.

flexibility and the brain networks-associated with these functions. Insulin is reported to play essential roles in the regulation of salience via its interaction with dopaminergic transmission, orchestrating motivational behaviour and classifying value to specific rewards (Daws et al., 2011). Diabetic rats were found to have dramatically reduced dopamine cellular uptake (~65%) (Owens et al., 2005a), with insulin administration proving beneficial in restoring dopaminergic homeostasis (Patterson et al., 1998a). Brain-specific insulin resistant mice demonstrate reduced dopamine signalling in dorsal striatum and nucleus accumbens in addition to increased anxious and depressive behaviour (Kleinridders et al., 2015). Insulin's links to memory were described by an elegant experiment which induced a hippocampal-specific insulin receptor and IGF1 receptor knockout in mice (Soto et al., 2019), generating abnormal spatial learning and memory. Indeed, intranasal insulin delivery is reportedly beneficial in alleviating dementia symptoms (Avgerinos et al., 2018). No literature as of yet describes a precise link between insulin and attention, despite a reported link between T2D and attention deficit (Chen et al., 2013a).

4.4.2. Glutamate

Glutamate as the primary excitatory CNS neurotransmitter is essential in processes including learning, plasticity and memory, however excess levels yield immediate or delayed neurotoxicity via increased Ca^{2+} influx into cells (Sanacora et al., 2008). Glutamate binds to both ionotropic and metabotropic receptors yielding immediate and slow modulation effects respectively, with excessive glutamate and excitotoxicity reported in fronto-striatal circuits of both ASD and OCD patients, particularly in frontal cortical regions and is correlated with symptom severity (Naaijen et al., 2017). Insulin, via downstream PI3K and MAPK signalling is reported to regulate glutamate levels and ameliorate excitotoxicity in addition to associated ATP and BDNF depletion (Krasil'nikova et al., 2019; Nampoothiri et al., 2014)). Insulin promotes internalization of glutamatergic AMPA receptors, hence impeding the proper functioning of mature glumatergic synapses (Renger et al., 2001). Additionally, insulin upregulates the expression of the membrane-bound excitatory amino acid transporters 1 and 2 (EAAT1,2) on astrocytes, which mediate glutamate uptake from the extracellular milieu (Han et al., 2016). Indeed, knockout of EAAT2 reported to yield synaptic hyperexcitability and increased repetitive behaviours in mice (Aida et al., 2015). Despite this, the robustness of this "glutamate hypothesis" is under question, with the EU FP7 project TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive syndromes) stating that preclinical studies offer insufficient evidence of changes in frontostriatal glutamate tone in animal models of compulsivity (Anon, 2020a) and failure of NMDA antagonists such as memantine to abolish behavioural inflexibility.

4.4.3. GABA

GABA accounts for the most important neurotransmitter in the inhibitory system, with three main receptors, $GABA_A$, $GABA_B$ and $GABA_C$, the former of which, the ligand-gated ion channel $GABA_A$, is the target of the anxiolytic medication benzodiazepine. Insulin is reported to potentiate $GABA_A$ receptor-mediated tonic inhibition via AKT signalling (Wang et al., 2003), and is capable of reducing excitability in brain regions including the amygdala (Korol et al., 2018) and hippocampus. Indeed, in vivo neuroimaging of panic disorder patients demonstrated significantly reduced $GABA_A$ receptor levels in fronto-cortical regions (Nikolaus et al., 2010). GABA is also a key neurotransmitter implicated in repetitive behaviours in ASD (Chao et al., 2010). Interestingly, 90–95% of all neurons in the nucleus accumbens, a region associated with mood and addiction, are GABAergic medium spiny neurons, with GABAergic projections to the ventral pallidum and amygdala important in regulating addiction-like behaviour (Xu et al., 2020). A computational model of synaptic plasticity of such neurons in the nucleus accumbens highlighted a possible seesaw-like effect of dopamine and glutamate, with dopamine innervation from the ventral-tegmental area promoting GABAergic potentiation and glutamate promoting synaptic depression (Qi et al., 2011).

4.4.4. 5-HT

Traditional medications for the treatment of compulsive disorders are based upon the hypothesis that reduced serotonin yields pathological changes, with FDA approval of selective serotonin reuptake inhibitors including fluoxetine and sertraline which aim to attenuate such

low levels. 5-HT is synthesised in the dorsal raphe nucleus of the midbrain, with receptors 5-HT1–7 mediating the release of neurotransmitters including GABA, dopamine and glutamate across brain regions. The $5HT_{2A}$ and $5\text{-}HT_{2C}$ receptors are of particular interest, with the mechanism of many anti-psychotic medications based upon their antagonism (Thorneloe, 2019; Adams et al., 2005). Serotonin is the basis of the majority of mainstream selective serotonin reuptake inhibitors (SSRI's) such as fluoxetine and sertraline, however surprisingly little evidence links its function to compulsive processes (Stein et al., 2019), with many patients unresponsive to SSRI medications.

Insulin is reported to downregulate $5HT_{2A}$ receptors, with insulin resistance hence yielding insufficient internalisation and excessive receptor binding (Ohkura et al., 2005). Such increased receptor expression and binding has been previously found in OCD patients (Adams et al., 2005; Flaisher-Grinberg et al., 2008). Insulin is also reported to block $5HT_{2C}$ activity (Hurley et al., 2003). Interestingly, patients with T2D show increased rate of polymorphisms in $5HT_{2A/2C}$ receptors (Kring et al., 2009). The influence of these receptors on behaviour can be better understood with the administration of the $5\text{-}HT_{2A/2C}$ agonist 2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI), with mice demonstrating elevated cortical glutamate levels, indicating excessive excitatory neurotransmission that was attenuated via the administration of a selective $5HT_{2A}$ antagonist (Scruggs et al., 2003). Interestingly, increased glutamatergic transmission has previously been associated with OCD tendencies, with symptom severity correlated to the extent of glutamate change (Naaijen et al., 2017). DOI also increases the firing rate of dopaminergic neurons in the mPFC and VTA, in addition to increasing dopamine release, an effect attenuated with the administration of a selective $5HT_{2A}$ antagonist (Bortolozzi et al., 2005). $5\text{-}HT_{2C}$ antagonism in the orbitofrontal cortex is reported to be particularly beneficial in attenuating compulsive lever pressing activity (Flaisher-Grinberg et al., 2008).

4.5. Inflammation and dysregulated immunity

Evidence suggests that dysregulated inflammation is a link underlying metabolic disorders including diabetes and obesity (Dandona et al., 2004), and disorders of behavioural rigidity including ASD (Siniscalco et al., 2018), OCD (Attwells et al., 2017) and Alzheimer's Disease (Akiyama et al., 2000). A common feature of these behavioural rigidity disorders is the elevation of proinflammatory cytokines including IL-1β, IL-6, IL-8 and IL-12p40 (Ashwood et al., 2011), increased microglia activation, elevated numbers of CD4 T cells and enhanced macrophage M1 polarization (Prata et al., 2017). Indeed, exposure of OCD patients to LPS elicited a higher monocyte proinflammatory cytokine response than in healthy controls administered LPS, including IL1beta, IL-6, IL-8 and TNFalpha (Rodríguez et al., 2017). Chronic inflammatory responses yield a constant supply of toxic ROS and NO species, damaging neurons and glia. The possible role of insulin resistance in mediating such effects is described in T2D patients, who demonstrate reduced BBB integrity, in addition to upregulation of inflammatory genes in brain including eNOS, TNFalpha, TGFbeta1 and several chemokines (Rom et al., 2019). Insulin is reported to exert an anti-inflammatory effect in vitro, with one *s*tudy reporting its regulation of IL-6 and IL-8 secretion in microglia and astrocytes (Spielman et al., 2015). Indeed, these cell types express the insulin receptor and IGF-1 receptor, in addition to downstream IRS-1 and IRS-2. Rats that underwent inflammation-inducing trauma were reported to show reduced inflammation following administration of insulin (Zhu et al., 2018). The precise mechanism through which insulin may exert its effects is unclear, however various downstream effectors show immune regulatory functions. PI3K exerts effects on immune function (Hawkins and Stephens, 2015), with knockout mice of the p110α isoform showing impaired T cell proliferation and function, and a reduced number of CD4 + T cells (Sasaki et al., 2002). Trem2, activated in part by PI3K/Akt signalling, elicits an anti-inflammatory effect via inhibiting microglia/macrophage activation, neutrophil infiltration and suppressed neuronal apoptosis, an effect that was dampened following administration of the PI3K inhibitor LY294002 (Chen et al., 2020). T2D patients also demonstrate increased activation of p38 MAPK, which promotes IL-6, IL-8 and MCP-1 expression (Brown et al., 2015). The p38 MAPK pathway regulates the expression of several MMPs involved in inflammation including MMP-2 and MMP-9, in addition to proinflammatory cytokines including IL-6 and TNFalpha (Song et al., 2006; Underwood et al., 2000). Interestingly, there is evidence that instead of insulin resistance inducing inflammatory changes, inflammation may instead induce insulin resistance. Studies in the 1990 s showed that TNFalpha application to adipocytes yielded a loss of IRS-1 and Glut4 expression (Stephens et al., 1997). Indeed, application of aspirin to T2D patients improves glycemic control (Hundal et al., 2002). Disruption to the normal balance of myeloid and lymphoid cells exacerbate insulin resistance (Stefanovic-Racic et al., 2012; Ricardo-Gonzalez et al., 2010; Winer et al., 2009)). Indeed, an unexpected effect of the Covid-19 virus was the development of hyperglycaemia and insulin resistance over time (Hayden, 2020).

The specific association between these neuroinflammatory mediators and neurodegeneration remains disputed however Witte et al. (2010) proposed that mitochondrial dysfunction and oxidative stress are central to this progression. They suggest that altered mitochondrial function leads to impaired energy metabolism and induces neuroinflammation via NO and ROS production, which results in neurodegeneration. Indeed, mitochondrial dysfunction is a feature of numerous neurodegenerative disorders including Alzheimer's Disease, Parkinson's Disease and Huntington's Disease (Lin and Beal, 2006). Insulin signalling plays into this function, with brain-specific insulin receptor knockouts demonstrating mitochondrial dysfunction with impaired oxidative activity, particularly in the dorsal striatum and NAc, increased levels of reactive oxygen species and elevated lipid and protein oxidation in striatum and nucleus accumbens (Kleinridders et al., 2015). This study suggests that such insulin-mediated mitochondrial dysfunction is hypothesised to occur in at least three possible ways. The first concerns decreased expression of electron-transport chain proteins, the second concerns increased monoamine oxidase in the mitochondrial membrane, and finally the third concerns changes in the morphology and number of mitochondria in brain, with fission favoured in place of fusion, reducing metabolic capacity. Insulin is reported to directly affect the first two processes, however its influence over mitochondrial fission remains unclear. The T2D medication metformin elicits an anti-inflammatory effect, and interestingly improves mitochondrial efficiency in ATP production, reduces oxidative stress and rescues reduced levels of citrate synthase and COX proteins in the mitochondrial membrane of insulin resistant brains (Ruegsegger et al., 2019). Hence, insulin may have important anti-inflammatory actions, which in turn may influence mitochondrial dynamics.

4.6. Aggregates

T2D has been associated with onset of aggregate-associated diseases including Alzheimer's Disease (Rad et al., 2018) and Parkinson's Disease (De Pablo-Fernandez et al., 2018). Studies investigating the link between repetitive behaviour and aggregate accumulation in brain have positively correlated repetitive negative thinking/rumination habits and Aβ and tau accumulation, in addition to a more rapid decline of global cognition and memory. Insulin may play a role in aggregate accumulation via what is called the "GSK3 hypothesis of Alzheimer's Disease". This encompasses the insulin-governed PI3K/Akt-GSK-3β cascade, which inhibits GSK3β activation. Overactivation of this kinase, as would occur in insulin resistance, yields tau hyperphosphorylation, elevated Aβ production and local plaque-mediated microglial inflammation (Hooper et al., 2008). This was reflected in brain-specific insulin resistant mouse models which demonstrated hyperphosphorylation of the tau protein via GSK-3β activation, consistent with AD (Kleinridders et al., 2015). Aberrant autophagy, responsible for aggregate clearance is another

hypothesised mechanism of neurodegeneration. Indeed, the insulin-regulated downstream PI3K/AKT/mTOR signalling cascade is a major regulator of autophagic flux, and is altered in Alzheimer's disease and Parkinson's Disease (Heras-Sandoval et al., 2014). In turn, accumulation is reported to impair insulin signalling by impairing autophosphorylation of the receptor and reducing receptor density on dendritic spines (Zhao et al., 2008), generating a detrimental feed-forward loop. Interestingly, metformin was also shown to decrease tau and amyloid accumulation in an obese mouse model of AD (Li et al., 2012). Such aggregation promotes apoptosis via mechanisms including the disruption of normal mitochondrial function and dynamics (Han et al., 2017) and cytoskeletal dysfunction (Gendron, 2009; Alonso et al., 1994), yielding neuronal decline and impairing axonal transport.

Recent literature suggests and interesting insulin-amyloid-beta crosstalk. Insulin resistance is shown to induce Aβ accumulation (Son et al., 2012), which in turn is reported to impair insulin signalling by impairing autophosphorylation of the receptor and reducing receptor density on dendritic spines (Zhao et al., 2008). Additionally, the insulin degrading enzyme, induced by insulin signalling and responsible for its breakdown in a negative feedback loop, is also capable of metabolising Aβ. Hence, hyperinsulinemia in T2D may increase susceptibility to Aβ accumulation, and likewise Alzheimer's-associated accumulation of AB may induce insulin resistance. Indeed, Type 2 diabetes has been associated with onset of Alzheimer's Disease in numerous studies (Rad et al., 2018). Brain-specific insulin resistant mouse models demonstrated hyperphosphorylation of the tau protein via GSK-3β activation, consistent with AD (Kleinridders et al., 2015; Gratuze et al., 2018; Schubert et al., 2004). In summary, insulin signalling is associated with changes in Aβ and tau accumulation, with the insulin-degrading enzyme also capable of metabolising both insulin and Aβ.

4.7. Myelination

Myelination involves oligodendrocyte synthesis of the lipid-rich myelin sheath, which coats axons to increase the speed of electrical impulse propagation, essential for the formation of connective networks between brain regions and hemispheres (Felts et al., 1997). White matter structural connectivity changes are reported across regions including the cerebellum, anterior cingulate gyrus, hippocampus and frontostriatal circuits in disorders including OCD (Ziegler et al., 2019; Gan et al., 2017)), ASD (Galvez-Contreras et al., 2020) and Alzheimer's (Nasrabady et al., 2018). Altered myelination patterns were also identified in quinpirole mouse models of compulsive behaviour (Straathof et al., 2020). Insulin is reported to govern oligodendrocyte precursor proliferation and maturation into myelinating cells, with early studies of insulin and IGF-1 administration to cultures demonstrating increased proliferation of oligodendrocyte precursor cells, increased maturation of oligodendrocytes and elevated myelin levels compared to unadministered controls (McMorris and Dubois-Dalcq, 1988; Mozell and McMorris, 1991). This occurs via IGF1-induced expression of Noggin and Smad6, which regulate oligodendrocyte differentiation and maturation via inhibiting BMP signalling (Hsieh et al., 2004). Indeed, IGF1 knockout mice demonstrate reduced volume of the corpus callosum and anterior commissure, in addition to reduced oligodendrocyte population (Beck et al., 1995). Patients with diabetes type 2 are reported to demonstrate white matter microstructure abnormalities while TALLYHO/JngJ mouse models of T2D demonstrate impaired white matter connectivity in corpus callosum, dorsomedial striatum and superior cerebellar peduncle (van de Vondervoort et al., 2019; Xiong et al., 2016; Breteler et al., 2003).

5. Insulin in disorders of behavioural inflexibility

5.1. OCD

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Obsessive-Compulsive Disorder is diagnosed on the basis of the* presence of obsessions, compulsions, or both, in which the obsessions or compulsions are time-consuming (e.g., take more than 1 h per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition or mental disorder (Anon, 2020b). Compulsions are repetitive behaviours or mental acts that the individual feels compelled to do in response to an obsession according to rigid rules, or to achieve a sense of 'completeness'. Common sets of obsessions and compulsions in patients with OCD include concerns about contamination together with cleaning, intrusive aggressive or sexual thoughts together with mental rituals, concerns about self-harm or harm to others together with checking, and concerns about symmetry together with ordering or counting (Bloch et al., 2008). Neuroimaging and cognitive-affective studies in animal models have indicated that hyperactivation of the parallel, partly segregated cortico-striato-thalamo-cortical loops responsible for motivational, sensorimotor, affective and cognitive processes is responsible for obsessive-compulsive symptomology (Ahmari et al., 2013; Parmar and Sarkar, 2016; J et al., 2019)). Extra-CSTC regions such as the hippocampus (Boedhoe et al., 2017b), governing learning and memory, and the cerebellum (Zhang et al., 2019a), regulating both motor control and impulsivity (Miquel et al., 2019) have also been associated with OCD pathology due to their interactions with regions implicated in flexible decision-making including the striatum and cingulate areas (Zhang et al., 2019b) PFC (Zhang et al., 2019a) and amygdala in conditioned response (Pikkarainen et al., 1998). Dopaminergic signalling is significant across studies, with administration of the D2 agonist quinpirole influencing stereotypy behaviour in mice (Korff et al., 2008), while glutamatergic and GABAergic neurotransmitter signalling has been implicated with the benefit of drugs including memantine and various anti-convulsants in symptom attenuation (Marinova, Z., Chuang, D.M., Fineberg, N. Z, 2017). Due to a lack of clear diagnostic biomarkers and heavy reliance on symptom-based diagnosis, large sample sizes are crucial to underpin relevant functional and structural brain changes in patients. This was the aim of the imaging genetics ENIGMA consortium, an international collaborative effort across 15 countries to better define functional and structural alterations in brain disorders including OCD (Heuvel et al., 2022). This study showed that patients had a larger thalamus and pallidum and smaller hippocampus. Medicated adult OCD patients, in comparison to controls, had widespread abnormalities in cortical thickness, mainly in relation to frontal, temporal, parietal and occipital regions. Centrality, mainly of the cingulate and orbitofrontal areas, was associated with OCD disease duration, indicative of greater involvement of these regions with chronicity. White matter structural connectivity changes are reported in OCD patients, with a study by Ziegler et al. (2019) ; Gan et al. (2017) demonstrating reduced myelination in the dorsomedial and dorsolateral frontal regions and ventral striatum, correlated with a compulsive phenotype. DTI studies across patients report decreased white matter integrity in the corpus callosum, cingulate bundle and internal capsule (Koch et al., 2014). Altered myelination patterns were also identified in quinpirole mouse models of compulsive behaviour (Straathof et al., 2020).

Insulin signalling is hypothesised to play a role in OCD based on a previous molecular landscape study (van de Vondervoort et al., 2016), in which results of GWAS studies of 1465 individuals affected with OCD, 5557 ancestry-matched controls and 400 complete trios were compiled into significant networks. Other literature supports this hypothesis, with a recent study correlating compulsivity in OCD with insulin-associated traits (T2D, HbA1C status of glycosylated hemoglobin, fasting insulin levels, fasting glucose levels and 2 h glucose levels) (Bralten et al., 2020). Indeed, animal models of T2D show increased compulsive-like behaviour, in addition to elevated anxiety, another feature of OCD (van de Vondervoort et al., 2019). Key mechanisms through which insulin elicits such effects include its regulation of synaptogenesis and

dendritic spine density (van de Vondervoort et al., 2016). According to this molecular landscape study, insulin additionally regulates glutamatergic and serotonergic signalling, both of which have been linked to OCD (Stein et al., 2019). Dysregulated immunity features in OCD (Marazziti et al., 2018), with insulin reported to exert an anti-inflammatory effect in vitro. One study reports a role of insulin in regulating the inflammatory status of microglia and astrocytes via the regulation of IL-6 and IL-8 secretion (Spielman et al., 2015) while the downstream effector PI3K regulates T cell proliferation and function (Hawkins and Stephens, 2015). Insulin antagonises the FOXO family of transcription factors, with FOXO1 in particular reported to regulate phagocytosis, chemotaxis and neutrophil recruitment in addition to macrophage proinflammatory signalling (Dong et al., 2017; Fan et al., 2010). Insulin is also hypothesised to yield an anti-inflammatory effect via its regulation of hyperglycaemia. High glucose levels may generate an inflammatory response due to "glucose toxicity", generating cell stress and ROS production (Kumar et al., 2014).

5.2. Addiction

Addiction is a neurophysiological disorder characterised by intense and persistent urges to engage in specific behaviours regardless of harm. Typical signs encompass a persistent, compulsive engagement with rewarding stimuli, and difficulty in inhibiting behaviours despite negative consequences, consequently yielding short-term benefits and long-term harms. Typical examples include alcoholism, drug addiction (eg. cannabis, cocaine, nicotine, opioid), video game addiction and gambling addiction. It is widely accepted that the means through which addictive behaviours achieve their effects is via stimulation of dopamine signalling in the mesolimbic circuit in regions including the nucleus accumbens, a centre for motivation control (Di Chiara and Imperato, 1988). Dopamine receptor 1 (D1R) and 2 (D2R) are the two key associated receptors expressed throughout the brain, with D1R associated with sensitisation to drug-related reward and D2R implicated with compulsive drug intake (Bertran-Gonzalez et al., 2008; Perez et al., 2011). An fMRI study examining the circuits implicated with vulnerability and resilience to developing drug addictions revealed significant hypoconnectivity in orbitofrontal and ventromedial prefrontal cortical-striatal circuits (implicated in goal-directed behaviour and behaviour switching) (Ersche et al., 2020). Insulin signalling and dopaminergic neurotransmission are arguably not independent, with studies suggesting that crosstalk exists. An in vivo study of dopaminergic uptake via the DAT transporter in rat brain showed that velocity of dopamine transport is significantly reduced in fasted rats with reduced circulating insulin; an effect that was rescued via insulin administration (Patterson et al., 1998b). Streptozocin administration to rats, depleting peripheral and central insulin levels, also reduced dopamine clearance in rat striatum by 65% (Owens et al., 2005b). DAT expression on neurons is also regulated via the insulin-Akt pathway in vitro (Garcia et al., 2005). A key paper by Kleinridders et al. (2015) shows that in mice with brain-specific insulin resistance, dopamine metabolism is increased, in addition to increased anxious behaviour. Insulin receptors are expressed on dopaminergic neurons within mesolimbic projections. For example, insulin administration to the VTA, the main source of dopaminergic neuronal projections in the mesocortical circuit, generated reduced somatodendritic concentrations of dopamine (Mebel et al., 2012). Interestingly, the T2D diabetes medication metformin, when injected into nucleus accumbens, effectively attenuates cue-induced cocaine seeking in rats, hypothesised as due to its activation of adenosine monophosphate activated protein kinase (AMPK), functioning as a cellular energy sensor (Chan et al., 2022).

5.3. Anorexia nervosa

Anorexia nervosa (AN) is an eating disorder that normally manifests during late childhood and adolescence that has one of the highest mortality rates among psychiatric illnesses. As consequence of the associated starvation and increased catabolic metabolism (Misra and Klibanski, 2014), clinical characteristics include loss of body fat and lean mass, decrease of bone mass, amenorrhea, hypertension, bradycardia and hypothermia (Von Schwanenflug et al., 2019). Additionally, patients present with increased cognitive and behavioural rigidity (expressed by traits such as self-demanding, perfectionistic, lack of spontaneous behaviour, poor cognitive flexibility and attention to details) (Buzzichelli et al., 2018; Maria et al., 2020), which was even contemplated as endophenotype with a high inherited and neurobiological component (Holliday et al., 2005; Milton et al., 2021). Neuropsychological studies report significant deficits in attention, memory and executive function (e.g. decision making, set-shifting and global processing) (Foldi et al., 2021), in addition to inflexible thought patterns and rigid behaviour in patients with AN, with excessive self-regulation of diet and exercise regimens, even in the face of a rapid decrease in body weight (Foldi et al., 2021; Miles et al., 2020), (Wierenga et al., 2014)). This inflexibility is further reflected in AN individuals, who make more perseverative errors on set-shifting tasks, including the Wisconsin Card Sorting Test (WCST), than control participants (Tchanturia et al., 2012, 2004), persisting even after weight recovery (Miles et al., 2020). Reports suggest an increased insulin sensitivity state in AN, with the potential to impact reward-based learning (Fukushima et al., 1993; Berner et al., 2019)). Central insulin signalling plays an important role in maintaining optimal dopamine (DA) tone in ventral and dorsal striatum by tuning rates of synaptic DA release (Stouffer et al., 2015b) and clearance (Schoffelmeer et al., 2011; Williams et al., 2007), with impairments in central insulin signalling having a direct impact on brain DA systems (Kleinridders et al., 2015; Könner et al., 2011; Schoffelmeer et al., 2011; Sevak et al., 2007; Williams et al., 2007). Specifically, insulin receptors are expressed on dopaminergic neurons in the ventral tegmental area (VTA), a major hub in the mesolimbic circuitry governing food seeking behaviours (Ilyas et al., 2019). Alterations in normal insulin balance may promote restrictive dietary and exercise practices and maintenance of the disorder.

5.4. Obesity and binge eating

Functional, molecular and genetic neuroimaging studies point to decreased basal metabolism in the prefrontal cortex and striatum, dopaminergic alterations and increased activation of reward brain areas in response to palatable food cues in people living with obesity. Elevated reward region responsivity may trigger food craving and predict future weight gain, whereas reduced activation of executive or inhibitory control pathways is associated with the development of obesity and weight regain after dieting. The direction of causality of these associations remains underexplored by a paucity of longitudinal studies and the underlying mechanism for these associations is not known. Dopamine pathways in particular are thought to play an important role in the processing of food reward salience (De Araujo et al., 2012; Lindgren et al., 2018; Martel and Fantino, 1996; Schultz, 2016). Reward from natural (e.g. food and sex) and non-natural (e.g. drugs of addiction, which supplant natural rewards in valence, and have no beneficial evolutionary purpose) sources, both lead to increased dopamine release in the nucleus accumbens and the ventral striatum. Dopamine pathways appear to be particularly important in processing the hedonic appeal rather than appetitive drive for food, for example preference for sugary food as opposed to hunger for any type of food (Szczypka et al., 2001; Volkow et al., 2008). Volkow's study found that the dopamine receptor 2 was reduced only at a BMI of over 50 (Wang et al., 2014), suggesting that binge eating or food addiction aligns more with dopamine hypofunction and reduced DRD2 availability. Binge eating, and the purchase and consumption of highly palatable calorie dense food has been associated with steeper discounting of delayed future rewards (Appelhans et al., 2011; Davis et al., 2010; Nederkoorn et al., 2009, 2007). Bello et al., in their review of the role of dopamine in binge eating, suggest

that sustained stimulation of the dopamine systems by bingeing, promoted by pre-existing conditions (e.g. genetic traits (D2 receptor polymorphisms), dietary restraint, stress, etc.) results in progressive impairments of dopamine signalling (Bello and Hajnal, 2010), which perpetuate the behaviour. People living with obesity exhibit difficulty inhibiting automatic responses on inhibitory control tasks, tending to engage in habitual or overlearned behaviours associated with weakened connectivity in executive control networks and enhanced connectivity in salience network and default mode networks and show a preference for smaller, immediate rewards over larger, delayed rewards relative to normal weight individuals (Donofry et al., 2020).

Insulin signalling alterations may induce executive functioning deficits in the brain, with T2D associated with cognitive decline (Ebady et al., 2008). Insulin receptors appear abundantly in the brain, with the IRS-2 receptor substrate particularly important in excessive eating behaviours. Indeed, knockout mice for IRS-2 develop a diet-driven obese phenotype (Lin et al., 2004). This effect may be partially attributed to insulin receptors in specific hypothalamic subnuclei. Furthermore, central insulin signalling may exert peripheral changes, with insulin signalling in the hypothalamus necessary for controlling hepatic glucose production (Heni et al., 2015). Insulin signalling may play a direct role in food reward processing via regulation of synaptic dopamine balance (Stouffer et al., 2015b; Schoffelmeer et al., 2011; Williams et al., 2007), thus altering the rewarding properties of food. In humans, the hedonic appeal for food is altered by intranasal insulin in women (Schneider et al., 2022); women who have already eaten a meal experienced reduced hedonic appeal toward a dessert (e.g. chocolate cookies).

5.5. Alzheimer's disease

Alzheimer's Disease (AD) is the most common neurodegenerative disorder and the most prevalent cause of dementia in aged people (>65 years) (Mattson, 2004; Qiu et al., 2009), with the incidence expected to increase three-fold by 2050 (Livingston et al., 2020). Almost two-thirds of AD patients are women. AD is characterised by a slow and progressive cognitive decline affecting learning and memory, language, and executive function, and the presence of amyloid plaques, neurofibrillary tangles, activated microglia, reactive astrocytes, synapse loss, and cortical atrophy (Deture and Dickson, 2019). These classical AD neuropathological signs are accompanied by compromised brain glucose uptake and insulin sensitivity (Baglietto-Vargas et al., 2016), and downregulation of insulin binding sites along the blood-brain barrier (Leclerc et al., 2023).

In AD animal models, the age of onset of progressive cognitive decline and amyloid beta deposition is rather variable, with memory impairments starting as early as 3 months and amyloidosis at 4–6 months (Platt et al., 1832). Glucose intolerance has been described in 3xTg-AD mouse model (Vandal et al., 2015) and APP/PS1 mice (Takeda et al., 2010). As memory loss is the primary AD symptom, behavioural testing in AD mouse models has predominantly focussed on (spatial) reference memory and assessing aspects of executive function is less common. However, several AD animal models have been shown to have deficits in set-shifting and reversal learning tasks, mostly in aged animals (Granger et al., 2016; Guarino et al., 2019; Romberg et al., 2013; Rorabaugh et al., 2017; Shepherd et al., 2021), reviewed in (Webster et al., 2014). Using a touchscreen-based reversal task which more accurately reflects testing in a clinical setting, Van den Broeck et al. (2019). showed early reversal impairment in 6-month-old APPPS1–21 mice). In human studies, compared to healthy controls, AD cases tend to complete fewer categories and make more perseverative errors in the Wisconsin Card Sorting Task, suggesting impaired set-shifting capability (Chiu et al., 2014; Guarino et al., 2019; Nagahama et al., 2003; Paulsen et al., 1995; Redondo et al., 2016; Tei et al., 1997).

How insulin might modulate AD-related neuropathology has been reviewed above (see section "Aggregates"). T2D is one of the most common comorbidities of AD (Wang et al., 2018) and the two disorders share pathophysiological characteristics, including insulin resistance, which suggests common or related underlying processes (Blázquez et al., 2014), although a recent study found no genetic overlap between Type 2 diabetes mellitus (T2DM) and AD (Hardy et al., 2022). T2DM increases the risk of developing dementia by 50% (Zhang et al., 2017), and the risk is more pronounced the earlier the onset of T2DM (Barbiellini Amidei et al., 2021). Manipulations which induce insulin resistance in AD animal models have been shown to exacerbate the amyloid beta plaque accumulation in the brain and worsen cognitive impairments (Kimura, 2016). Antidiabetic drugs, including intranasal insulin, have shown promise in ameliorating cognitive symptoms and some AD biomarkers in patients (Michailidis et al., 2022), but large-scale longitudinal studies are required to establish their efficacy.

5.6. Parkinson's disease

Parkinson's disease is a chronic neurodegenerative condition which manifests predominantly as motor abnormalities including rigidity, increased muscle tone and resistance. Cognitive deficits including executive dysfunction are a common feature, incorporating deficits in planning, problem solving and shifting attention on tasks. Psychiatric manifestations of Parkinson's can include features of a premorbid personality including emotional and attitudinal inflexibility, mental rigidity, anxiety and a tendency towards depressive symptoms including introversion, apathy, deficits on reward processing and novelty seeking (Rodriguez-Oroz et al., 2009).

Supraspinal and cortical mechanisms, in addition to the basal ganglia and motor thalamus, have been proposed in the pathophysiological origins of motor rigidity. GABA and cholinergic interneuronal regulation in cortico-nigral-palladial microcircuits are likely engaged. Depletion of nigrostriatal and overactivity of prefrontal dopamine are associated with executive dysfunction in early stages of disease (Baig et al., 2017). Other neurotransmitters including acetylcholine and noradrenaline are likely involved in cognitive manifestations of the disease (Solinas et al., 2019). Striatal dopaminergic deficits are strongly implicated in some of the psychiatric features of Parkinson's including novelty seeking, impulsive and addictive behaviours (Baig et al., 2017). Psychiatric features in Parkinson's such as punding, hobbyism, impulse control disorders, behavioural addictions such as gambling, compulsive eating, shopping and hypersexuality manifest as complications derived from dopaminergic treatment. Other symptoms such as apathy may improve with treatment and symptoms may vary associated with on-off drug fluctuations and altered dopaminergic states.

T2D is reported to increase risk of developing Parkinson's disease, with a faster progression and worsening of motor and cognitive symptoms over time (Cheong et al., 2020). Neuroimaging has revealed that T2DM has an adverse effect on striatal dopamine transporter binding and cortical thickness, consistent with a decline in executive function (Cheong et al., 2020). Higher cerebrospinal fluid (CSF) Tau, a non-specific fluid biomarker in several neurodegenerative diseases are reported to be higher in Parkinson's patients with T2DM compared to patients without T2DM (Pagano et al., 2018). Insulin receptors are expressed in areas of the brain implicated in Parkinson's disease including the basal ganglia, substantia nigra, cerebral cortex and hypothalamus. Systemic insulin resistance observed in metabolic conditions such as T2DM is reflected in the brain, with the failure of cells to respond appropriately to insulin signalling. As insulin sensitivity declines, regions in the brain including the frontal lobes and hippocampus are susceptible to cerebrovascular disease and neurodegeneration reflected through infarcts, reduced grey and white matter volume from atrophy (Ryan et al., 2014). Coupled to underlying biochemical alterations these may contribute to motor, cognitive and psychiatric impairments in Parkinson's patients with T2DM. Insulin in turn may play a role in neuroprotection. A recent meta-analysis of antidiabetic agents for the treatment of Parkinson's disease suggests that treatment with the diabetes medication exenatide is associated with the alleviation of

cognitive, motor and nonmotor symptoms (Aviles-Olmos et al., 2013). However, the insulin-Parkinson's link has yet to be concretely established, and long-term studies with a large sample size of patients with Parkinson's are required.

6. Conclusion

Accumulating evidence points towards the significance of insulin, not only in metabolic roles, but also as a major regulator of neurophysiological functions. Insulin and IGF1 receptors are highly expressed across brain, with T2D associated with changes in white and grey matter volume and functional connectivity. Indeed, there is evidence that T2D medication such as metformin can be repurposed for the treatment of associated behavioural alterations. Next steps involve elucidation of which specific mechanisms generate the strongest downstream behavioural impact, and how these may be therapeutically targeted.

As the English comedian Jasper Carrott once said, "laughter is the best medicine… unless you're diabetic, then insulin comes pretty high up the list". Perhaps the same can be said for behavioural inflexibility.

Declaration of competing interest

The authors declare no conflict of interest.

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