Interception refers to the process of sensing the internal state of the body. Context-dependent variations in interception signaling inform subjective experience and contribute to emotional and social behaviors, including empathy and emotion recognition [1]. Dysregulations in interception processes are increasingly recognized as a transdiagnostic marker across psychiatric and psychosomatic entities associated with severe impairments in the social-emotional domain, with autism spectrum disorder (ASD) being a prime example [2, 3]. Overarching frameworks propose that early disturbances in context-sensitive interception signaling lead to a failure to establish generative models to infer the emotional state of self and others [2], and thus may underpin the core symptomatic emotion recognition and empathy deficits in ASD. On the other hand, accumulating evidence suggests that these core symptomatic deficits in ASD may be contributed to by high levels of alexithymia – characterized by impairments in identifying and describing one’s own emotions – rather than autistic symptoms per se [3]. However, these initial findings in patient populations are hampered by frequently elevated levels of alexithymia in ASD, and thus were not able to differentiate the common and distinct contributions across the entire spectrum of variations of autism and alexithymia. Moreover, the multifactorial nature of interception-associated functional domains, such as distinct neural pain empathic responses towards perceiving physical and affective pain in others [4], has not been accounted for.

Against this background, the present fMRI study employed a dimensional trait approach in a sample of 242 healthy subjects (122 males; mean age, 21.60 ± 2.35 years) to determine common and distinct associations between individual variations in both traits and the domain-specific pain empathic neural responses towards physical and affective pain (online suppl. material, for all online suppl. material, see www.karger.com/doi/10.1159/000495122). Neural responses to visual stimuli depicting painful situations were measured via fMRI to assess pain empathic neural reactivity. To delineate domain-specific activity patterns, participants were presented with stimuli displaying a nociceptive agent applied to body limbs (physical pain) or painful facial expressions (affective pain), as well as matched nonpainful control stimuli (Fig.1a; stimuli previously evaluated in [5, 6]). In order to minimize interference by cognitive processes, subjects were instructed to passively watch condition-specific blocks of the visual stimuli in a randomized order. fMRI acquisition, preprocessing, quality control (e.g., collinearity test between the scales) and nonparametric regression models were identical to our previous study on common and distinct contributions of pathologically relevant traits to affective neural responses [7]. Briefly, on the first level condition-specific regressors were modeled to generate the main contrast of interest [(physical pain > physical control) > (affective pain > affective control)] which was subjected to whole-brain nonparametric regression models testing distinct and interactive effects of alexithymia (assessed by the Toronto Alexithymia Scale, TAS) and autism traits (assessed by the Autism Spectrum Quotient, AQ).

The results demonstrated that higher alexithymia is associated with increased responses in the left anterior insula during pain empathy (Fig.1b.1). Disentangling these effects by extraction of parameter estimates revealed a positive association with alexithymia scores during perceived physical pain, but a negative one

Fig. 1. a Study procedures and the fMRI pain empathy paradigm during which physical and affective (facial) pain stimuli and corresponding control stimuli were presented. b Levels of alexithymia were significantly associated with pain empathic responses in the left insula (peak MNI coordinates [−36, 6, 18], k = 109, t_{238} = 4.76, p_{FWE-cluster} = 0.045); (2) extraction of parameter estimates from the left insula revealed that alexithymia showed opposite associations with insula reactivity towards physical and affective pain stimuli. c The interaction term between alexithymia and autism was associated with the pain empathic response in the mid-cingulate cortex (peak Montreal Neurological Institute, MNI, coordinates [6, −6, 36], k = 347, t_{238} = 4.46, p_{FWE-cluster} = 0.011); (2) extraction of parameter estimates from the mid-cingulate revealed opposite associations during the processing of physical versus affective pain. d To further disentangle the significant moderation effect of alexithymia on the impact of autism on mid-cingulate reactivity, the moderator variable was split into three levels using the Johnson-Neyman approach. This approach revealed moderator effects of alexithymia on the association between autism and midcingulate reactivity towards physical (1) and affective (2) pain stimuli as determined by the SPSS 22 PROCESS macro. ALEX, alexithymia; L, left; R, right.

(For figure see next page.)
Study procedures

$n = 242$ healthy subjects

Trait assessment (autism, alexithymia)

Functional MRI assessment

Pain

Control

Physical

Affective

Interactive effects

1. Mid-cingulate

2. Domain-specific associations

Associations with alexithymia

1. Left insula

2. Domain-specific associations

Moderator effects

1. Physical pain empathy

2. Affective pain empathy

Interactive effects

1. Mid-cingulate

2. Domain-specific associations

$N = 242$ healthy subjects

Trait assessment (autism, alexithymia)

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Interactive effects

1. Mid-cingulate

2. Domain-specific associations

Associations with alexithymia

1. Left insula

2. Domain-specific associations

Moderator effects

1. Physical pain empathy

2. Affective pain empathy

Interactive effects

1. Mid-cingulate

2. Domain-specific associations

$R = 0.226$

$p < 0.001$

$R = -0.147$

$p < 0.05$

Interactive effects

1. Mid-cingulate

2. Domain-specific associations

$R = 0.211$

$p = 0.001$

$R = -0.162$

$p < 0.05$
Alexithymia and Autism Contribute to Domain-Specific Interoceptive Failure

Psychother Psychosom 2019;88:187–189
DOI: 10.1159/000495122

during affective pain (Fig. 1b.2; \( p < 0.025 \); correlation difference \( p = 0.007 \), percentile bootstrap). Whereas no significant associations with trait autism scores were found per se, there was an interaction effect between the two trait dimensions in the mid-cingulate cortex (Fig. 1c.1). Extraction of parameter estimates demonstrated that the interaction term was positively associated with mid-cingulate reactivity during perceived physical pain, yet negatively with that for affective pain (Fig. 1c.2; \( p < 0.013 \); correlation difference \( p = 0.002 \)). Subsequent moderation analysis revealed significant moderation effects of alexithymia for mid-cingulate responses to both perceived physical and affective pain (\( p < 0.01 \)). Further disentangling the effects by splitting the moderator variable into three levels demonstrated that autism only impacted mid-cingulate reactivity towards physical pain in subjects with high alexithymia (Fig. 1d.1; \( t_{238} = 2.80, p = 0.006 \)), whereas its reactivity towards affective pain was specifically associated with autism in subjects with low alexithymia (Fig. 1d.2; \( t_{238} = 2.48, p = 0.014 \)).

In line with research in ASD patients [3], the present dimensional trait approach confirmed that alexithymia rather than autism per se drove altered insula interoceptive processing in the domain of pain empathy. Importantly, this dimensional approach could demonstrate for the first time that the impact of alexithymia on interoception-related insula processing varies as a function of physical versus affective pain empathy induction. The anterior insula is a functionally heterogeneous region and interoceptive signaling within it not only underlies empathetic responses but also inner affective experience and salience attribution to environmental stimuli [8], including emotional faces [9]. The present results indicate that higher levels of alexithymia may be associated with deficient attenuation of interoceptive signaling in response to physical pain signals, accompanied by under-responsivity towards socially transmitted pain signals. Given that early dysregulations in the oxytocin system may contribute to interoception-related deficits in ASD [2] and oxytocin administration can decrease insula responsivity to pain empathy [10], but increase it to social salience [9], the present findings may suggest that alexithymia is the moderating factor for both ASD-related deficits and oxytocinergic modulation of interoception-related insula processes.

Finally, the moderating role of alexithymia on the impact of autistic traits on mid-cingulate empathic reactivity supports a multifactorial view on alexithymia’s contribution to ASD symptomatology. Together with the anterior insula, the mid-cingulate represents a key node for empathic processing as well as awareness of negative affect [4]. The observed interaction suggests that alterations in the subdomains further vary as a function of alexithymia with high values in both traits leading to exaggerated reactivity towards perceived physical pain, whereas aberrant responses to affective pain may represent a unique feature of autism. Given the high symptomatic heterogeneity of ASD, concomitant assessments of alexithymia and subdomain specific pain empathic responses may thus help to determine diagnostic- and treatment-relevant ASD subtypes.

Acknowledgements
This work was supported by the National Natural Science Foundation of China (NSFC; 91632117 to B.B. and 31530032 to K.M.K.), Fundamental Research Funds for the Central Universities (ZYGX2015Z002 to B.B.), and the Sichuan Science and Technology Department (2018YJ0001 to B.B.).

Disclosure Statement
The authors report no biomedical financial interests or potential conflicts of interest.

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