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Brain structure and trait impulsivity: A comparative VBM study contrasting neural correlates of traditional and alternative concepts in healthy subjects

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ABSTRACT

Impulsivity as a trait modulates a range of cognitive functions, e.g. planning, decision-making, or response inhibition. Recent behavioural and psychometric findings challenge both the neurobiological models as well as the conceptualisation of psychometric measures of impulsivity. In the present study, we aimed to test the association of brain structure with the Barratt Impulsiveness Scale (BIS-11), a commonly applied self-rating instrument for impulsivity, using both the classical three-factor-model for impulsive behaviour (motor (*IM*), attentional (*IA*) and non-planning impulsivity (*INP*)), as well as the recently proposed alternative model contrasting inability to wait for reward (*IWR*) as an index of impulsive choice and rapid response style (RRS) as an index of impulsive action. We analysed brain structural data in a community sample of 85 healthy individuals, who completed the BIS-11, using voxel-based morphometry (CAT12: Computational Anatomy Toolbox 12). Regional volumes were correlated with the three traditional BIS-11 subscales, as well as *IWR* and *RRS*. BIS-11 total score was positively correlated with right inferior parietal, postcentral, and supramarginal grey matter ($p < 0.05$, FWE cluster-level corrected). Attentional impulsivity (IA) was also positively correlated with right inferior and superior parietal and supramarginal gyri. Comparison of the other scales did show some divergence, but most correlations did not survive correction for multiple comparisons. Our findings suggest that difference facets of trait impulsivity might be related to different brain areas, and might thus dissociate along distinct but overlapping neural networks. In contrast to lesion or patient studies, these analyses delineate physiological variance, and can thus help to conceptualise network models in the absence of pathology.

1. Introduction

Impulsivity is a complex trait construct, whose neurobiological basis has been the topic of an increasing number of recent studies (Dalley et al., 2011; Dalley and Robbins, 2017). A frequently used conceptualisation is that of impulsivity "as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others" (Moeller et al., 2001). However, the development of the concept has frequently encountered shifting definitions (Evenden, 1999).

The degree to which this trait is found in an individual appears to be a strong factor in multiple behaviours, ranging from planning over response inhibition to decision making (Dalley and Robbins, 2017; Dalley and Roiser, 2012). Trait impulsivity does not only influence life of healthy individuals but when abnormally strong is a common symptom in several psychiatric disorders, like substance abuse (Allen et al., 1998), affective disorders (Jimenez et al., 2016; Swann et al., 2001), personality disorders (Mulder et al., 1999) or psychotic disorders (Nanda et al., 2016). It complicates course of disease and treatment through contributing to aggressive behaviour and suicidality (E. S. Barratt et al., 1999; Rimkeviciene et al., 2015).

As a complex trait, impulsivity has cognitive, emotional and behavioural aspects, and there is no final consensus whether these aspects are neurobiologically independent (Dalley and Robbins, 2017). There are two behaviourally distinct concepts, which were initially derived from animal models: the reward-discounting model, where impulsivity is defined as inability to wait for a larger reward, also called impulsive choice (Monterosso and Ainslie, 1999), and the rapid response model, which defines impulsivity as responding without adequate assessment of context, also called impulsive action (Evenden, 1999). These models laid groundwork to laboratory measurements of impulsivity like the

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Immediate Memory-Delayed Memory Task (D. M. Dougherty et al., 1999) or the Two-Choice Test (Cherek and Lane, 1999). Such tasks aimed to contrast subjective self-report measurements like the repeatedly revised Barratt Impulsiveness Scale (Patton et al., 1995; Swann et al., 2002), because it was unclear, whether BIS-11 really reflected these biological models of impulsivity. Several behavioural studies in rats and humans indicate independence of impulsive choice and impulsive action (Broos et al., 2012; Solanto et al., 2001; van den Bos et al., 2014). Another recent study employing behavioural tasks and among others BIS-11 similarly suggests a three-factor model of discounting of delayed rewards; inability to inhibit a prepotent motor response and impulsive personality traits, reflecting self-reported attributions of self-regulatory capacity (MacKillop et al., 2016).

In children and adolescents with attention deficit/hyperactivity disorder several studies associated impulsive action to response inhibition neural networks and impulsive choice to reward processing neural networks, suggesting a distinct neurobiological foundation for both aspects (Ortal et al., 2015; Patros et al., 2016).

But evidence for neuroanatomical links of these factors based on self-report measurements remains scarce, because most structural MRI-studies employ BIS-11, which captures different sub-dimensions of trait impulsivity. Therefore further studies of neuroanatomical links based on the two behaviourally distinct factors are needed to evaluate ways of self-report data acquisition, that are much easier applicable than behavioural measures.

BIS-11 is often seen as a gold standard, which is most widely used in studies of impulsivity and its biological, psychological, and behavioural correlates.

The scale has been extensively validated in healthy samples and was translated in 11 languages. Stanford et al. created a big pooled sample consisting of 1577 healthy adults, mostly college students. The test-retest reliability of BIS-11 total score at one month is significant with $p < 0.01$ in 153 participants and Spearman's Rho 0.83 in 1577 participants. They also reviewed about 60 published studies in healthy populations using BIS-11 to explore the nature of impulsivity (Stanford et al., 2009).

The scale is highly correlated with similar self-report measures (convergent validity) like Zuckerman Sensation-Seeking Scale (SSS-V), Eysenck Impulsiveness Scale (I7) and Behavioral Inhibition/Activation Scales (BIS/BAS), but not significantly correlated with behavioural measures of impulsiveness (Barratt and Patton, 1983; Lane et al., 2003). It is suggested that self-report measures tend to capture impulsivity over a longer period of time in a person's biography as a trait, whereas behavioural tasks focus on state-dependent aspects of impulsivity (Dougherty et al., 2003).

The total score and the three sub-constructs did not differ significantly between healthy men and women (Stanford et al., 2009). A smaller study found decreasing BIS-11 total scores in a subgroup of healthy participants older than 50y compared to two younger subgroups (Moustafa et al., 2017). To our best knowledge further correlations of BIS-11 scores to age or IQ have not been examined in healthy subjects.

The scale has been used to measure trait impulsivity in functional, but most of all in structural, especially voxel-based morphometry (VBM) studies. Therefore, we chose this anatomical parameter for our analysis for better comparability. Most former VBM-studies employed BIS-11 to characterise and compare trait impulsivity between patients and healthy samples. Most of these studies do not report GMV analyses associated with BIS-11, though (Crunelle et al., 2014; Du et al., 2016; Kaag et al., 2014; Kogachi et al., 2017; T. Y. Lee et al., 2013; Matsuo et al., 2009a, b; Olivo et al., 2018; Qiu et al., 2013; Soloff et al., 2008; Sousa et al., 2017; Y. Wang et al., 2016b; Yip et al., 2018). Derived from structural and functional case-control studies like these a neuroanatomical model of impulsivity has been proposed. It assumes a cortico-striatal network with prefrontal regions mediating cognitive control (in particular vmPFC, OFC and ACC) and a striatal component driving the impulse (Fineberg et al., 2014; Kim and Lee, 2011; Miller and Cohen, 2001). The right inferior frontal cortex is proposed to be an internally or externally triggered “brake” to this system and is therefore connected to all sensory cortical areas (Aron et al., 2014).

Only two VBM studies in healthy subjects report correlations of grey matter volume (GMV) with BIS-11 and its subscales, which are not entirely in line with the findings in patients. In 34 healthy subjects positive correlations in dorsolateral prefrontal gyrus (DLPFC) and middle and anterior cingulate cortex (ACC) with BIS-11 total, non-planning (*INP*) and attentional impulsivity (*IA*) subscales and orbitofrontal cortex (OFC) with *INP*, as well as negative correlation of putamen GMV with *INP*, but no correlations with BIS-11 motor subscale (*IM*) were identified (Cho et al., 2013). And in 62 healthy subjects also negative correlations of GMV in OFC and ACC with BIS-11 total and in OFC with *INP* and *IM* were shown (Matsuo et al., 2009a, b). Voxel-based lesion–symptom mapping (VLSM) in 131 war veterans with focal, penetrating traumatic brain injury revealed an association of higher global BIS-11 scores with bilateral prefrontal as well as lateral temporal cortical damage, while motor impulsivity has been associated more specifically with left prefrontal damage also hinting towards a prefrontal involvement in motor and global trait impulsivity (McDonald et al., 2017).

Linking trait impulsivity to brain structure is crucially dependent on the clear conceptualisation of the phenotype, especially since impulsivity is typically assessed through either behaviour or self-report, and the above fractionation depends on these instruments (Sharma et al., 2013). However, recent studies have challenged BIS-11 for some psychometric properties (Steinberg et al., 2013), raising the question whether BIS-11 subdomains are fit to specifically measure biologically different aspects of impulsivity. Recent findings have fostered an alternative model emerging from both experimental work as well as self-report items on which BIS-11 is based: a two factorial solution derived from the original BIS-11 was suggested, directly reflecting the above-mentioned concepts of inability to wait for a larger reward and rapid response style (Haden and Shiva, 2008; Reise et al., 2013). This has been paralleled in the re-conceptualisation of two main facets of impulsivity, which can be described as impulsive action and impulsive choice (Hamilton et al., 2015a, b).

Our current study is a reappraisal of association variation in brain structure with self-report impulsivity in human subjects. Using the BIS-11 we tested both the classical three-factor model as well as the more recently emerged two-factor model based on rapid-response impulsivity and choice impulsivity. Since there is much evidence for the two dimensions of impulsive action and impulsive choice to be biologically independent, e.g. in animal models and in behavioural laboratory measurements of impulsivity, we hypothesised that these recent two-factor formulation would capture these two biologically distinct aspects, although to our best knowledge no correlational studies with behavioural measures yet exist. We therefore aimed to detect more specific biological links to brain structural correlates of trait-impulsivity. Since most former VBM-studies are based on BIS-11 total and the classic three-factor model mixing items of these two distinct dimensions, we expected links to implicated brain structures like the ACC and orbitofrontal cortices applying the conventional model (Matsuo et al., 2009a, b). However, we also anticipated differing results associated with the two-factor model, such as correlations in dorsal and ventral striatum, dorsolateral prefrontal cortex (Cho et al., 2013; Magen et al., 2014), corresponding to the fewer MRI studies applying behavioural tasks for assessment of impulsivity.

2. Methods

2.1. Participants and BIS-11

We included 85 healthy young adults from the community (57 female, 28 male; mean age 24.06 ± 2.98 yrs, range 19–38 yrs). All

participants gave written informed consent to a study protocol approved by the local Ethics Committee of Jena University Medical School.

All participants were screened for the exclusion criteria of major neurological, current or former psychiatric conditions and unmedicated internal medical conditions, as well as psychiatric history in first-degree relatives. To exclude major cognitive impairment, IQ was estimated using the MWT-B, a German language inventory similar to the NART (National Adult Reading Test), which showed a mean IQ (SD) across subjects of 116.07 ± 13.53 (Antretter et al., 2013). The participants also completed the Edinburgh Handedness Inventory (Oldfield, 1971) showing a mean value of 0.72 ± 0.47. Scale values range between maximum left-handed (−1.00) to maximum right-handed (1.00).

To measure trait impulsivity participants underwent the German adaptation of Barratt Impulsiveness Scale, 11th version (BIS-11) (Patton et al., 1995; Preuss et al., 2008; Stanford et al., 2009), an established self-report questionnaire with 30 items, first suggested by Barratt in 1985. Participants rated how often they think or act as described in each item on a four-point Likert-type scale (1 rarely, 2 occasionally, 3 often, and 4 almost always). Values were summed up as chosen, except for items 1, 7, 8, 9, 10, 12, 13, 15, 20, 29 and 30, which were rated inversely. Overall results can range from 30 to 120, higher values corresponding with higher impulsivity. Barratt also proposed three subtraits of impulsivity, namely non-planning impulsivity, attentional and motor impulsivity, consisting of 8 (attentional subscale) to 11 items (motor and non-planning impulsivity), which were added up accordingly.

Furthermore, we calculated the two scores proposed by Reise et al. The scale characterizing “inability to wait for reward” (*IWR*) resulted from BIS-11 items 1, 7, 8, 9, 12 and 20 and “rapid response style” (*RRS*) from items 6, 16, 17, 19, 21, 24 and 26, also taking inverse items into account as in the original version (Reise et al., 2013). An overview of scale value distribution in our sample as well as internal consistency between item scores of each subscale (Cronbach's α) is given in Table 1a.

None of the subscales was significantly correlated with age and gender ($p < 0.05$, two-tailed Pearson correlation), but subscales were significantly correlated with each other (Table 1b) Male and female participants showed no significant differences regarding IQ, handedness or each of the five BIS-11 subscales ($p > 0.1$, 2 -sample t-test). Age differed significantly between men and women in our sample though ($p < 0.05$, 2 -sample t-test).

Magnetic resonance imaging (MRI) and voxel-based morphometry (VBM).

All subjects underwent high–resolution T1-weighted MRI on a 3 T S Tim Trio scanner (Siemens, Erlangen, Germany) using a standard quadrature head coil and a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, α 9°, 192 contiguous sagittal slices, in-plane field of view 256 mm, voxel resolution 1 × 1 × 1 mm; acquisition time 5:21 min).

2.2. Voxel-based morphometry

For voxel-based morphometry (VBM), we used the CAT12 toolbox (Structural Brain Mapping group, Jena University Hospital, Jena, Germany) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). All T1-weighted images were corrected for bias – field inhomogeneities, then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) (Ashburner and Friston, 2005) and spatially normalised using the DARTEL algorithm (Ashburner, 2007). The segmentation process was further extended by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997). After pre-processing all scans passed an automated quality check protocol offering visualization of the correlation between the volumes using a boxplot and correlation matrix and, thus, helping to identify outliers, which were then inspected for artefacts or pre-processing errors. No scans had to be excluded due to poor quality. Scans were smoothed with a Gaussian kernel of 12 mm (FWHM). For exclusion of artefacts on the grey/white matter border (i.e. incorrect voxel classification), we applied an absolute grey matter threshold of 0.1.

To replicate former VBM-findings in DLPFC, OFC and ACC we calculated masks according to the Neuromorphometrics Atlas implemented in SPM12 and performed additional small volume corrections on the correlations of GMV and BIS-11 total and traditional subscales.

2.3. Statistics

For statistical analysis, we used the general linear model (GLM) implemented in SPM12, which makes use of Gaussian random field theory. We computed two sets of analyses: a) one GLM each (total of six separate GLMs) correlating the BIS-11 total score and each of the five subscales (i.e. IM, INP, IA, RRS, and IWR); this was intended to provide an association analysis of BIS as well as the subscales with regional brain structural variation, and b) two separate GLMs, in which the more recent two-factor model was tested with their three-factor counterpart as nuisance variable (i.e. one GLM with RRS as regressor with IM as nuisance variable; another GLM with IWR as regressor with INP as nuisance variable); this was intended to assess the association pattern of the more recent two-factor model isolating associations relatively specific to these new subscales, hence providing a formal statistical comparison between two corresponding subscales and controlling for neurobiological overlap.

For all VBM analyses, we included total intracranial volume (TIV) as a covariate in order to remove variance related to this global parameter of brain morphometry. We then performed whole-brain voxel-wise analyses calculating both positive and negative correlations between regional brain volumes and each of the (sub)scales separately. In order to correct for multiple comparisons, we employed cluster-level family-wise error (FWE) correction (with initial peak-level thresholding at $p < 0.001$ and subsequent cluster-level inference). In addition, we performed exploratory analyses at uncorrected $p < 0.001$ levels

Table 1a
Overview of distribution and internal consistency of the BIS – 11 subscales.

	BIS-11 total	BIS-11 IA	BIS-11 IM	BIS-11 I NP	BIS-11 IWR	BIS-11 RRS
mean (SD)	58.1 (± 9.4)	14.67 (± 3.83)	20.14 (± 4.04)	23.28 (± 3.87)	13.3 (± 2.51)	11.83 (± 3.14)
range	40–82	9–26	14–31	13–32	7–21	7–21
Cronbach's α	0.827	0.777	0.679	0.603	0.579	0.726

SD – standard deviation.
IA – BIS-11 subscale measuring attentional impulsivity.
IM – BIS-11 subscale measuring motor impulsivity.
INP – BIS-11 subscale measuring non-planning impulsivity.
IWR – alternative BIS-11 subscale measuring inability to wait for reward.
RRS - alternative BIS-11 subscale measuring rapid response style.

Table 1b
Correlation between subscales.

	BIS-11 total	BIS-11 IA	BIS-11 IM	BIS-11 INP	BIS-11 IWR	BIS-11 RRS
BIS-11 total	1	0.736 (0.0001 ***)	0.87 (0.0001***)	0.791 (0.0001***)	0.736 (0.0001***)	0.713 (0.0001***)
BIS-11 IA		1	0.477 (0.0001***)	0.3 (0.005 **)	0.606 (0.0001***)	0.724 (0.0001***)
BIS-11 IM			1	0.597 (0.0001***)	0.475 (0.0001***)	0.711 (0.0001***)
BIS-11 INP				1	0.692 (0.0001***)	0.274 (0.011*)
BIS-11 IWR					1	0.478 (0.0001***)
BIS-11 RRS						1

Correlations are given as Pearson correlation coefficients with two-tailed significance and p values in brackets (*p < 0.05, **p < 0.01, ***p < 0.001).
IA – BIS-11 subscale measuring attentional impulsivity.
IM – BIS-11 subscale measuring motor impulsivity.
INP – BIS-11 subscale measuring non-planning impulsivity.
IWR – alternative BIS-11 subscale measuring inability to wait for reward.
RRS - alternative BIS-11 subscale measuring rapid response style.
*p < 0.05, **p < 0.01, ***p < 0.001.

without extent thresholding (supplementary materials).

3. Results

3.1. Impulsive action

In BIS-11 *IM* and *RRS* subscales both including items measuring impulsive action, correlations with GMV did not survive FWE-correction for multiple comparisons. All uncorrected results are shown in the supplement (supplemental Fig. 1,supplemental Table 1).

3.2. Impulsive choice

The traditional BIS-11 INP subscale did not show any GMV correlations after FWE-correction for multiple comparisons. IWR subscale, also reflecting aspects of impulsive choice, showed significant positive correlations with GMV in left middle and inferior occipital gyri and in left fusiform gyrus and left cerebellum after eliminating the overlap with BIS-11 INP by including it into the statistical model as a nuisance variable (Fig. 1, Table 2).

Additional uncorrected analyses are shown in the supplement (supplemental Fig. 2, supplemental Table 2).

3.3. BIS-11 total and BIS-11 attentional

As a comparison to similar studies of impulsiveness measured by BIS-11, we also calculated VBM-correlations of BIS-11 total score and BIS-11 attentional subscale. BIS-11 total score showed significant, FWE-corrected, positive correlations with GMV in right inferior parietal, postcentral and supramarginal gyri and BIS-11 IA showed significant, FWE-corrected, positive correlations with right inferior and superior parietal and supramarginal gyri (Table 2).

The uncorrected exploratory analyses revealed several smaller clusters of positive correlations, listed in the supplement (Fig. 2, supplemental Table 3).

A re-analysis of all above findings including age as a co-variate confirmed this pattern of clusters. In order to replicate former VBM findings we performed additional small volume corrections on BIS-11 total and its three subscales with an uncorrected threshold at p < 0.001 for DLPFC, ACC and OFC bilaterally. We did not find any

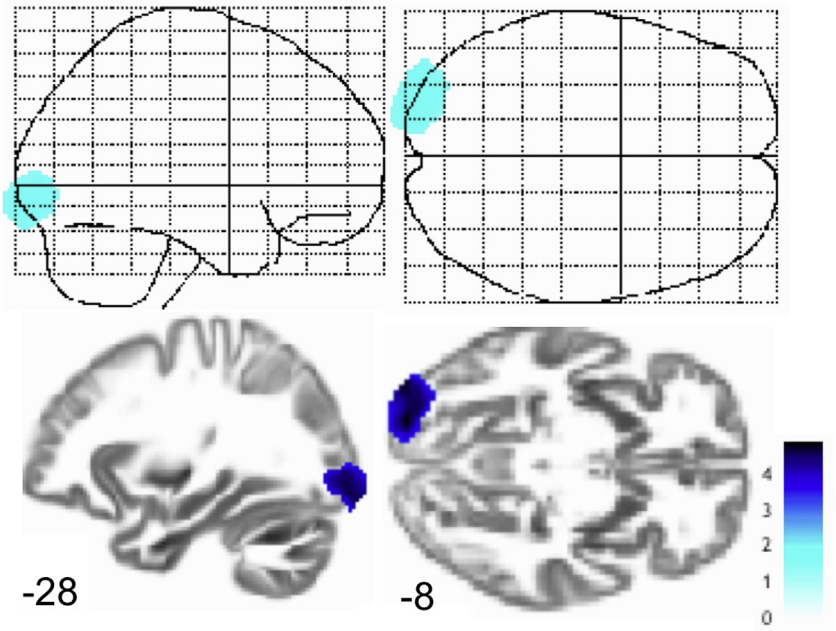

Fig. 1. –Clusters of significant positive correlation (p < 0.05, FWE-corrected) of GMV with BIS-11 *IWR*, an index of impulsive choice.

Table 2
Positive correlations ($p < 0.05$, FWE-corrected) of GMV with BIS-11 *INP* and *IWR subscales* as indices of impulsive choice independently and for *IWR* excluding *INP, as well as BIS-11 total score and IA* subscale.

Anatomical region	co-ordinates of peak voxel	*k*	p (FWE-corrected at cluster-level)	T
BIS-11 INP				
			No voxels survived	
BIS-11 IWR				
Left middle and inferior occipital gyri	−21; −94; −6	1984	0.016	4.43
	−36; −94; −9			4.39
	−27; −99; −15			4.08
BIS-11 IWR excluding BIS-11 INP				
Left fusiform gyrus, left cerebellum	−22; −94; −4	2085	0.013	4.87
BIS-11 total score				
Right inferior parietal, postcentral and supramarginal gyri	44; −38; 51	1835	0.001	5.83
	52; −52; 52			3.69
	40; −34; 34			3.47
BIS-11 attentional				
Right inferior and superior parietal and supramarginal gyri	45; −38; 48	1714	0.024	4.93
	45; −46; 54			4.63
	54; −51; 54			4.16

k – cluster size (voxel count).
INP – BIS-11 subscale measuring non-planning impulsivity.
IWR – alternative BIS-11 subscale measuring inability to wait for reward.

significant positive or negative correlations in these regions-of-interest for BIS-11 total or its subscales.

4. Discussion

In this study, we aimed to elucidate the associations between trait impulsivity and brain structure in healthy subjects, based on two different conceptualisations of impulsivity subscales or concepts, both derived from the commonly used BIS-11 scale. We provide analyses for each subscale individually as well as combined analyses aimed at isolating associations for the impulsive action and impulsive choice subscales being relatively specific to the two-factor derived subscale solution (as compared to their three-factor counterparts).

As a main finding of this study, we demonstrate how different conceptualisations of sub-components of impulsivity might be related to different patterns of associations with regional brain structure – even when derived from a mostly similar pool of questions. Interestingly, most scales showed positive (rather than negative) correlations with distinct regional cortical volumes. Comparing our findings with the two previous VBM studies reporting GMV associations with traditional global and three-factor BIS-11 scoring in healthy subjects (Cho et al., 2013; Matsuo et al., 2009a, b), we failed to replicate correlations in DLPFC, OFC and ACC. This was the case for both whole-brain analyses as well as small volume corrections. Our failure to replicate might have been related to our limited sample size. However, the two previous studies analysed samples similar in size to ours, and the impulsivity phenotype as well as the age range in those studies was rather similar to the values in our present study. Post-hoc computation using G*Power 3.1 showed that a correlation (using the point biserial model for post-hoc power analysis to compute achieved power) with two-tailed analysis, effect size of 0.3, an assumed α error probability of 0.05 and sample size of n = 85 would result in a power of 0,817.

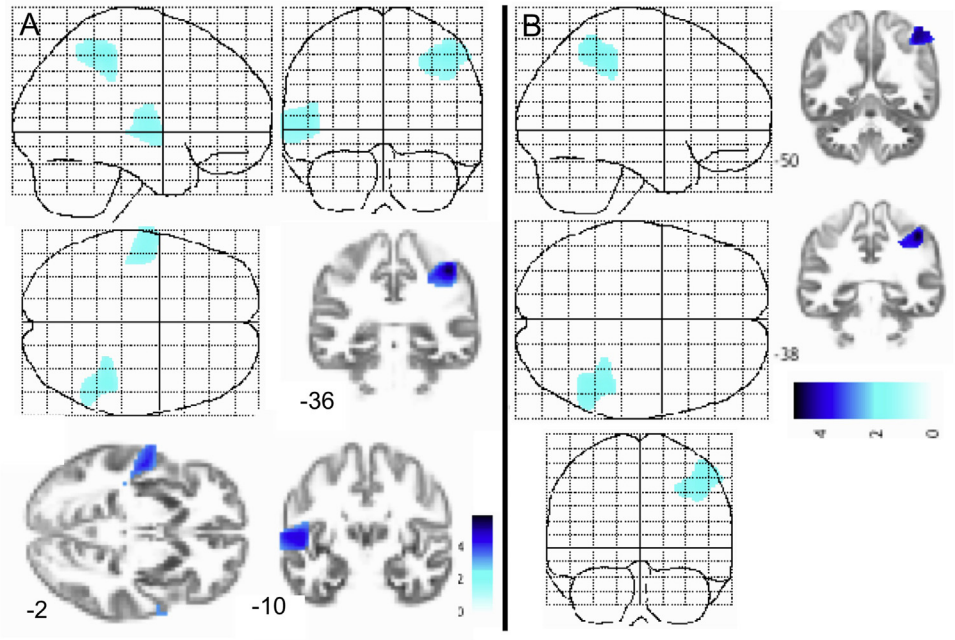

Fig. 2. Clusters of significant positive correlation ($p < 0.05$, FWE-corrected) of GMV with (A) BIS-11 total score and (B) BIS-11 *IA*.

A main difference to previous studies was the consistently positive direction of the correlations found in our analysis. While it might seem intuitive that a phenotype associated with dysfunctional (or sub-optimal) behavioural responses might be associated with less grey matter, there are several examples from the recent literature that positive correlations might also occur. For example, we recently identified brain areas in a multi-centre sample of non-clinical healthy subjects that were positively correlated with an aggression/hostility phenotype Indeed, several recent studies using a correlational approach between subclinical or personality measures and brain structure have identified positive correlations (Besteher et al., 2017; Botvinick et al., 2004; Hatano et al., 2014; Hu et al., 2018; Liu et al., 2016; Mansouri et al., 2007). However, there is little basic research to mechanistically explain how higher GMV could result in a decrease of function. One aspect to consider is the actual range of impulsivity scores in a sample. Indeed, subjects with slightly elevated BIS-11 trait impulsivity are not necessarily impaired in everyday functioning. Inter-individual variation in this range might thus not conform to a linear relationship seen in clinical samples.

Taken together, it is unclear, whether there is a linear, decreasing GMV curve for a certain brain area across a putative spectrum (i.e. from low-impulsivity healthy over high-impulsivity-healthy towards high-impulsivity pathology). There are several possible explanations for this. Considering a fully-dimensional model (spanning healthy and disease), one explanation might be that the relationship of GMV and impulsivity is better characterised with a non-linear or "inverted U-shape curve" relationship: this might result in positive correlations in the "non-clinical" part of the spectrum, but negative correlations in the pathological part of the spectrum. Such relations have been shown for inter-individual differences in cognitive performance, where some studies report worse task-performance associated with larger cortical volume (Kanai and Rees, 2011; Takeuchi et al., 2011) rather than volume decrease.

However, this raises difficulties in linking VBM findings to cellular substrates. Lower GMV might be interpreted as a "sub-clinical" manifestation of "atrophy" or some structural deficit. Higher GMV (i.e. positive correlations with GMV) could be mediated by different structural and/or functional effects, including compensatory increases in the volume of neuropil, glial cells or tissue water, but also differences in synaptic pruning (Amodio and Frith, 2006; Buckner et al., 2008; Decety et al., 2004), lack of inhibition or even rapid changes in T1 scans reflecting regional cerebral blood flow (Hoflich et al., 2017). This could also include resilience towards the expression of a clinically relevant phenotype, which might counteract volume decreases. Clearly, our findings do not disclose the cellular underpinnings of these correlations, calling for further research on mechanistic models.

Aiming to reconcile our findings with the previous literature, we also need to take into account other potential explanations. One is the range of expression of traits: although including only healthy or non-clinical subjects, cohorts from different studies might have different characteristics with regards to range of impulsivity trait values. Non-linear relations across a wider range of (non-clinical/non-pathological) impulsivity might result in diverging results when using linear statistical models. Also, we need to consider that although BIS self-report focuses on presumably stable traits, additional state fluctuations (through uncontrolled variables like stress, adverse life events, substance intake, etc.) might aggravate or obscure effects. Conversely, effects unrelated to (trait) impulsivity might impact on regional brain structure in areas shown in this VBM analysis, but not leading to compromised function or structure in impulsivity-related networks.

Following the rationale of our study, we discuss the differential regional associations of RRS (an index of impulsive action) and IWR (an index of impulsive choice) with brain structure in comparison with the classical three-factor model underlying BIS-11 (IM, INP, IA). While our interpretation rests on the FWE cluster-level corrected findings, we shall also refer readers to additional complementary uncorrected analyses (see supplement).

4.1. Impulsive action

Both BIS-11 motor (*IM*) and rapid response style (*RRS*) subscales are aimed at measuring the tendency to act rashly without proper assessment of context, commonly interpreted as a failure of motor inhibition. The scales are calculated from overlapping groups of items. *IM* contains more items due to redundancy of content and had lower internal consistency than *RRS* in our sample (Table 1). While there were no significant differences (at corrected levels) in our VBM analysis, we might point out that our additional uncorrected analyses did show some divergence of brain structural associations (see supplemental Table 1 and Fig. 1): *IM* was positively correlated with cortical volume in right inferior parietal and left superior temporal cortex, whereas corresponding *RRS* was statistically stronger correlated with these areas and also with a left, anterior cerebellar cluster), but these findings are not corrected and therefore might serve for generation of hypotheses in future studies, but are not substantiated by our data.

Following the current neurobiological model of impulsivity the right inferior frontal cortex might act as a "brake" to the execution of actions by a prefronto-striatal network (Fineberg et al., 2014; Kim and Lee, 2011; Miller and Cohen, 2001) and receives input from sensory areas like the superior temporal cortex (Aron et al., 2014). Both subscales identified a positive correlation of GMV with impulsive action in the superior temporal cortex. This cluster extended towards the insula, raising the possibility of two confluent foci.

A VBM-study among impulsive patients similarly describes GMV reduction in left superior temporal gyrus correlated with *IM* (BIS-11) and a positive correlation with anterior cerebellum GMV (A. K. Lee et al., 2011). Comparable VBM findings in healthy cohorts are rare; one mentions a negative correlation of GMV in OFC as a part of the prefrontal network of cognitive control correlated with *IM* (Matsuo et al., 2009a, b). Although the association between structure and function is yet not fully understood, more insight comes from functional MRI studies in healthy participants. The available fMRI studies also point to fronto-parietal, fronto-striatal and fronto-temporal networks involved in reactive and proactive inhibition of behaviour (van Belle et al., 2014; White et al., 2014). Especially inferior parietal gyrus was shown to exhibit activation during decision-related tasks (Karch et al., 2009). Also insula and ACC appear to be involved in response inhibition measured by behavioural tasks (Aron et al., 2014; Cai et al., 2014; Seger, 2008). Our structural findings did not reflect the last-mentioned associations with either scale, possibly due to low motor impulsiveness values in our sample and the fact, that behavioural tasks rather measure state impulsivity whereas BIS-11 captures trait impulsivity, which could point to comparably more consistent alterations in activation and volume in right inferior parietal and left superior temporal cortex in healthy adults.

4.2. Impulsive choice

Both BIS-11 non-planning (*INP*) and inability to wait for reward (*IWR*) aim to measure preference of immediate reward compared to larger, but delayed reward. *IWR* was made up of less and slightly different items than *INP*, also to avoid redundancy. In our sample the scale had lower internal consistency than INP, which showed only uncorrected effects in the same areas as *IM*. This corresponds with the above-discussed model of fronto-parietal, fronto-striatal, and fronto-temporal networks mediating reactive and proactive inhibition of behaviour, but in our study does not reflect a distinct neurobiological pattern specific for impulsive choice (unlike the analyses on impulsive action).

IWR on the other hand yielded a significant, FWE-corrected correlation wit GMV in the left middle and inferior occipital gyri. And after statistically removing the overlap with INP subscale the correlation

shifted to a cluster spanning left fusiform gyrus and left cerebellum.

Comparable VBM studies in healthy subjects also identify positive correlations of cortical volumes in the occipital cortex with higher impulsivity, but also other areas like bilateral medial parietal cortices, the right OFC and left insula associated with delay discounting (Ide et al., 2017; Mohammadi et al., 2016). The study by Ide et al. even found the occipital association only with the non-planning and not the motor sub-scale of BIS-11, proposing the area of the peripheral visual field (V6) (Pitzalis et al., 2013) as a distinct region involved in impulsive choice. One might speculate, that higher GMV in area V6 could mean higher vulnerability to distractions and therefore lower attention on the choice at hand.

There is a considerable number of studies identifying associations of impulsive choice, mostly in behavioural tasks, with the occipital cortex, but also other areas: High choice consistency during Iowa gambling task is associated with greater GMV in right hippocampus, middle frontal, superior and middle temporal gyri and occipital cortex as well as left post-central, posterior cingulate gyri and cuneus. The occipital effects in healthy controls were distinct from patients with gambling disorders respectively psychosis. (Premkumar et al., 2008). As for functional MRI (fMRI) studies, there has been an emphasis on the frontostriatal network again; especially OFC and PFC are implicated in making a choice between immediate and delayed reward and choosing delayed reward by reframing value of immediate rewards (Hare et al., 2008; Lim, O'Doherty and Rangel, 2011; Magen et al., 2014). Furthermore a temporo-hippocampal connection is activated in the process of evaluation of future outcome (Bari and Robbins, 2013). Concurrent with prefrontal areas and paracentral gyri, occipital pole and lateral occipital cortex are activated at impulsive choice tasks in resting state-fMRI analysis, which also identified impulsive choice and impulsive action as two behaviourally and neurobiological distinct aspects of impulsiveness in healthy participants (Q. Wang et al., 2016a). Summing up, there is a considerable number of studies stating occipital involvement in impulsive choice, sometimes only in healthy subjects and mostly limited to impulsive choice compared to impulsive action emphasising the critical role of the visual input on the prefronto-striatal network. This network has been stressed to be of importance for impulsive behaviours from several other previous studies (Choi et al., 2017). Taken together, our analyses on the impulsive choice subscales demonstrate divergence of IWR and INP subscales with regards to their associations with regional grey matter, in particular in the occipital cortex. Still, additional differences might have been too minute to be picked up in this sample limited in size.

4.3. The concept of attentional impulsivity and BIS-11 total score results

IA and BIS-11 total score results can only be compared with earlier VBM-studies. Attentional impulsivity is positively correlated ($p < 0.05$, FWE-corrected) with GMV in right inferior, superior parietal and supramarginal gyri and therefore partly differs from the initially mentioned studies in healthy controls. The scale emerged from the former BIS-11 cognitive impulsiveness subscale, which could not be shown to represent an independent dimension of impulsivity (Luengo et al., 1991; Patton et al., 1995). Also reliability of measuring these cognitive aspects through self-report was doubted (E. S. Barratt, 1991). As a consequence results cannot be interpreted meaningfully, because there is no strong behavioural evidence for this scale.

BIS-11 total score showed positive correlations ($p < 0.05$, FWE-corrected) with GMV in right inferior parietal gyrus, postcentral and supramarginal gyri. It is therefore similar to the *IA* result but does not fully correspond with previous VBM studies in healthy samples. Compared to VBM studies in patients there is some overlap with results by Yip et al.: They report negative association between BIS-11 total score and GMV within bilateral insula, amygdala, parahippocampal gyrus, hippocampus as well as superior temporal gyrus, precuneus and superior parietal lobule in a sample of patients with gambling and cocaine-use disorders and healthy controls (Yip et al., 2017). Additionally to prefrontal areas and ACC, students with higher BIS-11 score and mobile phone dependence showed decreased GMV in right middle occipital gyrus and thalamus compared to healthy controls (Y. Wang et al., 2016b). BIS-11 total score did not show any associations with GMV in healthy subjects and schizophrenia but was negatively correlated with orbitofrontal volume in schizoaffective and psychotic bipolar patients (Nanda et al., 2016). Other case-control studies in patients with elevated BIS-11 total scores add GMV alterations in insula, amygdala and fusiform gyrus to the discussion (Du et al., 2016), which strongly points to the conclusion, that neuroanatomical correlates of impulsivity are as complex as the discussed theoretical concepts. Finally, additionally investigating early neurodevelopmental markers like cortical folding might uncover a certain predisposition for impulsive behaviour in healthy subjects (Hirjak et al., 2017).

While BIS-11 remains a gold standard for self-report examination of overall impulsivity of healthy people and psychiatric patients, it has become clear, that its sub-constructs might diverge not only with regards to psychometric properties, but also their associations with brain structural variation, and therefore might not be as specific to the behaviourally evident concepts of impulsive choice and impulsive action as necessary for linking the phenotypes to brain circuitry at least in healthy subjects.

A main limitation of our analysis is the problem of shared variance between different conceptualisations of subscales/facets of impulsivity. Being based on the same set of questions, the two-factor solution inevitably overlaps with variance reflected in the subscales of the more conventional three-factor model. However, approaching the correlation analysis of the two-factor model through removing variance related to one (or more) of the three-factor subscales likely introduces distortions by removing facets/features inherent to the quality of the factor tested. Since the main aim of our study was focused on evaluating similarities and differences of the brain structural correlates of two different conceptualisations, further studies using other psychometric as well as experimental measures of impulsivity are needed to provide additional links between core qualities of subscales or different features of impulsivity.

Further limitations of our study include the sample size, which has also limited further analyses of interactions with variables like age or gender, which might be modulators of the effects of impulsivity – although they did not correlate significantly with BIS subscales in our sample, and therefore cannot explain the associations identified in VBM analyses. This aspect is important, as age and gender are associated with certain (although not all) facets of impulsivity (Cross et al., 2011; Mather, 2016; Weafer and de Wit, 2014), although some of the literature is not fully conclusive (Hosseini-Kamkar and Morton, 2014). The normative healthy sample of Stanford and colleagues revisiting BIS-11 in 2009 did not show any associations of BIS-11 total score and the three sub-scales with gender. But compared to their normative sample our sample had slightly lower mean values of total BIS-11 (58.1 vs. 62.3), *IM* (20.14 vs. 22.0) and *IA* (14.67 vs. 16.7). *INP* was nearly equal (23.28 vs. 23.6) (Stanford et al., 2009). These differences may also have altered the structural results. Also, we need to consider that impulsivity appears to decrease across the life-span (Moustafa et al., 2017), and our cross-sectional sample might not have captured fluctuations. Furthermore, we need to consider that the associations identified in a healthy non-clinical sample, as the one studied here, are not necessarily identical with those found in patient samples.

Our study was intended to provide a comparison of the brain structural correlates of different facets of impulsivity. However, future studies with BIS-11 in patients using MR morphometry might consider the divergence of effects across different subscale concepts.

Results are given for BIS-11 *IWR* as maximum intensity projections (MIP) and overlays on an average image of unsmoothed grey matter maps of the sample.

IWR – alternative BIS-11 subscale measuring inability to wait for

reward.

Results are given for (A) BIS-11 total score and (B) BIS-11 *IA* as maximum intensity projections (MIP) and overlays on an average image of unsmoothed grey matter maps of the sample. *IA* – BIS-11 subscale measuring attentional impulsivity.

CRediT authorship contribution statement

Bianca Besteher: Conceptualization, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Christian Gaser:** Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing. **Igor Nenadić:** Conceptualization, Data curation, Project administration, Resources, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2019.04.021.

5. Compliance with ethical standards

Conflicts of interest: None.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local Ethics Committee of Jena University Medical School approved the study protocol accordingly. Informed consent was obtained from all individual participants included in the study.

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