



Same salience, different consequences: Disturbed inter-network connectivity during a social oddball paradigm in major depressive disorder

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ARTICLE INFO

Keywords:

Salience network
Default mode network
Depression
Oddball paradigm
Target detection
Functional connectivity

ABSTRACT

Background: So far findings on emotional face processing among depressed individuals reveal an inconsistent image, with only some studies supporting a mood-congruent bias in salience processing. Thereby, many results are based on the processing of sad emotions and mostly focused on resting-state connectivity analysis. The present study aimed to target this misbalance by implementing a social oddball paradigm, with a special focus on the amygdala, the ACC, the insula and subdivisions of insula and ACC.

Methods: Twenty-seven depressed patients and twenty-seven non-depressed controls took part in a fMRI event-related social oddball paradigm based on smiling facial expressions as target stimuli embedded in a stream of neutral facial expressions. fMRI activation and functional connectivity analysis were calculated for the pre-defined ROIs of the salience network (SN), with a special focus on twelve insular subdivisions and six ACC subdivisions.

Results: For both groups the social oddball paradigm triggered similar BOLD responses within the pre-defined ROIs, while the quality of functional connectivity showed pronounced alterations from the salience network to the ventral attention- and default mode network (DMN).

Conclusion: On a first level of target detection, smiling faces are equally processed and trigger similar bold responses in structures of the salience network. On a second level of inter-network communication the brain of depressed participants tends to be pre-formed for self-referential processing and rumination instead of fast goal directed behavior and socio-emotional cognitive processing.

1. Introduction

Anhedonia describes an individual's diminished hedonic capacity to experience pleasure through rewarding stimuli, e.g. a nice scent of flowers, a beautiful landscape or social interaction with family and friends. Particularly depressed individuals show a lack of hedonic capacity, which is subsequently reflected in a loss of drive and a growing indifference. Playing a key role in the psychopathology of depressive disorder, anhedonia is included as a core symptom in the diagnostic criteria of DSM-V and ICD-11 (American Psychiatric Association, 2013; World Health Organization, 2020).

Prior literature has linked this reduced sensitivity towards rewarding stimuli to alterations within salience network processing (Disner et al., 2011; Yang et al., 2016). Salience describes the detection of a striking

stimuli in the - momentarily - irrelevant surroundings (Itti and Koch, 2001), e.g. a hot cup of coffee in a pile of paper. This pivotal neural mechanism is subjective to each person's current internal bodily & emotional state (Craig, 2009; Critchley et al., 2004) and distinct physical stimuli features (Fecteau and Munoz, 2006).

A suitable paradigm for studying salience processing is the oddball paradigm, where few target stimuli are unexpectedly embedded in a stream of non-target stimuli. Compared to task-irrelevant target stimuli, task-relevant target stimuli lead to enhanced activation patterns in the anterior insula and the ACC, supporting a stimulus - driven engagement of those structures (Kim, 2014). Hereby, two subfunctions can be distinguished within the salience network: While the anterior insula rather serves as a stimuli detector, the dorsal ACC represents a structure of action, triggered by attentional switching processes (Han et al., 2019).

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<https://doi.org/10.1016/j.nicl.2021.102731>

Received 13 December 2020; Received in revised form 28 May 2021; Accepted 12 June 2021

Available online 17 June 2021

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The ACC further stands out for its modality specific connectivity patterns, suggesting a top-down modulation effect on primary sensory areas, such as the striate cortex in visual oddball tasks (Crottaz-Herbette and Menon, 2006).

Disturbed salience processing in major depressive disorder is reflected in a) altered activation of each of the single components of the salience network and b) altered temporal synchronization within the structures of the salience network and between the salience network and other large brain networks, such as the default mode network.

Depressed people exhibit hyperactivity in saliency structures towards negative stimuli (Hamilton et al., 2013), whereas positively connotated pictures evoke attenuated responses in the dACC and the anterior insula (Yang et al., 2016). These findings also transfer to the processing of emotional facial expressions, possibly reflecting the social withdrawal behavior often observed in depressed patients: The amygdala shows a mood-congruent bias with reduced BOLD responses following the subliminal presentation of happy faces and enhanced BOLD responses following the subliminal presentation of sad faces (Stuhrmann et al., 2013). Henderson et al. (2014) described similar findings in the anterior insula and the ACC with a negative association of anhedonic symptoms and neural responses following happy facial expressions.

Still, this bias towards negative and away from positive facial expressions in depressed patients was not always reflected in altered activation patterns in each of the structures (ACC, Amygdala, Insula) and in each study (Stuhrmann et al., 2011): Only half of the included studies in the meta-analysis found any significant difference in amygdala activation. Hyperresponsivity in the sad vs baseline contrast was observed for the insula and the amygdala, while the happy vs baseline contrast led to both hyper- and hyporesponsivity. For the ACC significant alterations in activation were mostly reported for the processing of sad facial expressions. In line with its heterogeneous function, different ACC subdivisions showed different findings in functional connectivity, such as a) enhanced links from the amygdala to the subgenual ACC and b) reduced links from the amygdala to the supragenual/dorsal ACC (C. H. Chen et al., 2008; Dannlowski et al., 2009; Matthews et al., 2008).

A part of this inconsistency in fMRI findings might be attributable to the differences in sample characteristics and methodology. Especially, the latter being reflected in variations of visual stimuli types with a bias towards studies focusing on sad facial expressions (Stuhrmann et al., 2011) and differences in experimental paradigms, e.g. explicit emotion face-matching task (Frodl et al., 2010) vs implicit passive face viewing task (Dannlowski et al., 2009).

Over the past decade functional connectivity analysis has led to a further understanding of the disrupted central nervous processing underlying major depressive disorder by highlighting the importance of interaction between three dynamically organized functional networks, the Default Mode Network (DMN), Salience Network (SN) and the Central Executive Network (CEN). While activation in the DMN is particularly related to self-referential processing and rumination (Zhou et al., 2020), the CEN is strongly engaged in planning and goal directed behavior and in turn represents an inhibitory input to the DMN (Chen et al., 2013). Thereby the salience network is crucial for inter-network switching between the DMN and CEN (Goulden et al., 2014). In patients with major depression, these inter-network connections are mainly altered in two directions: 1) Enhanced connectivity within the anterior DMN and to the SN, possibly reflecting a bias of network switching towards the DMN instead of the CEN. 2) Diminished connectivity between the DMN and CEN, supporting the tendency towards self-referential processing often seen in major depressed patients (Mulders et al., 2015). Particularly, the enhanced connectivity to structures of the default-mode network has gained large attention and fits well with the clinical symptoms often observed in depressive disorder (Hamilton et al., 2015).

Since most findings on SN connectivity are based on the ACC and the insula, it is important to note, that these ROIs are composed of

functionally differentiable subdivisions. Anatomically the insula is often divided into its posterior and anterior part, while cytoarchitectonally the primate insula can be separated in granular, dysgranular and agranular regions. The granular region is seen as primary interoceptive cortex, while the dysgranular region is strongly involved in somatosensory processing and the agranular region is linked to the olfactory bulb and the amygdala (Evrard, 2019). Focusing on emotion perception in insula subdivisions, Zhang et al. (2019) summarized the hypergranular, the dorsal granular and the ventral granular parts as anterior insula, and the dorsal dysgranular, dorsal agranular and ventral agranular parts as posterior insula. Here, the anterior insula was particularly sensitive to emotional value, while the posterior insula was linked to sensory cortices (Zhang et al., 2019). In line with the heterogeneous functions and connections of insular subdivisions, resting state connectivity patterns in depressed patients are differentially altered in insula subregions, with contrary findings for the anterior and the posterior insula (Wang et al., 2018).

Based on its position in relation to the corpus callosum, the ACC can be classified in three subdivisions: the subgenual, the pregenual and the supracallosal ACC (Rolls et al., 2020). Similar to the insula subdivisions, differences in connectivity patterns in the ACC subregions were observed in depressed individuals with enhanced functional connectivity from the pregenual ACC to the medial orbitofrontal cortex (OFC) and from the supracallosal ACC to the lateral OFC and inferior frontal gyrus (IFG) (Rolls et al., 2019).

However, this present knowledge is mostly based on resting state data and comprehensive findings on network connectivity during task performance remain rare, leaving open the question how well these findings transfer to neural processing during task performance

In summary, both, altered BOLD responses and functional connectivity patterns have been reported for the core saliency structures: the ACC, the amygdala and the insula. Still, inconsistencies become evident within different task paradigms and especially for functionally dissociable subdivisions. We therefore aimed to study the salience network activity and connectivity in depression in an explicit social oddball paradigm, based on the detection of positive social cues, namely smiling faces, embedded in a stream of neutral facial faces. To better distinguish the heterogeneous task engagement of the ACC and the insula, different subregions were included in the analysis.

We hypothesized that 1a) depressed individuals, 1b) especially those with enhanced anhedonia symptomatology, show reduced activation patterns in the salience network towards positive social target stimuli as compared to non-depressed controls and that 2) these altered activation patterns among patients are further reflected in diminished functional connectivity within the salience network following target detection.

2. Methods and materials

2.1. Ethic statement

Following the declaration of Helsinki on Biomedical Research involving human subjects the study was approved by the local Ethics Committee, traceable under the identification number EK40410 2017. Before starting the measurements the participants were informed about the experimental design and data security. All of the participants gave written consent. The study was registered in the German Clinical Trials Register (DRKS) DRK00016497.

2.2. Participants

The sample contained two groups of right-handed participants, twenty-seven participants with major depression (referred to as "patients") and twenty-seven non-depressed participants (referred to as "controls"). Inclusion criteria for the patient group was: a main diagnosis of major depressive disorder (MDD), validated by the Structured Clinical Interview (SCID-II) for DSM-IV, exclusion criteria was a history

of schizophrenia or bipolar disorder and alcohol or other substance dependence (*Diagnosis and comorbidities are listed in Table S1*). The sample of the experimental group subsequently guided the recruitment of the 1:1 control group, so that each patient was aimed to be sex- and age - matched with a control participant (*Table 1*). The control group was required to not suffer from mental illness as ensured by the Patient Health Questionnaire, PHQ, cut-off score = 8 (*Spitzer et al., 1999*) and the Beck's Depression Inventory, BDI II, cut-off score = 13 (*Beck et al., 1996*). Exclusion criteria for both groups were: 1) history of severe head injury; 2) concurrent neurological or otorhinolaryngical illness; 3) hypo- or anosmia; 4) contraindication for MRI. To quantify hedonic capacity among participants, a German Version of the Snaith Hamilton Pleasure Scale, SHAPS (*Franz et al., 1998; Snaith et al., 1995*) was implemented. The 14 items of the SHAPS questionnaire follow a 4 dimensional approach with the subsequent subcategories: social interaction, sensory experience, interests, food and drinks.

As a result of this recruitment, the control group showed significantly less depressive and anhedonic symptoms than the patient group (BDI II patients: $M = 27.6 \pm SD9.20$, controls: $M = 3.06 \pm SD2.83$; SHAPS patients: $M = 4.63 \pm SD2.82$, controls: $M = 1.04 \pm SD2.16$).

Power calculation was performed with G*Power (version 3.1.9.2.) and calculated to cover a small effect ($f^2(V) = 0.15$) with an Alpha of 0.05 and a 1-Beta of 0.80 for a repeated measurement ANOVA with two groups (controls vs patients), three ROIs (Amygdala, Insula, ACC) and two sides (left, right) and an assumed intercorrelation of $r = 0.6$. This resulted in a total sample of 40 participants. We decided to oversample by 1/4 in order to cover potential drop outs due to movement, technical problems or subjective reasons e.g. sickness, sudden claustrophobia.

2.3. Study design

A social oddball paradigm was chosen to evoke neural responses in the salience network. Infrequent smiling facial expressions served as target stimuli and were embedded in a stream of frequent neutral facial expressions which served as non-target stimuli, *compare Fig. 1*. Faces (and study instructions) were displayed on a flat screen behind the MRI chamber and visible for the participants through a mirror on top of the head coil. Stimulus presentation duration was set to 1500 ms, with a narrow inter-stimulus interval (ISI) of 500 ms. Mean response time data (RT = 502–509 ms) from another visual oddball study implies, that this selected time frame will leave enough time for participants to perform a button response (*Rozenkrants and Polich, 2008*). Participants were asked to push the response button on the right thumb as soon as they recognized a smiling facial expression. For each correct button-press the 500 ms feedback "Great!" was presented instead of the fixation cross. For an incorrect button-press no feedback was presented, just the fixation cross. An in-between target stimuli interval with a minimum of 14000 ms was chosen to ensure that the BOLD signal has time to return to baseline in-between target presentation (*Downar et al., 2000*). The latter was jittered from 14 000 ms to 18 000 ms within runs, leading to

Table 1

Descriptives. Sample data of the applied questionnaires, the valence ratings of the target stimuli and the reaction times in the social oddball paradigm. The two groups differed significantly in depressive and anhedonic symptomatology (SHAPS: $t(52) = -5.262$, $p < .001$; BDI: $t(52) = -13.217$, $p < .001$), but not in facial valence ratings ($t(52) = 1.428$, $p = .160$) or recorded response times ($t(52) = 0.234$, $p = .816$).

	Mean		SD	
	controls	patients	controls	patients
SHAPS*	1.04	4.63	2.16	2.82
BDI*	3.07	27.6	2.83	9.20
Valence rating	2.93	2.26	1.38	1.99
Reaction time	0.601	0.596	0.0847	0.0752
Age	36.30	37.56	11.53	11.10
Sex (female, male, non-binary)	18/9/0	17/10/0		

the presentation of one smiling facial expression in-between either seven, eight or nine neutral facial expressions. Orientated at the target frequency of 10% in previous studies (*Wang et al., 2006*), we worked with a relation of 12% targets to 88% non-targets in order to enhance the power for subsequent analysis of the BOLD signal. This led to the amount of 176 faces during a 6 min run, whereof 21 (11.93%) faces had smiling expressions, while 155 (88.06%) had neutral expressions. The presentation order of the facial expressions was randomized for every participant. The whole study sequence was designed by the application of the Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) and synchronized to the fMRI signal. At the end of the social oddball paradigm, the subjects were asked to verbally rate the overall valence of the presented smiling facial expressions on a scale from -5 to 5 (-5 = unpleasant; 0 = neutral, 5 = pleasant).

For the emotional faces we used the Karolinska Directed Emotional Faces – KDEF stimulus set (*Lundqvist et al., 1998*), which showed reliable valence ratings in different study samples (*Garrido and Prada, 2017; Goeleven et al., 2008*). From the KDEF we made use of all 140 emotional facial expressions from 70 different individuals, except for 11 stimuli which were sorted out due to overexposure (the applied stimuli are listed in *Table S2*). Additionally, sixteen facial expressions were randomly picked from the Nimstim facial database (*Tottenham et al., 2009*) for the practice task before the experiment. This short exercise task included 10 neutral faces and 6 smiling faces in a randomized order. In order to enable participants to get familiar with the button pressing the exercise task was performed inside the scanner directly before the start of the experiment.

Since the current study was part of a larger project the oddball paradigm was also presented in additional runs with simultaneous olfactory or trigeminal sensory stimulation. For the current analysis on salience network activity in major depression, we only focused on the run without any additional sensory stimulation.

2.4. (Functional) magnetic resonance imaging – data acquisition

The experiment was performed in a Siemens 3 T Magnetom Prisma scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. In terms of functional imaging a total of 248 scans were conducted per run with twenty-four axial slices (2,5 mm thick); FoV = 220 mm; TR 1510 ms; TE 30,0ms; flip angle 90° and 2.5x2.5x2.5 mm voxel size. Subsequently, structural high-resolution T1 weighted images were recorded with a slice thickness of 1,00 mm; TR 2300,0 ms; TE 3,43 ms; Field of View = 256 mm; TI 900 ms; flip angle 9° and a voxel size of 1x 1 × 1x mm in order to map functional to anatomical images. The acceleration mode GRAPPA was used for both functional and structural measurements.

2.5. Behavioral data

Statistical analysis was performed with SPSS (Version 27.0, SPSS Inc., Chicago, IL, USA), R Studio (*Team, 2020*) and jamovi. A one sample *t*-test was calculated to test the obtained valence ratings against the neutral valence value. Then, a two samples *t*-test between patient- and control group was calculated for the valence ratings and the mean reaction time data. Stimulus accuracy was measured as the amount of correct button responses (0–21) among the total amount of presented target stimuli (21). To further examine the relation of anhedonia severity and both, behavioral data and activation patterns, a linear regression analysis was performed between the SHAPS-D Scores and a) the reaction time data and the valence ratings and b) the extracted BOLD signal for each of the pre-defined ROIs. The subsequent SHAPS plot was designed with R Studio. Estimates of effect size are given as Cohen's *d*.

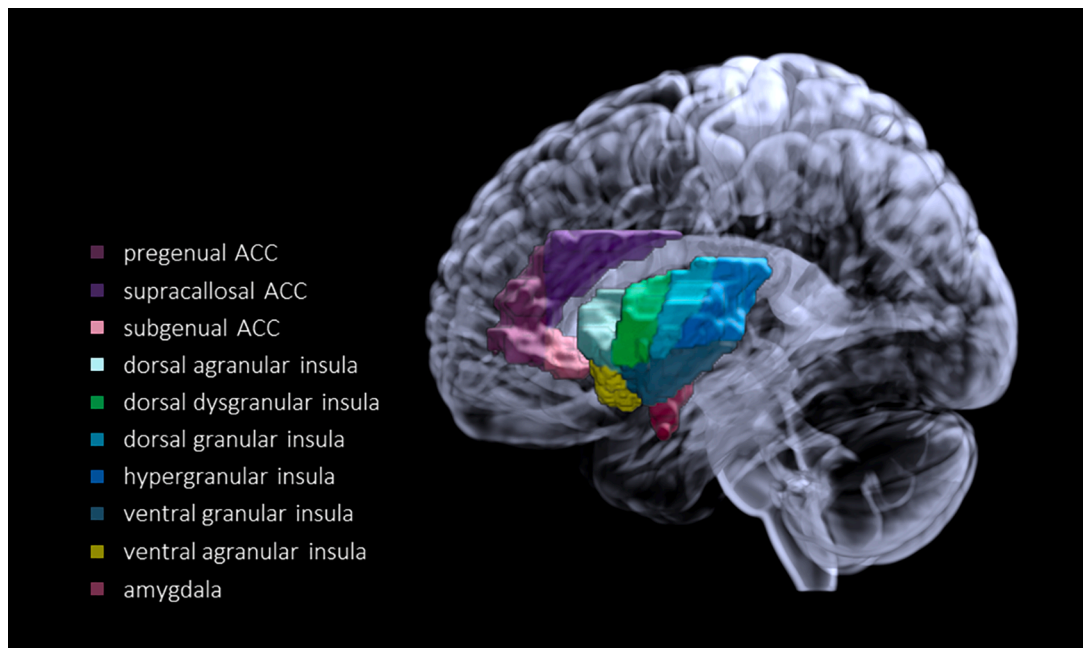


Fig. 2. Visualization of the amygdala, the ACC subdivisions and the insula subdivisions. The ACC subdivisions were taken from the AAL3 (Rolls et al., 2020), while the insula ROIs were retrieved from the Brainnetome atlas (Fan et al., 2016).

significant between-group contrast, the seeds' peak voxel was extracted. Using the marsbar toolbox (Brett et al., 2002), a sphere (radius = 6 mm) was created around each of the extracted peak-voxels (R. Zhang et al., 2020). These created spheres were entered separately for each group in the SPM 2nd level results GUI to see if they also showed significant BOLD responses thresholded at $p_{FWE-corrected} < 0.05$ (Table S5). The group level analysis was supplemented by two covariate analysis, one for the BDI and one for the SHAPS scores. Contrast results and effect sizes were visualized and extracted through the results explorer tool implemented in the CONN toolbox. The functional connectivity results are presented FDR corrected.

3. Results

In order to determine the validity of the paradigm, we first tested, whether control participants a) rate the smiling faces as pleasant, b) accurately react to those and c) display the expected BOLD signal enhancement in the salience network. Those analyses showed that the control group perceived the smiling faces as mildly to very pleasant ($M = 2.93$) and significantly more pleasant than the neutral value ($t = 10.998$, $p = .000$).

They were further able to correctly react to the stimuli with an accuracy of 98%. The target vs non-target contrast analysis showed a significant change in BOLD signal in the left ($t = 9.17$, $p_{FWE} = 0.00$) and right insula ($t = 8.81$, $p_{FWE} = 0.00$), the left ACC ($t = 4.83$, $p_{FWE} = 0.00$) and right ACC ($t = 4.98$, $p_{FWE} = 0.00$) and the left ($t = 4.08$, $p_{FWE} = 0.00$) and right amygdala ($t = 3.24$, $p_{FWE} = 0.03$). Inter-correlation of the pre-defined ROIs showed a mean value of 0.494 and a median of 0.569.

Compared to the control group, the patient group showed no difficulties in behavioral performance. Patients did recognize the target stimuli with the same high accuracy as the controls ($t(52) = -0.929$, $p = .357$, $d = -0.253$). Analysis of the recorded response times showed no significant group difference ($t(52) = 0.234$, $p = .816$) and a very small effect size of $d = 0.065$ indicating that the groups reacted comparably fast. The patients rated the smiling faces as less pleasant than the controls (Table 1). This effect was medium sized ($d = 0.389$), but it did not reach the significance level ($t(52) = 1.428$, $p = .160$). Severity of anhedonic symptomology neither correlated with valence ratings nor with reaction times ($p > .05$).

The smiling face vs neutral face contrast of the social oddball paradigm led to enhanced activation patterns within almost all of the pre-defined ROIs ($p_{FWEcorr} < 0.05$) for both the patient and the control group. Only for the subgenual ACC and the hypergranular insula no suprathreshold clusters were observed (Table S3). Particularly the right ventral - and dorsal agranular subdivisions of the insula presented strong BOLD signal changes (Table S3).

Overall, the BOLD responses were similar for the patient and the control group (Fig. 3, Table S3). No significant differences became evident between the two groups ($F(1, 52) = 0.371$, $p > .05$, $partial \eta^2 = 0.007$).

Focusing on the core symptom of MDD, the anhedonic symptomology, a negative correlation between the SHAPS scores and the activation of the left amygdala was observed ($R = -0.270$, $p = .049$), (Fig. 4). The other pre-defined ROIs did not show any significant link between BOLD signal and anhedonia severity ($p > .05$).

In both groups, we observed connectivity from key nodes of the salience network to structures of both DMN and CEN. For the control group, the Seed-to-Voxel Analysis showed enhanced connectivity for the bilateral insula, the left amygdala and the right supracallosal ACC (Table S4). Thereby the right insula showed strong links to structures of the CEN, the bilateral frontal pole and the medial frontal cortex, whereas the left amygdala was connected to a node of the DMN, the precuneus cortex.

For the patient group the Seed-to-Voxel Analysis showed enhanced connectivity for the bilateral insula, the bilateral amygdala, the bilateral pregenual ACC, the left supracallosal ACC and bilateral subgenual ACC (Table S4). Hereby, similarities became evident for the supracallosal ACC and the amygdala, which were both linked to the precentral, postcentral and supramarginal gyrus. The patient group also presented several negative links from the ACC and the insula to structures involved in action selection, such as the bilateral frontal poles and the bilateral paracingulate gyrus (Table S4). In general, connectivity from the salience network seeds to other brain areas was more pronounced in the patient group than in the control group.

The patients vs controls contrast analysis showed significant between-group differences for seeds in the insula and the ACC, but not for seeds placed in the amygdala (Table 2). **Anterior cingulate cortex.** The left ACC presented enhanced connectivity to the right

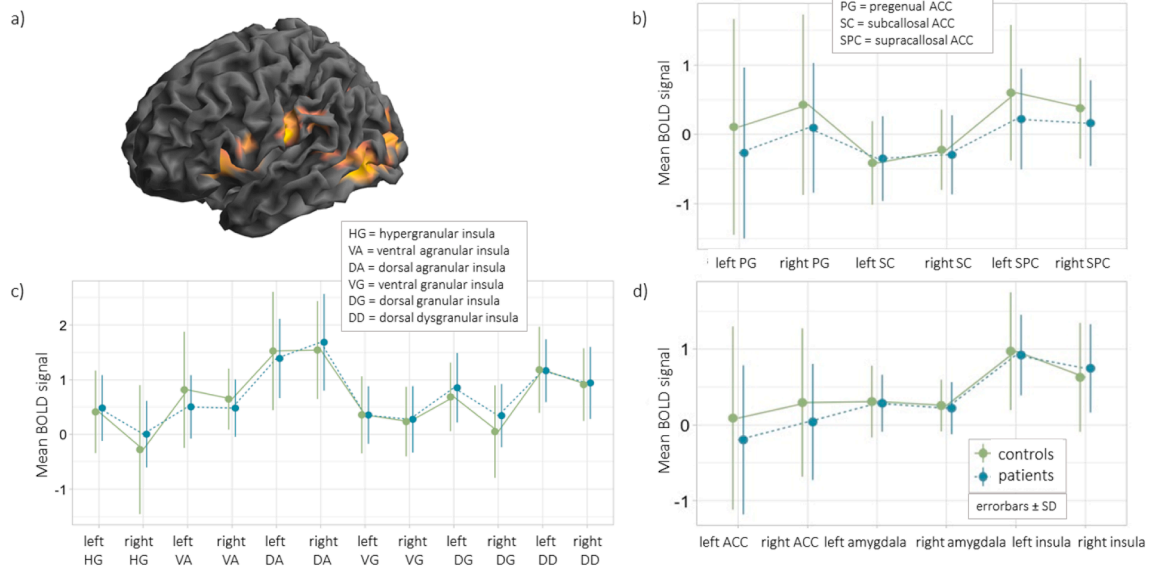


Fig. 3. Target vs non-target BOLD signal contrast for the patient and control group over all pre-defined ROIs. a) Activation pattern following the smiling faces in the social oddball paradigm. b) mean Bold signal in the ACC subdivisions c) mean Bold signal in the insula subdivisions d) mean bold signal in the structures of the salience network. No significant differences between patient and control group were observed.

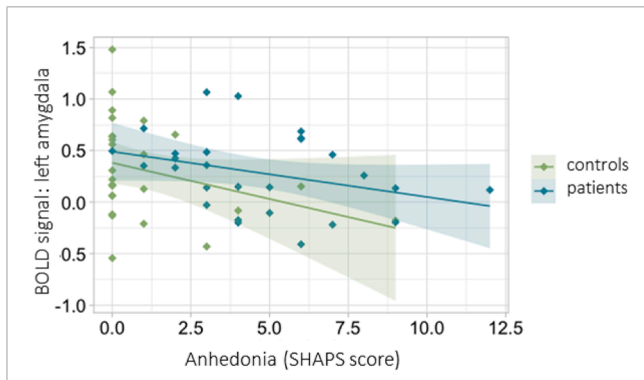


Fig. 4. Hyporesponsivity in the Amygdala negatively correlated with anhedonic symptoms. Individuals who scored high in the SHAPS questionnaire, testing for anhedonic symptoms in everyday life interaction, showed a reduced mean BOLD signal during task performance in the social oddball paradigm ($R = -0.270$, $p = .049$).

supramarginal gyrus, while its subregion, the left supracallosal ACC further showed enhanced connectivity to the bilateral supramarginal gyrus, the right parietal operculum cortex and the left postcentral gyrus (Fig. 5).

Insula. Similar to the left ACC, the left insula presented strong connectivity to the left supramarginal gyrus and the left parietal operculum cortex. The dorsal granular subregion of the left insula further showed enhanced links to the right lateral occipital cortex. The ventral and dorsal granular subregions of the right insula were linked to the left occipital cortex, the precuneus cortex and the right thalamus. The right dorsal dysgranular subregion presented enhanced connectivity to the right precentral gyrus and the inferior frontal gyrus (Table 2 and Fig. 6).

The control vs patient contrast analysis revealed links from the right ACC to substructures of the left frontal lobe, the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG) (Table 2), while the ventral granular subdivision of the left insula was more connected to the right temporal pole. No other suprathreshold differences were observed within the pre-defined ROIs in the between-group contrasts.

The peak voxel sphere extraction revealed significant BOLD

Table 2

Between-Group Contrast of the Seed-to-Voxel Functional Connectivity Analysis. In the Between-group contrast structures of the Salience Network present enhanced connectivity patterns to structures associated with the Default Mode Network, the Precuneus Cortex and the Supramarginal Gyrus. Results are presented $p_{FDRcorr} < 0.05$.

Seed	Cluster	size p-FDR	Peak × y z
Controls vs Patients			
right ACC	Cluster 1: Left Inferior Frontal Gyrus, Left Middle Frontal Gyrus	0.031078	-44 + 30 + 18
Left ventral granular insula	Cluster 1: Right temporal Pole	0.039540	+36 + 26-34
Patients vs Controls			
Left ACC	Cluster 1: Right Supramarginal Gyrus (anterior and posterior division)	0.024972	+62-38 + 38
Left Supracallosal ACC	Cluster 1: Right Supramarginal Gyrus (anterior division), Right Parietal Operculum Cortex	0.005598	+54-22 + 28
	Cluster 2: Left Supramarginal Gyrus (anterior division), Left Postcentral Gyrus	0.012348	-64-26 + 30
Left insula	Cluster 1: Left Parietal Operculum Cortex, Left Supramarginal Gyrus (anterior division)	0.005161	-48-36 + 30
Left dorsal granular insula	Cluster 1: Right Lateral Occipital Cortex	0.021595	+30-82 + 38
Right dorsal granular insula	Cluster 1: Left Lateral Occipital Cortex (superior and inferior division)	0.000105	-42-80 + 02
	Cluster 2: Left Lateral Occipital Cortex (superior division), Precuneus Cortex	0.000451	-20-68 + 30
Right ventral granular insula	Cluster 1: right Thalamus	0.005592	+04-12 + 22
Right dorsal dysgranular insula	Cluster 1: Right Precentral Gyrus, Inferior Frontal Gyrus	0.001218	+50 + 04 + 24

activations for most of the suprathreshold clusters of the seed-to-voxel analysis, except for the spheres related to the left dorsal granular insula (+30-82 + 38), the left ventral granular insula (+36 + 26-34) and the right ACC (-44 + 30 + 18) (Table S5).

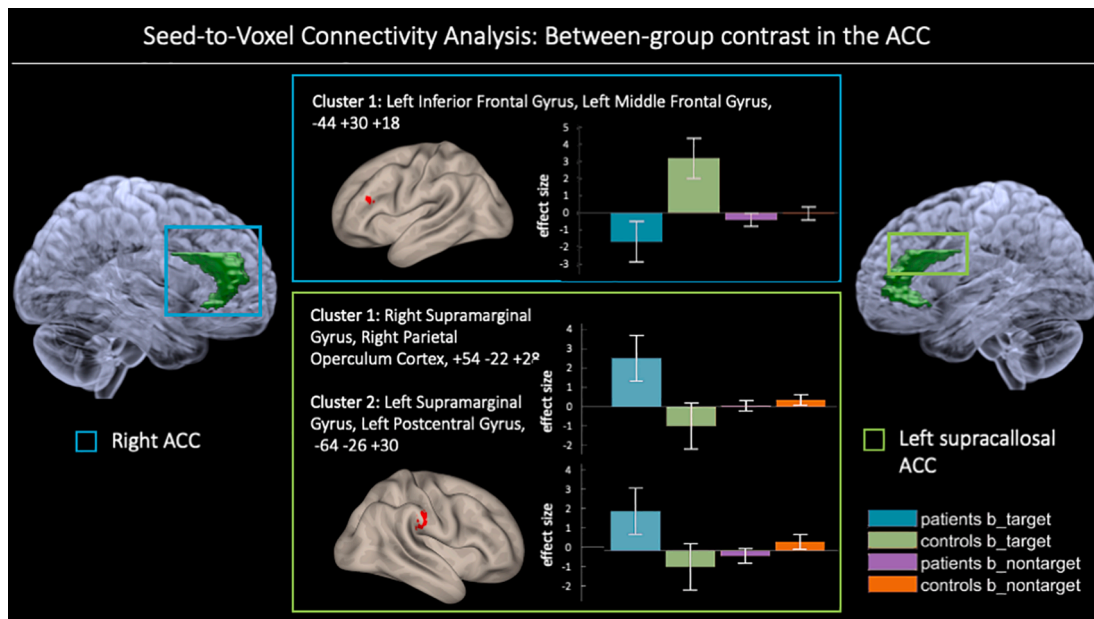


Fig. 5. Seed-to-Voxel Connectivity Analysis: Between-group contrast for the ACC and its subdivisions.. Suprathreshold Clusters are presented on an inflated brain surface with the effect sizes plotted per group and per condition next to it.

These between-group results were supplemented by two covariate analysis: Higher BDI scores were positively linked to an elevated connectivity from the left amygdala and the left ventral agranular insula to nodes of the DMN, such as the precuneus cortex. At the same time higher BDI scores were negatively linked from the left ventral granular insula to the temporal pole (Table S6a). Severity of anhedonic symptoms, reflected in higher SHAPS scores was linked to reduced connectivity from the left ACC and the right insula to the right frontal pole and the right MFG (Table S6b).

4. Discussion

In the explicit task paradigm of the present study, major depression is not reflected in diminished salience network activation patterns, but rather coded in alterations in SN-DMN inter-network connectivity. The smiling faces were perceived similarly fast, pleasant and accurate by both, the patient and control group. Hand in hand with these behavioral findings, the pre-defined ROIs of the SN showed equally enhanced BOLD signal changes within both groups. For the connectivity patterns a different picture emerged, with altered links between the default-mode, salience and face-perception network among major depressed individuals.

Behavioral and functional imaging results for the patient vs control contrast are discussed in detail below.

4.1. Behavioral data

The smiling faces of the social oddball paradigm were perceived as mildly pleasant by both groups, still major depressed individuals rated the smiling faces as slightly less pleasant. The reaction times during the social oddball paradigm were similar to the ones reported in other oddball paradigms (Rozenkrants & Polich, 2008), reflecting regular attention engagement. Since no significant differences in target accuracy or reaction time data were observed in the between-group contrast, the social oddball paradigm seemed equally demanding for both groups. The lack of differences in behavioral performance, e.g. similar valence ratings and reaction time data, has been reported in prior studies (Colich et al., 2017; Henderson et al., 2014) and probably suggests that major depressed individuals only have task-dependent but no general difficulties.

4.2. BOLD activation

Consistent with expected oddball effects in the pre-defined ROIs, both groups showed hyperresponsivity to the smiling faces compared to the neutral faces. Thereby, the BOLD signal changes were most pronounced in the right ventral-dorsal agranular parts and the left dorsal dysgranular part of the insular cortex. These agranular areas of the insular cortex are linked to viscerosensory integration and executive function. They are also known to inhabit specialized neurons that are strongly linked to self-consciousness, the Von Economo (VEN) and Fork neurons (FN) (Evrard, 2019). Due to these specialized characteristics, these particular neurons are discussed to pave the way for networking switching processes (Sridharan et al., 2008).

Compared to the control group, major depressed patients did not show any significant differences in BOLD signal changes in the pre-defined ROIs. These findings might seem contradictory, since they are inconsistent with prior literature on diminished activation patterns in structures of the salience network. But the results go hand in hand with the main statements of a recent study, which only partially found support for the mood-congruent hypothesis and rather indicated no universal deficits in the processing of emotional faces in depressed individuals (Van Vleet et al., 2019). In our view, the absence of significant differences in BOLD activation patterns in the present and prior studies might further support an inter-network based theory underlying major depressive disorder.

The anhedonia symptomatology however negatively correlated with left amygdala activity following smiling facial expressions. This link between reduced hedonic capacity and hyporesponsivity in the amygdala has been reported before in an implicit task design, following the subliminal presentations of happy facial expressions (Henderson et al., 2014).

This study now transfers the relation of anhedonia severity and hyporesponsivity in the amygdala to explicit task performance in a social oddball paradigm. The data suggests an attenuated response pattern in the left amygdala, which is not limited to a passive, subconscious perception of positive stimuli, but also expands to task-relevant positive stimuli. A recent simultaneous EEG/fMRI study on the processing of facial expressions has particularly outlined the amygdala as a fast responder in detecting the relevance of upcoming social stimuli (Müller-Bardorff et al., 2018). In line with its function in monitoring the

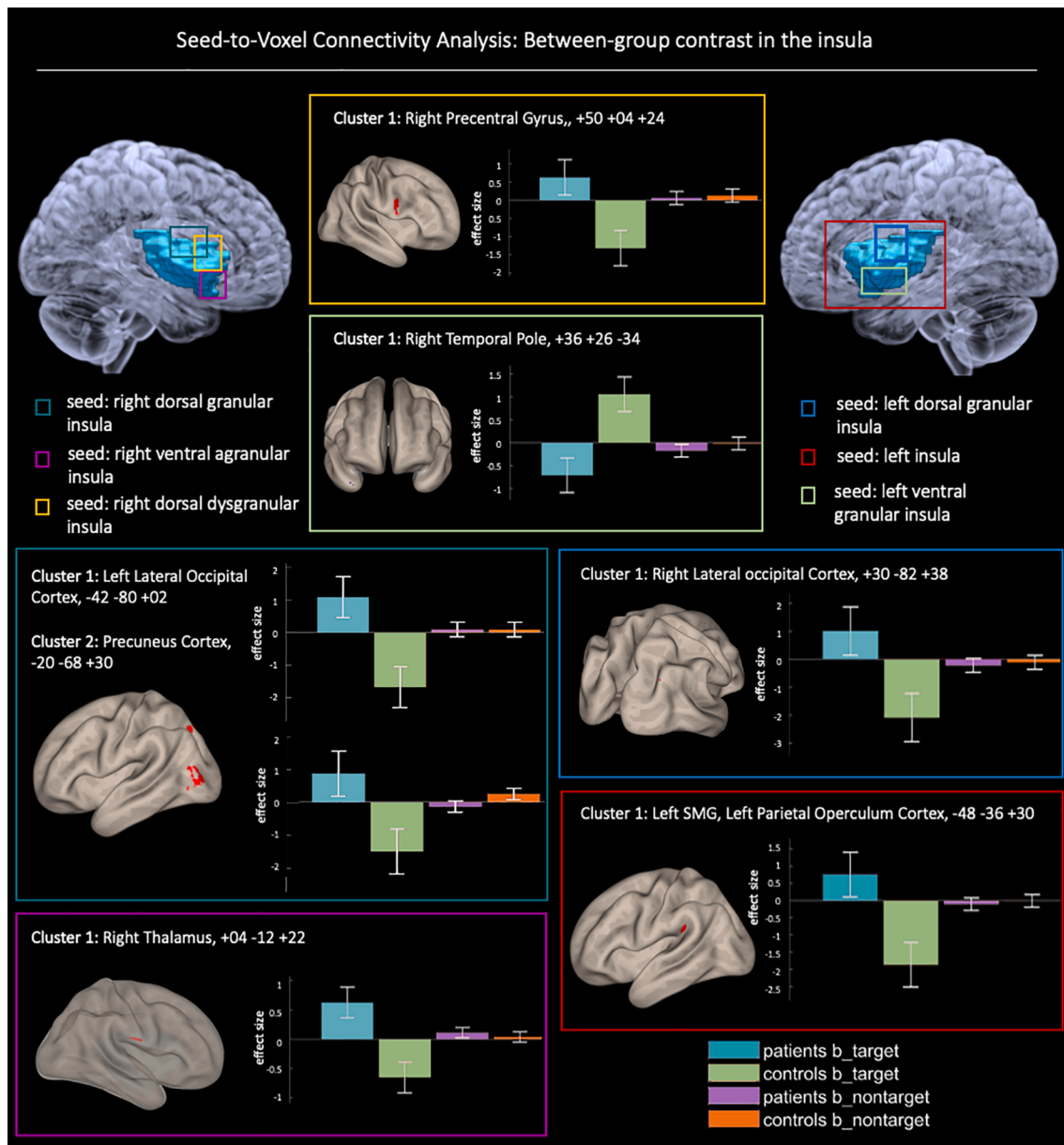


Fig. 6. Seed-to-Voxel Connectivity Analysis: Between-group contrast for the insula and its subdivisions. Suprathreshold Clusters are presented on an inflated brain surface with the effect sizes plotted per group and per condition next to it.

emotional salience value of surrounding stimuli, we anticipate a disrupted processing of both, subliminal and task-relevant positive facial expressions as a central nervous correlate of social anhedonia. Alterations in amygdala activation following the presentation of positive stimuli have been used as a target for real-time MRI neurofeedback and psychopharmacological treatment (Young et al., 2020, 2017). Interestingly, activation patterns in the amygdala were shown to be positively influenced through SSRI therapy (Young et al., 2020). So the present findings further support the idea of activation modulation in the amygdala as a therapy approach and also highlight its relevance in treating severe anhedonic symptomatology. Still, it is noteworthy that in the present study this effect seems to be limited to the BOLD signal pattern in the left amygdala, since there are no significant correlations of the SHAPS scores and the behavioral data (e.g. reaction times).

4.3. Functional connectivity

The functional connectivity analysis in the control group revealed a

strong link from the salience network, particularly from the right supracallosal ACC and the right insula, to other higher order brain structures associated with a) goal directed behavior and b) socio-emotional cognitive processing. Those brain structures included the bilateral frontal poles, the medial frontal cortex and the left paracingulate cortex. While the medial frontal cortex integrates multiple functions, such as pain, emotion and cognitive control (Kragel et al., 2018), the paracingulate gyrus is involved in allocating cognitive resources (Gennari et al., 2018) and the subdivisions of the frontal poles are largely engaged in planning behavior and social cognition tasks (Bludau et al., 2014)

In the depressed, those network connectivities showed the following alterations: 1) Reduced connectivity from SN to the ventral attention network and to structures of socioemotional cognition and 2) enhanced connectivity from SN to the face perception network and to the DMN.

Reduced connectivity from SN to the ventral attention network was reflected in diminished connectivity from the ACC to the MFG and IFG. While the MFG is engaged during division of attention and top-down

integration (Salo et al., 2017), both MFG and IFG are also involved in bottom-up processing during attention reorientation, e.g. due to unforeseen stimuli (Corbetta et al., 2008; Japee et al., 2015; Kim, 2014).

Reduced connectivity from SN to structures of socioemotional cognition was shown in altered links between the left ventral granular insula to the temporal pole. Being involved in a pre-dominantly right network of emotion recognition and empathy (Hillis, 2018), the temporal pole plays a key role in social cognition. DCM findings further highlighted its crucial role in top-down modulation of lower level perceptual processing within the ventral visual stream (Pehrs et al., 2017).

Enhanced connectivity from the salience network to the face perception network was reflected in strong links from the dorsal granular insula to the lateral occipital cortex. Based on its bidirectional link to the occipital face area and the fusiform face area, the lateral occipital cortex presents a core structure of the triangular face perception network, (Nagy et al., 2012). Increased recruitment of lateral occipital cortex connectivity is reported during enhanced task demands, possibly reflecting an intensified cognitive load during the social oddball paradigm in depressed participants.

Enhanced connectivity from the SN to the DMN became evident in a) increased connections from both ACC and insula to the Supramarginal Gyrus and b) increased connections from the insula to both the thalamus and the precuneus cortex.

Being part of the inferior parietal lobule, the SMG is seen as a higher order associational cortex and an additional structure of the DMN (Mulders et al., 2015). The precuneus cortex is located in the posterior parietal cortex and strongly engaged during resting-state, with its ventral part being mostly involved in self-referential processing (S. Zhang and Li, 2012). Together with the thalamus the precuneus cortex shares strong levels of functional and structural connectivity with the DMN (Cunningham et al., 2017). This profound link from SN to DMN during task performance might reflect an additional recruitment of self-directed cognition among major depressed individuals.

These between-group findings were further supported by the covariate analysis focusing on the effect of SHAPS and BDI scores. Thereby, higher BDI Scores were related to an increased connectivity from the SN to the DMN, particularly reflected in links from the left amygdala to the precuneus cortex. Anhedonia severity negatively correlated to functional connectivity from the SN, the left ACC and the right insula, to nodes of the Ventral Attention Network, the right MFG and the right frontal pole.

Taken together, the reduced connectivity patterns suggest an impaired bottom-up and top-down regulation processing within the ventral attention and socio-emotional cognition network in depressed individuals and the enhanced connectivity patterns go hand in hand with prior findings on altered SN-DMN inter-network connectivity in major depressed individuals.

An important limitation of the present study and other studies on emotional face processing, is a reported insufficient test-retest reliability in the amygdala (McDermott et al., 2020). Also, the effect of the smiling face presentation is confounded by the effect of salience detection, since the smiling faces were always presented as target stimuli. Hence, we cannot disentangle whether depression is characterized by enhanced SN-DMN network connectivity in the presence of any salient stimulus, in the present of social relevant stimulus or specifically in the presence of positive smiling faces. As we did not investigate negative facial expressions, our results do not necessarily contradict the mood-congruent hypothesis. However, the patterns of disrupted network connectivity from the SN to the socio-emotional cognition network and the enhanced connectivity to the facial perception network suggest that the social nature of the presented stimuli played a key role for the observed effect. Since we did not collect valence ratings for the neutral facial expressions, we do not know if they were perceived as less pleasant by the depressed group compared to the non-depressed group. If this is the case, our results would be biased by an enhanced non-target

vs target contrast in the depressed participants.

Another possible confounder is the positive reinforcement we introduced by showing the word great after each correct answer, this was done in order to achieve a stable attention, however it could have biased our results as prior studies showed an altered reaction to reward-learning in depressed patients (Kumar et al., 2008).

Nevertheless, our data generates the following explanatory model of social processing in major depressive disorder: On a first level of target detection the smiling faces are similarly processed and trigger regular bold responses in the salience network structures. However, on a second level of inter-network communication the brain of depressed participants seems to be wired for self-referential processing and rumination instead of fast goal directed behavior and socio-emotional cognitive processing. This bias towards enhanced rumination during task performance may be an explanation for the rapid exhaustion and sensory overload often perceived by major depressed individuals. As future perspective we suggest a comprehensive clinical assessment regarding the quality of exhaustion and sensory overload before, during and after task performance

5. Conclusion

The present study observed a trend, but no differences in BOLD responses during explicit task performance in a social oddball paradigm between the control and patient group. However, significant differences in salience connectivity patterns within the ACC and insula subdivisions were observed. This leads to the assumption that depressed individuals do not show deficits in activation recruitment itself, but instead suffer from alterations in the quality of network interaction. These alterations were particularly reflected in two networks, the ventral attention network and the default-mode-network. Further, anhedonia severity is related to hyporesponsivity in the left amygdala during the social oddball paradigm, which might reflect its impaired functioning in monitoring emotional-salient stimuli. One of the reasons for the inconsistency in literature on MDD might also be the existence of patient-subgroups within MDD which show different vulnerabilities to different paradigms (Cooper et al., 2018). As a future perspective, studies could try to implement a “subgroup categorization”, possibly through blood testing for cytokine levels, indicating an inflammatory subgroup (Miller and Raison, 2016).

CRedit authorship contribution statement

Carina J. Koeppel: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Software, Investigation. **Theresa Herrmann:** Investigation. **Kerstin Weidner:** Resources. **Jennifer Linn:** Resources, Funding acquisition. **Ilona Croy:** Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2021.102731>.

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