Association Between White Matter Fiber Structure and Reward-Related Reactivity of the Ventral Striatum

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Abstract: Individual responsiveness to rewards or rewarding stimuli may affect various domains of normal as well as pathological behavior. The ventral striatum/nucleus accumbens (NAcc) constitutes a key brain structure in the regulation of reward-appetitive behavior. It remains unclear, however, to which extent individual reward-related BOLD response in the NAcc is dependent on individual characteristics of connecting white matter fiber tracts. Using tract-based spatial statistics (TBSS) and statistical parametric mapping (SPM) this combined DTI - fMRI study investigated this question by correlating NAcc BOLD signal upon receipt of a monetary reward with different white matter characteristics (FA, axial diffusivity, radial diffusivity). The results show that increased integrity of white matter as assessed by FA in the cingulate and corpus callosum, the inferior fronto-occipital fasciculus, the anterior thalamic radiation and the anterior limb of the internal capsule was positively correlated with reward-related activation in the NAcc. There were no negative correlations as well as no significant results regarding axial and radial diffusivity. These findings indicate that microstructural properties of fiber tracts connecting, amongst others, the cortex with the striatum may influence intensity of reward-related responsiveness of the ventral striatum by constraining or increasing efficiency in information transfer within relevant circuitries involved in processing of reward. *Hum Brain Mapp* 35:1469–1476, 2014. © 2013 Wiley Periodicals, Inc.

Key words: nucleus accumbens; DTI; reward; internal capsule; anterior thalamic radiation

INTRODUCTION

Interindividual differences in the responsiveness to rewards or rewarding stimuli such as pleasant tastes or money may influence various domains of normal behavior

like, e.g., food habits as well as pathological divergence such as addiction. A deeper understanding of the mechanisms underlying these differences is therefore not only of general but also clinical significance. Not surprisingly, a large number of imaging studies has investigated the brain

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areas and networks that are involved when people anticipate or receive positive reinforcement or reward. As a commonly activated 'reward circuitry' a network consisting of anterior cingulate, orbital frontal cortex (OFC), medial prefrontal cortex (MPFC), amygdala, insula and the ventral striatum has been identified—all areas innervated by mesolimbic dopamine projections [Camara et al., 2009; Cauda et al., 2011; Knutson et al., 2003; McClure et al., 2004; Yacubian et al., 2006]. Amongst these, the nucleus accumbens (NAcc) constituting a major portion of the ventral striatum and receiving direct mesolimbic projections from the ventral tegmental area (VTA) has been proposed as the key brain structure in the regulation of reward-appetitive behavior [Admon et al., 2013; Camara et al., 2009; Cohen et al., 2012; Lam et al., 2013; Liu et al., 2011]. Correspondingly, individual reward-related behavioral patterns seem to be directly linked to activation of the ventral striatum/NAcc [Cohen et al., 2009] and NAcc has been found to be involved in the processing of positive feedback or reward and – to a lesser extent – negative feedback and reward omissions [Ernst et al., 2005; Koch et al., 2008] as well as in reinforcement-based learning [Ablner et al., 2006; Aron et al., 2004].

The question, however, whether NAcc function in terms of individual reward-related reactivity of the ventral striatum is influenced by or directly linked to structural characteristics in terms of connecting white matter fiber tracts has barely been investigated up to now.

Several white matter fiber tracts connect the NAcc with other areas critically involved in the processing of reinforcement and reward. Amongst them is the anterior limb of the internal capsule containing fibers connecting the cortex with the striatum and receiving fibers from the anterior cingulate and the medial frontal cortex [Schmahmann and Pandya, 2006]. Thus, the anterior limb of the internal capsule plays a vital role within the fronto-striatal network that is strongly involved in reward processing.

Of importance is moreover the anterior thalamic radiation (ATR) that connects thalamus, prefrontal cortex (PFC) and ventral periaqueductal gray (vPAG) with fibers running to temporomedial regions (e.g., amygdala and hippocampus) [Coenen et al., 2012]. Its horizontal fibers are connected to areas likewise relevant in the context of reward processing including the rostral part of the anterior cingulate gyrus and the orbitofrontal cortex.

First evidence from multimodal DTI – fMRI studies investigating learning and visual processing points towards a significant association between activation of certain structures or networks and underlying white matter structure [Camara et al., 2010; Koch et al., 2010; Toosy et al., 2004]. As parts of brain networks are known to be connected through white matter pathways these findings are intuitive and indicate that white matter fiber characteristics constrain information processing within networks and critically influence efficiency, speed and functioning of signal transfer [Fields, 2008].

Against this background the current study explores the question whether individual differences in reward-related responsivity of the NAcc are directly linked to its underly-

ing white matter connectivity. Diffusion tensor imaging (DTI) is the method of choice to investigate white matter characteristics and a number of parameters have been put forward to describe white matter structures and its diffusion [O'Donnell and Westin, 2011]. The most commonly used is fractional anisotropy (FA) which indicates the degree of anisotropic diffusion along a fiber tract and reflects different characteristics of axonal microstructure like extent of myelination or axonal size. In addition, mean, axial, and radial diffusivity can be assessed to receive additional information about the structural aspects [Alexander et al., 2007]. Here, radial diffusivity may predominantly mirror specific alterations in myelination whereas axial diffusivity has been proposed as a characteristic of axonal structure. Hence, in the present study we aimed at investigating whether FA, axial and radial diffusivity as characteristics of individual white matter structures connecting the NAcc with other areas and components within a network are directly linked to reward-related activation in the NAcc. Considering that white matter structure should critically influence information flow between relevant regions we expected to find significant associations between NAcc reactivity and characteristics of white matter fiber tracts connected to this structure.

MATERIALS AND METHODS

Subjects

The study sample comprised 42 healthy subjects (17 male, 25 female). All participants were right-handed, according to the modified version of Annett's handedness inventory [Annett, 1967].

On average, participants were 25.5 ± 5.2 years old. They were screened by comprehensive assessment procedures for medical, neurological, and psychiatric history. Exclusion criteria were current and potentially interfering medical conditions, any current or previous neurological or psychiatric disorder, and first-degree relatives with axis I psychiatric or neurological disorders. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was used to exclude current psychiatric disorders. Moreover, participants were screened for previous psychiatric disorders and not included in the study if there was any indication for current or previous psychiatric problems. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent to a study protocol approved by the Ethics Committee of the Friedrich-Schiller-University Medical School.

Experimental Design

Using the Presentation software package (Neurobehavioral Systems Inc., USA) stimuli were projected onto a transparent screen inside the scanner tunnel which could be viewed by the subject through a mirror system mounted on top of the MRI head coil. The subjects' responses were

Figure 1.

Reward task trial consisting of the presentation of a probability condition-specific figure (1.5 s), inter-stimulus interval (4.5 s), response period (2.5 s), second interstimulus interval (4.5 s plus temporal jitter), presentation of the correct solution followed by reward or punishment (2.5 s) and inter-trial interval (3.5 s). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

recorded using an MRI-compatible fiber optic response device (Lightwave Medical Industries, Canada) with four button keypads for the right hand. Participants were informed that they were presented a card with a geometrical figure on it (i.e., cross, half-moon, triangle, or pentagon) and were asked to guess whether the figure on the card predicted a number higher or lower than the number five. Each figure predicted the respective number with a probability of either 50% or 100%. Totally, 50% and 100% conditions were chosen to investigate reward processing after maximum and minimum decision uncertainty. As such the task has a probabilistic character and is adequate for investigating reward processing.

Each correct guess was followed by a monetary reward (+0.50 €) whereas each wrong guess was followed by a punishment (−0.50 €). Participants were instructed that the figure predicted the respective number with a certain probability but were not informed about the predictive probabilities of the respective figures. The whole paradigm consisted of a series of 64 interleaved trials with 32 trials for each probability condition distributed across the whole task sequence. Each trial started with the presentation of the probability condition-specific figure which was shown for 1.5 s. After an inter-stimulus interval lasting 4.5 s a question mark was presented for 2.5 s during which participants had to answer by button press. After another interstimulus interval of 4.5 s the correct solution followed by the indication of a reward or punishment appeared for 2.5 s (Fig. 1).

Participants were compensated according to their performance, although the minimum of € 20 was guaranteed for volunteering. Each trial ended with an inter-trial interval lasting 3.5 s. In addition, we introduced a temporal jitter by varying the second inter-stimulus interval between 4.5 and 5.5 s in order to increase sensitivity.

DTI Procedure

Diffusion data were collected on a 3 T whole body system (Magnetom TIM Trio, Siemens, Erlangen, Germany) equipped with a 12-element receive-only head matrix coil.

Diffusion-weighted images were obtained using a twice-refocused spin echo (TRSE) based echo-planar imaging sequence [Reese et al., 2003] (TR = 6,900 ms, TE=91 ms, field-of-view = 240 mm, in-plane resolution = 1.25 mm², slice thickness = 2.5 mm, number of slices = 55, matrix = 192 × 192, GRAPPA = 2). Diffusion-sensitizing gradient encoding was applied in 70 different directions with a diffusion-weighted factor of $b = 1,000 \text{ s/mm}^2$ and six b_0 ($b = 0$) images. Images were acquired parallel to the anterior-posterior commissure.

fMRI Procedure

fMRI data were collected on the same system as the DTI data. Foam pads were used for positioning and immobilisation of the subject's head within the head coil. T₂*-weighted images were obtained using a gradient-echo EPI sequence (TR = 2,040 ms, TE=26 ms, flip angle=90°) with 40 contiguous transverse slices of 3.3 mm thickness covering the entire brain. Matrix size was 72 × 72 pixels with in-plane resolution of 2.67 mm × 2.67 mm corresponding to a field of view of 192 mm × 192 mm. A series of 645 whole-brain volume sets were acquired, with the first three images of each series being discarded. High-resolution anatomical T₁-weighted volume scans (MP-RAGE) were obtained in sagittal orientation (TR = 2,300 ms, TE = 3.03 ms, TI = 900 ms, flip angle=9°, FOV=256 mm, matrix=256 × 256, number of sagittal slices=192, acceleration factor (PAT) = 2, TA= 5:21 min) with an isotropic resolution of (1 × 1 × 1) mm³.

Data Analysis

DTI data

DTI data analysis was performed using the FSL (FMRIB Software Library, FMRIB, Oxford, UK) software package [Smith et al., 2004]. First, data were corrected for the effects of head movement and eddy currents. After creating a brain mask the diffusion tensor model fit was performed to create individual FA images. Based on these FA images voxel-wise analysis was then calculated using TBSS [Smith et al., 2006]. As implemented in the TBSS analysis pipeline, all subjects' FA images were first nonlinearly normalized to a group-specific target image before the entire aligned data set was affine-transformed into 1 × 1 × 1 mm³ MNI 152 space (Montreal Neurological Institute, McGill, USA). Then, a mean FA image was created and filtered to retain only the center of the white matter tracts so as to create the mean FA skeleton. A threshold of FA>0.2 was applied to the skeleton to include only major fiber bundles and to restrict analysis to white matter which has been successfully aligned across subjects. Afterwards, each subject's aligned FA image was projected onto the mean FA skeleton in order to account for residual misalignments between subjects after the initial nonlinear registration. The significance threshold was set at $P < 0.05$

(corrected for multiple comparisons across voxels with a spatial extent threshold of $k = 20$) using the threshold-free cluster-enhancement option (TFCE). In addition to FA, individual axial and radial diffusivity maps were analyzed. Axial diffusivity describes the diffusivity along or parallel to the axon (λ_1), radial diffusivity describes the diffusivity perpendicular to the axon (average between λ_2 and λ_3) and fractional anisotropy (FA) measures the degree of directionality in diffusivity according to:

$$FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{2}\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

The white matter atlas by Mori et al. [2005] was used for precise identification of the fiber tracts. In-house software was employed to localize and characterize white matter clusters regarding size (i.e., number of voxels).

FMRI data

Preprocessing and statistical analysis of the fMRI data was performed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Functional data were corrected for differences in time of acquisition by sinc interpolation, realigned to the first image of every session and linearly and non-linearly normalized to the Montreal Neurological Institute (MNI, Montreal, Canada) reference brain (MNI 152). Data were spatially smoothed with a Gaussian kernel (8 mm, full-width at half-maximum) and high-pass filtered with a 128 s cut-off. All data were inspected for movement artifacts. Subjects with movement parameters exceeding 3 mm translation on the x -, y -, or z -axis or 3° rotation were excluded. In addition, individual movement parameters entered analyses as covariates of no interest.

On the first level, brain activations were then analyzed voxel-wise to calculate statistical parametric maps of t -statistics for the 50% probability condition (i.e., activation during responding to triangles and pentagons), the 100 % probability condition (i.e., activation during responding to half-moons and crosses) and positive compared to negative reinforcement (i.e., activation during presentation of monetary win vs. monetary loss).

Blood oxygenation level dependent (BOLD) signal changes for the different conditions were modeled as a covariate of variable length boxcar functions and convolved with a canonical hemodynamic response function (HRF). These HRFs were then used as individual regressors within the general linear model (GLM). A one-sample t -test was performed on the second level to analyze reward-related activation (i.e., activation during presentation of monetary win vs. monetary loss). Results were based on a FWE corrected threshold of $P < 0.05$.

To investigate the hypothesized association between reward-related NAcc activation and white matter microstructure we extracted individual parameter estimates

from the NAcc and correlated them with individual axial diffusivity, radial diffusivity and FA using age as covariate. To this aim, ROIs were drawn around the NAcc voxel with maximum activation ($x = 8$, $y = 8$, $z = -10$) including all voxels within a 4 mm radius. Beta values were then extracted from all voxels within this ROI and the first eigenvariate was calculated via singular value decomposition (SVD). Finally, an age-corrected correlation between these beta values and white matter (i.e., axial diffusivity, radial diffusivity, and FA) was performed using the randomize function implemented in TBSS.

To post-hoc investigate whether the significant findings reported in the results section are specific or rather reflect a generic, whole brain relationship between BOLD and FA we correlated whole brain FA with activation in a control region. As a control region we chose the occipital lobe/cuneus. Thus, we built an 8 mm sphere around its center coordinates ($x = -14$, $y = -100$, $z = 8$), extracted beta values from all voxels within this ROI and performed an age-corrected correlation between these beta values (i.e., their first eigenvariate) and white matter FA.

RESULTS

The one-sample t -test analyzing reward-related activation (i.e., activation during presentation of monetary win vs. monetary loss, $P < 0.05$, FWE corrected) yielded significant activation in a network containing predominantly the ventral striatum (NAcc / putamen, $T = 10.48$, $x = 8$, $y = 8$, $z = -10$, $k = 235$, Fig. 2), parietal and superior temporal areas, insula, anterior cingulate (BA 24), orbital frontal cortex (OFC, BA 11) as well as medial prefrontal cortex (MPFC, BA 10) (Table I).

The correlation between reward-related activation extracted from the NAcc (4 mm sphere around maximum activated voxel at $x = 8$, $y = 8$, $z = -10$) and axial diffusivity (corrected for age) yielded no significant results, neither regarding the positive nor the negative association. The same applied to the age-corrected correlation between NAcc BOLD signal and radial diffusivity. The positive correlation between reward-related NAcc activation and FA with age as a covariate illustrated that fractional anisotropy in major parts of the corpus callosum, the cingulate bundle, the inferior fronto-occipital fasciculus (IFOF), the anterior limb of the internal capsule (alic) and the anterior thalamic radiation (atr) predicted NAcc activation (Table II, Fig. 3). The negative correlation between NAcc BOLD signal and FA, corrected for age, yielded no significant results. The correlation between activation in the control region (i.e., the cuneus) and FA, corrected for age, yielded likewise no significant results.

DISCUSSION

This study investigated the question whether reward-related activity in the NAcc is constrained by the structural

Figure 2.

Reward-related activation (i.e., activation during presentation of monetary win vs. monetary loss, I-sample t-test at $P < 0.05$, FWE corrected) and parameter estimates of the *N. accumbens*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

characteristics of connecting white matter fiber tracts. As expected, the individual intensity in reward-related NAcc activation was directly related to the integrity of the underlying white matter, i.e., the higher the white matter integrity as reflected by the degree of fractional anisotropy, the higher the reward-related NAcc activation.

The analysis of the reward-related BOLD activation demonstrated that the receipt of positive reinforcement and monetary reward as compared with negative feedback and monetary loss was associated with activation increases in a network containing predominantly the ventral striatum (NAcc, putamen), parietal and superior temporal areas, insula, anterior cingulate, orbital frontal (OFC) as well as medial prefrontal cortex (MPFC). These are areas known to closely interact in the processing of reward and reinforcement [Camara et al., 2009]. As demonstrated in primate

studies the anterior cingulate, the OFC and the MPFC are directly connected to the ventral striatum and interact with the NAcc in the context of processing of reward and reinforcement. Major parts of this network are innervated by mesolimbic dopamine projections thus constituting central components of the mesolimbic dopamine system [Haber and Knutson, 2010]. Especially the insula has been shown to interact with the NAcc during reward delivery [Camara et al., 2008]. Results of studies demonstrating the connection between insula and NAcc to increase under the influence of dopamine receptor agonists emphasize the relevance of dopaminergic projections within this network in the context of reward processing [Ye et al., 2011]. The present findings which constitute the result of a comparison between processing of monetary gain and monetary loss moreover indicate that this network's activation is

TABLE I. MNI coordinates of activation maxima (SPM value, k = number of voxels in cluster) for reward-related activation (i.e., activation during presentation of monetary win vs. monetary loss, I-sample t-test at $P < 0.05$, FWE corrected)

Region	Side	T	x	y	z	k
N. accumbens, putamen	r	10.48	8	8	-10	235
Parietal lobe, BA 2	l	8.14	-48	-26	44	1016
Occipital lobe, BA 18	r	7.78	14	-84	-10	243
Parietal lobe, BA 7	l	7.40	-28	-52	56	165
Superior temporal gyrus, BA 42	r	7.20	60	-26	12	92
Parietal lobe, BA 3	r	7.17	36	-28	48	144
Cingulate gyrus, BA 31	r	7.00	10	-24	46	128
Posterior cingulate, BA 30	l	6.61	-6	-50	18	64
Insula, BA 13	r	6.29	44	0	12	25
Occipital lobe, cuneus, BA 18	l	6.14	-14	-100	8	21
Cingulate gyrus, BA 24	r	3.60	12	13	33	29
Frontal lobe, BA 10	l	6.10	-10	38	-8	14
Superior temporal gyrus, BA 22	r	6.04	58	-2	2	14
Frontal lobe, BA 11	r	6.00	6	30	-14	44
Parietal lobe, BA 2	l	5.93	-62	-20	28	6

TABLE II. White matter tracts showing a positive correlation (age-corrected, $P < 0.05$ TFCE corrected) with reward-related NAcc activation (k = number of voxels)

White matter structure	x	y	z	k
Cingulum, corpus callosum	89	156	87	2642
Inferior fronto-occipital fasciculus	60	64	90	193
Forceps minor, anterior thalamic radiation	110	174	87	120
Inferior fronto-occipital fasciculus	56	69	73	116
Anterior limb of internal capsule	109	175	73	39
Anterior thalamic radiation	108	180	79	26
Anterior thalamic radiation	112	156	89	20

Identification of fiber tracts was based on the white matter atlas by Mori et al. [2005].

predominantly strong when a positive feedback or a reward is presented, although parts of the network have also been found to be active when a reward is omitted. Parameter estimates in Figure 2 illustrate that this is true for the NAcc activation in the present study also. They show strong NAcc activation during monetary gain and weak but measurable activation in association with monetary loss. This is in line with the assumption that processing of positive and negative reinforcement recruits similar networks and it is predominantly the activation intensity that differentiates both processes [Dreher, 2007].

As a most central result of this study the reward-related activity in the NAcc turned out to be correlated with struc-

tural integrity (in terms of FA) of several functionally relevant tracts, namely the cingulum bundle, parts of the corpus callosum, the inferior fronto-occipital fasciculus (IFOF), the anterior limb of the internal capsule (alic) and the anterior thalamic radiation (atr). The results are partly in agreement with findings of a recent study that demonstrated a correlation between FA of the IFOF and reward-related BOLD response in the NAcc [Camara et al., 2010]. Although this study found no significant results in the anterior limb of the internal capsule and the anterior thalamic radiation the authors emphasized that these structures (i.e. the anterior thalamic radiation and parts of the alic) pass the IFOF and constitute relevant frontostriatal connections to the NAcc. Thus, the anterior limb of the internal capsule contains fibers connecting the cortex with the corpus striatum and receives fibers from the anterior cingulate (BA 32), the orbitofrontal and medial frontal cortex [Schmahmann and Pandya, 2006]. Accordingly, the present results suggest that integrity of this connecting fiber tract critically influences the intensity of the reward-related reactivity of the ventral striatum and connected frontal areas. We assume that larger FA values reflect increased efficiency in transmitting information within the fronto-striatal network involved in reward processing resulting in higher BOLD response.

Extensive white matter fiber tracts connect the anterior cingulate cortex, the orbitofrontal cortex, the NAcc and the medial temporal lobe [Johansen-Berg et al., 2008; Schmahmann and Pandya, 2006]. These connecting pathways have also been identified in primate tracing studies which displayed extensive connections between the ventral striatum and the medial and orbitomedial prefrontal cortex [Haber et al., 1995] as well as subcortical limbic regions including amygdala and hippocampus [Friedman et al., 2002].

Considering that the NAcc is a key integrative region receiving inputs from orbitofrontal and medial frontal areas, insula, and limbic regions current data showing a close association between NAcc reactivity and white matter connectivity are plausible and emphasize the relevance of white matter fiber integrity for the integrative function of the ventral striatum. The correlation between FA and NAcc BOLD response indicates that interindividual differences in reward-related reactivity are linked to the structural characteristics of relevant connecting fiber tracts. Hence, present data suggest that the efficiency or intensity of reward-related signal transfer is critically dependent on the constraints imposed by structural characteristics of connecting fiber tracts, such as axonal myelination or fiber thickness. It should not go unnoticed, however, that the differences in white matter fiber characteristics in the present sample of healthy people indicate, most likely, normal variations in white matter structure (e.g., varying degree of myelination, axonal branching, fiber complexity, or diameter). These microstructural characteristics have been shown to change with experience [Zatorre et al., 2012], e.g., as a result of training [Scholz et al., 2009; Takeuchi et al., 2010]. Here, myelinogenesis, caused by neural

Figure 3.

White matter tracts showing a positive correlation with reward-related NAcc activation. cg, cingulum bundle; cc, corpus callosum; alic, anterior limb of internal capsule; atr, anterior thalamic radiation; ifo, inferior fronto-occipital fasciculus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

activity in fiber tracts during training, is one possible mechanism underlying the observed FA increases. This mechanism has been demonstrated in mice studies. In these studies increasing neuronal electrical activity by the use of specific neurotoxins known to increase the firing of neurons caused increased myelination [Demerens et al., 1996].

Individual white matter characteristics have also been found to be linked to feedback-based learning performance and associated functional activation. For instance, Cohen et al. [2008] investigated functional and structural connectivity (i.e., fiber tracking) to investigate fronto-limbic network function during feedback-based reversal learning. They found that the strength of estimated white matter tracts from the amygdala to the hippocampus, orbitofrontal cortex, and ventral striatum predicted how subjects adapted their behavior following positive and negative feedback, as well as the functional connectivity within this network. Hence, present results displaying an association between reward-related activation in the NAcc and white matter microstructure in connecting fiber tracts may indicate plastic processes as a result of interindividual differences in experience. Finally, as NAcc and connecting white matter fiber tracts like the internal capsule are becoming increasingly popular stimulation targets in various psychiatric disorders [Bewernick et al., 2012; Bourne et al., 2012; Heldmann et al., 2012] present findings may also be of clinical relevance. Further multimodal studies focusing on specific relevant white matter connections – ideally by making use of newly developed fiber tracking methods – are however needed to obtain a better understanding of the precise anatomy, its association with changes in BOLD signal and, last but not least, its relevance regarding mental disturbances.

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