



Pathologically reduced neural flexibility recovers during psychotherapy of OCD patients

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ARTICLE INFO

Keywords:

Dynamic functional connectivity (dFC)
fMRI
Neural flexibility
OCD
Depression

ABSTRACT

Flexibility is a key feature of psychological health, allowing the individual to dynamically adapt to changing environmental demands, which is impaired in many psychiatric disorders like obsessive–compulsive disorder (OCD). Adequately responding to varying demands requires the brain to switch between different patterns of neural activity, which are represented by different brain network configurations (functional connectivity patterns). Here, we operationalize neural flexibility as the dissimilarity between consecutive connectivity matrices of brain regions (jump length). In total, 132 fMRI scans were obtained from 17 patients that were scanned four to five times during inpatient psychotherapy, and from 17 controls that were scanned at comparable time intervals. Significant negative correlations were found between the jump lengths and the symptom severity scores of OCD, depression, anxiety, and stress, suggesting that high symptom severity corresponds to inflexible brain functioning. Further analyses revealed that impaired reconfiguration (pattern stability) of the brain seems to be more related to general psychiatric impairment rather than to specific symptoms, e.g., of OCD or depression. Importantly, the *group × time* interaction of a repeated measures ANOVA was significant, as well as the post-hoc paired *t*-tests of the patients (first vs. last scan). The results suggest that psychotherapy is able to significantly increase the neural flexibility of patients. We conclude that psychiatric symptoms like anxiety, stress, depression, and OCD are associated with an impaired adaptivity of the brain. In general, our results add to the growing evidence that dynamic functional connectivity captures meaningful properties of brain functioning.

1. Introduction

1.1. Flexibility as a mechanism of mental health

Flexible adaption to external and internal requirements is one of the key demands on humans for successfully mastering life. Flexibility

allows us to respond adequately to situational demands, shift perspectives, and balance competing desires (Kashdan and Rottenberg, 2010). To accomplish these challenges, flexibility is required not only in the cognitive domain, but also in emotional and behavioral responses. Rigidity, i.e., reduced flexibility, is associated with a variety of psychological disorders like obsessive–compulsive disorder (OCD), major

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<https://doi.org/10.1016/j.nicl.2021.102844>

Received 14 April 2021; Received in revised form 24 August 2021; Accepted 25 September 2021

Available online 7 October 2021

2213-1582/© 2021 The Author(s).

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depressive disorder (MDD), anxiety disorders, and addiction. Patients are, for example, unable to experience the full repertoire of emotions, but are stuck in anxiety and sadness, respectively (Holtzheimer and Mayberg, 2011). They suffer from ruminations and worries (Nolen-Hoeksema et al., 2008), craving, impaired executive control (e.g., shifting cognitive sets and attention) (Rock et al., 2014; Snyder et al., 2015), thereby limiting self-control and goal-directed behavior (Kashdan and Rottenberg, 2010). Rigidity in *behavior* is primarily associated with OCD, reflecting the repetitive rituals like washing, ordering, or checking, but is also prevalent in depression and anxiety. Avoiding social contacts and/or subjectively threatening situations are prevalent in all three disorders, presenting an overall reduced repertoire of behavior. As Kashdan and Rottenberg put it, "... the pervasive and widespread nature of evidence for inflexibility in so many different response systems in so many different mental disorders is potentially overwhelming" (Kashdan and Rottenberg, 2010, p. 870). Of course, cognitive, emotional, and behavioral rigidity are not independent from each other. Coherent experiences arise from the coordination of cognitions, emotions, and behavior, that influence each other. Such psychological patterns are a combination of these three basic aspects of experience and are called cognitive-emotional-behavioral (CEB) patterns (Haken and Schiepek, 2010). For example, a patient suffering from OCD who has just washed his hands experiences obsessive thoughts about whether the hands are properly clean now at the cognitive level, accompanied by fear of contamination at the emotional level, that elicit the urge to wash the hands again at the behavioral level. All levels exhibit rigidity, and none of these aspects exists independent of the other. In consequence, when aiming to investigate flexibility, CEB patterns have to be treated as an entity. Likewise, successful therapeutic treatment does not only imply symptom reduction or improving the quality of life but implies changes in the dynamic qualities of mental processing.

The aim of this study is to translate the psychological concept of mental flexibility into neuroscience. We propose a formal operationalization and measurement of flexibility at the neural level and investigate this in a sample of patients with OCD (with comorbid depression and/or anxiety disorder). Given that research on static or effective functional connectivity did not yield consistent effects or patterns associated with psychopathology (e.g., in Major Depressive Disorder, Helm et al., 2018), a high-level measure of dynamic functional connectivity like neural flexibility might better capture features of the brain's functioning. We

further investigate how neural flexibility is affected by psychotherapy. Assuming a correspondence between flexibility at the neural and at the cognitive-emotional-behavioral level, neural flexibility should improve during psychotherapy.

1.2. Operationalizing flexibility

Nonlinear dynamic systems theory (Haken, 1982, 2006; Haken and Schiepek, 2010) may help to operationalize abstract concepts such as flexibility, which are commonly difficult to concretize. In particular, the concept of state space is useful, which we illustrate by the following general considerations: State variables unambiguously describe the current state of a system and span a space, in which the trajectory traces out its temporal evolution. Assuming that every cognitive-emotional-behavioral state corresponds to a specific point in a state space, flexibility can be defined as the availability and accessibility of a sufficient range of different cognitive-emotional-behavioral patterns (Fig. 1). We interpret these patterns as attractor states, which define a domain in state space, towards which trajectories evolve over time to. This implies that (1) a variety of different attractor states is available, and that (2) these states are accessible. In addition, a healthy functioning will also require the ability to correctly judge the appropriateness of the state by a *meta*-conscious monitoring and controlling process (Schooler, 2002) – which is usually subjective and culture dependent. The first two requirements of flexible behavior, however, can be empirically observed by measuring how many different states are accessed during a given period of time (Beirle and Schiepek, 2002). In the upper row of Fig. 1, stable CEB patterns are represented as the valleys of the potential landscape. The current state of the system can be visualized as a ball moving in the landscape, and by this laying out the trajectory. Each valley can be understood as an attractor which forces the trajectory towards its bottom, where it will rest until external and/or internal forces (e.g., perceptions, thoughts, needs) or noise push it towards a different state. If no other stable CEB states are available in the mental landscape, the ball will roll back into the pathological state (Fig. 1B). If other stable valleys exist, but are too deep, the forces will not be strong enough to transcend the "mountain" to a different stable CEB state and will likewise fall back into the pathological state (Fig. 1C). Exemplary trajectories in the corresponding state spaces are depicted in the lower row of Fig. 1.

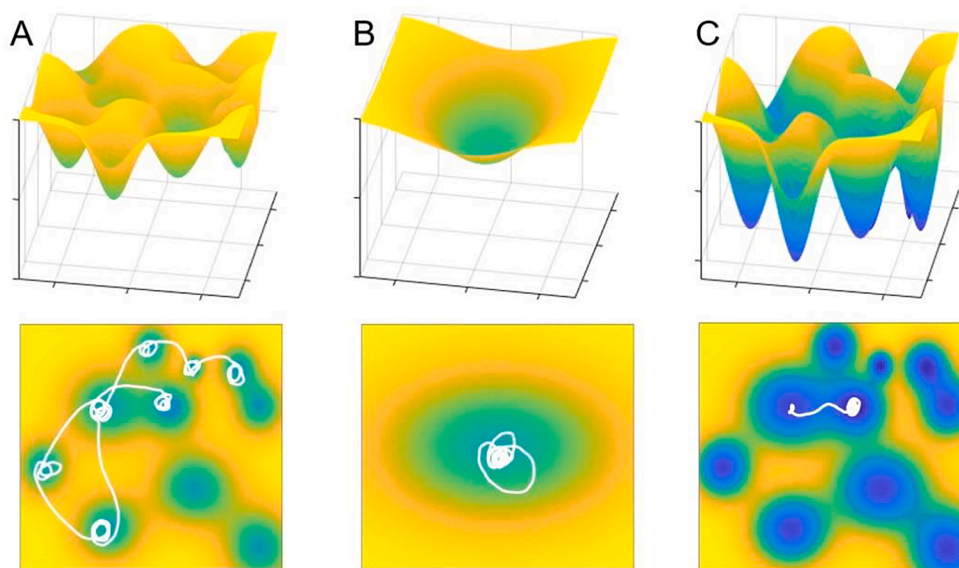


Fig. 1. Toy examples of healthy (A) vs. impaired (B and C) psychological functioning in potential landscapes (upper row) and corresponding state spaces (lower row). In column (A), the potential landscape of a healthy person is relatively flat and contains many possible (stable) attractor states (valleys). Switching between different stable cognitive-emotional-behavioral (CEB) patterns (valleys/attractors) is easy, as can be seen by the white lines below, which show an exemplary trajectory in the state space. In contrast, (B) and (C) show two kinds of pathological potential landscapes. In (B), only one (pathological) CEB pattern (valley/stable state) is available. External or internal forces (perturbations) push the system away from the stable floor of the valley, but it quickly falls back. The other possibility of impaired flexibility is shown in (C): here, the potential landscapes comprises all the stable states of a healthy person, but they are not accessible because the valleys are too deep – even strong forces are unable to overcome the saddles of the mountains. The patient is stuck in a pathological state, because potentially existing alternatives are not accessible.

Over the previous years, consensus has been achieved among neuroscientists that cognitive-emotional-behavioral patterns are represented by specific network configurations of brain regions (Gonzalez-Castillo and Bandettini, 2018; Nomi et al., 2017). A formalization of the link between psychological and neural states has been established recently by Pillai and Jirsa (2017) making use of Structured Flows on Manifolds (SFMs), a mathematical framework for the self-organization and emergence of low-dimensional behaviors from network dynamics. The change between network configurations over time can be quantitatively captured by dynamic functional connectivity (dFC) (Calhoun et al., 2014; Hutchison et al., 2013), which is a measure of the temporal variance of functional links between brain regions. Importantly, dFC has been explained as the visible manifestation of brain dynamics structured by complex SFMs (Hansen et al., 2015). In Fig. 1, similar dynamical brain states (here represented by similar CEB patterns) lie in close proximity establishing an attractor of invariant or similar functional connectivity, whereas states with very different properties lie far apart (so that transitions between attractors map to network changes and to non-trivial dFC). A measure that captures the (dis)similarity of FC networks along time, the *jump length* d , has recently been introduced by Battaglia et al. (2020) and Lombardo et al. (2020). They showed that the jump length was reduced in aging and in subjects with lower cognitive abilities – both domains that are commonly associated with rigidity. Here, we hypothesize that the compression of time-evolving brain network activity into the measure of dFC preserves properties of the full high-dimensional brain dynamics, which are relevant and predictive with regard to brain health in terms of its functional capacity, including cognitive function. In other words, dFC shows properties of a biomarker of brain health. Jump length captures one feature of dFC (albeit one amongst others), which is linked to switching dynamics, and bears promise to quantify the link between brain activity with CEB patterns. Several studies hinted at dFC as a measure of cognitive and behavioral flexibility (Braun et al., 2015; Jia et al., 2014).

Switching between CEB patterns or states should be encoded in the brain in a general, not task-dependent way. Neural (in-)flexibility should thus be (also) observable in a state of rest, i.e., when a person lies in the MRI scanner and is instructed not to think of anything particular (Raichle, 2011). When the mind is “wandering” freely, it should give a good representation of typical states that are accessed (Deco et al., 2013). Flexible (healthy) participants should visit a variety of states (patterns) and not linger in them for an extended period of time, whereas pathological dynamics only offer access to a restricted subarea of the mental state space, or do not provide a sufficient amount of stable states.

2. Methods

2.1. Study procedure and participants

Patients were eligible to participate in the study if OCD was the main illness by clinical judgement based on ICD-10 and DSM-IV criteria and on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First et al., 2002). Exclusion criteria were neurological impairment and/or neurological diseases, acute psychosis, substance abuse, and/or suicidality. Mean age (SD) of the patients was 40.2 (10.2) and 39.9 (9.0) for the controls, with 65% female participants in both groups. The study was approved by the Ethics Commission Salzburg (Ethikkommission Land Salzburg, No. 415-E/1203/5–2012). Detailed information on the study was provided and written informed consent was obtained from all participants according to the Declaration of Helsinki.

The patients received treatment at the Department of Inpatient Psychotherapy, University Hospital of Psychiatry, Psychotherapy and Psychosomatics at the Paracelsus Medical University, Salzburg, Austria. Psychotherapeutic treatment consisted of an integrative approach including weekly individualized psychotherapy sessions based on the concept of cognitive-behavioral therapy with an experienced therapist,

gradual exposure to situations provoking obsessions and compulsions, psychoeducation, mentalization/mindfulness training, focused groups, skills training following Dialectic Behavioral Therapy, music and arts therapy, indoor climbing, and Nordic walking. Pharmacological treatment included antidepressants (mostly SSRI). All but one patient were medicated with at least one antidepressant, 7 of them in addition with neuroleptics (mostly quetiapine), 3 with anticonvulsants, 2 with benzodiazepine, and 1 with lithium. One patient also had to be medicated for high blood pressure, thyroid dysfunction, and incontinence.

Several psychological symptom scales were applied: at their first and last fMRI scans, patients filled in the Beck Depression Inventory II (BDI-II) (Beck et al., 1996; Hautzinger et al., 2009), and the Symptom Checklist (SCL-90-R) (Derogatis et al., 1977; Glöckner-Rist and Stieglitz, 2012); three patients did not fill in the BDI-II and SCL-90-R at the last scan. In addition, the Depression-Anxiety-Stress Scale (DASS) (Lovibond and Lovibond, 1995; Nilges and Essau, 2015), and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman, 1989; Hand and Büttner-Westphal, 1991) were applied every week by the online-based real-time monitoring system SNS (Synergetic Navigation System) (Schiepek et al., 2018). If the Y-BOCS and the DASS were not filled in on the exact day of the fMRI scan, the value following the scan was used (note that both questionnaires assessed the symptoms within the last week, i.e., including the day of the scan). For results of the psychological assessment see Supplement D (Table S3). Comorbidities, as commonly found in OCD patients, included depression and anxiety disorders. In addition, three patients were diagnosed with a disorder from the schizophrenia spectrum, alcohol and substance abuse (currently abstinent), and posttraumatic stress disorder, respectively. Controls were psychologically assessed with the SCL-90-R and BDI-II before the first scan to exclude any psychiatric disorders.

2.2. fMRI scans

A total of 132 fMRI scans were acquired with a 3 T Siemens TIM TRIO whole-body scanner by scanning the 17 patients and the 17 controls 3–5 times each in intervals of approximately 4 weeks, depending on the lengths of the inpatient psychotherapy (see Supplement A for technical details of the fMRI scans and Supplement C for an assessment of statistical power respecting both inter- and intrasubject variance). The mean (SD) number of days between scans was 24 (5) days for patients and 38 (13.7) days for controls. All but one patient were scanned at least 4 times. For 8 patients, whose treatment was prolonged, an additional 5th scan was available ($N = 75$ scans). For controls, all but 1 subject were scanned 3 times, 5 controls 4 times, and 2 controls 5 times ($N = 57$ scans). The first scan of patients was done within their first week of hospitalization, the last scan within their last week. During the resting state scans, participants were asked to close their eyes, to not think of anything particular, and to relax, but to avoid falling asleep.

Standard preprocessing of the fMRI scans was performed using an inhouse Matlab script (for details see Supplement A). The neural activity (BOLD signal) of 119 brain regions spanning the whole brain was extracted for each subject and scan (Supplement A, Table S1). In addition, we re-ran the analysis without the bandpass filter, first because there is evidence that there is information in the BOLD signal beyond the usual cutoffs (Chen and Glover, 2015; DeRamus et al., 2021), and second because variation in the signal might be caused by the bandpass filter stop band ripple. We compared the difference between the resulting time series by calculating $d = \sum (x_t - \mu_t)^2$, where μ is the mean of the time series. We then calculated the difference between the d with bandpass filter and the d without bandpass filter for each signal. A one-sample t -test confirmed that the differences were not significantly different from zero. We can hence conclude that the filtering does not introduce considerable noise and continued the analyses using the bandpass filtered time series.

2.3. Jump lengths d

We will demonstrate the time-varying functional connectivity, i.e., the assessment of FC over time (dFC), and the calculation of a measure of flexibility, the jump length d , in a simple example using the BOLD signals of three brain regions. These regions (left and right putamen and the anterior cingulate cortex) are known to relate to the pathology of obsessive-compulsive disorder (Del Casale et al., 2016; Thorsen et al., 2018). For illustration (Fig. 2), the section between $T = 42$ and $T = 78$ was extracted from the whole time series. The measurements were taken in intervals of $TR = 1.95$ s (TR : repetition time), which is the time the MRI scanner takes to acquire a functional scan of the whole brain.² One time step (sampling point) in Fig. 2A therefore represents approximately 2 s.

In order to assess the dynamics of FC, the time series were split into segments of 6 sampling points, so each window comprises ~ 12 s. In the following, this is referred to as *window size*. It becomes intuitively clear that the choice of the window size might have an effect on the results. We chose here a window size of 6 TRs. While this window is very short with respect to conventional FC analyses, it also allows to observe a larger number of jumps between FCs estimated from non-overlapping windows, a factor which is here more important than precision on the estimation of instantaneous FC networks themselves (see Materials and Methods). Recent evidence of meaningful and converging results stress the validity of using a higher temporal resolution in dFC analyses (Alonso Martínez et al., 2020; Tagliazucchi et al., 2012) and is confirmed by the robustness of our results over different window sizes (see Supplement E and F).

In the actual example of Fig. 2A from a representative resting state session, we define different non-overlapping windows W_1, W_2, \dots, W_6 . The fluctuating nature of FC can be clearly seen in this example: The BOLD signals of the left and right putamen (dark and light blue) correlate strongly within the first three windows. Then, the correlation is dissolved during W_4 – it switches from correlation to anti-correlation (W_5 und W_6).

Dynamic functional connectivity (dFC) is assessed by calculating the correlations between the time series separately within each window. Here, the Pearson correlations between the three signals in Fig. 2A are calculated and stored in a correlation matrix (Tables in Fig. 2B). Instead of one correlation matrix like in conventional FC, as many correlation matrices as windows are calculated, forming a time-ordered sequence of network frames (also known as a “temporal network”) (Holme and Saramäki, 2012; Li et al., 2017).

Next, we are interested in how similar consecutive correlation matrices are, in order to quantify a time-resolved rate of connectivity reconfiguration. This can easily be achieved by correlating pairs of consecutive matrices with each other (between Fig. 2B and 2C)³. In the example of Fig. 2B, the network configurations of the first three windows are very similar, as reflected by the high correlation coefficients r_{12} and r_{23} between consecutive temporal network frames. A change in the network configurations occurs at W_4 , so the correlation coefficient r_{34} is considerably lower. A new correlation pattern (network configuration) appears at W_5 , so the correlation coefficient r_{45} drops close to zero. At W_6 , the new pattern has established, leading to a high correlation coefficient between W_5 and W_6 . The period of the transition (W_4 and W_5) is highlighted in grey (Fig. 2A).

So far, the *similarity* between consecutive windows was calculated. To obtain a measure for the *dissimilarity*, we subtract the correlation coefficient from 1 (Fig. 2C). This difference measures “how long is the

² In this context, please note that the time series were slice-time corrected, which adjusts for the different times that upper and lower areas of the brain were scanned.

³ For computational sparsity, only the upper triangles of the matrices were correlated. The grey ones in Fig. 2B are given for a better understanding only.

jump” along the sequence of explored network configurations. Since inter-network distances are always measured over time intervals of equal duration (given by the window size), such *jump length* $d_{ij} = 1 - r_{ij}$ can also be interpreted as a speed of reconfiguration, hence the alternative name of *dFC speed* used by Battaglia et al. (2020) and Lombardo et al. (2020). In Fig. 2C, its increase correctly identifies the changed connectivity pattern at W_4/W_5 .

For each subject and each scan, a sequence of K jump lengths is now available, where K is the number of windows minus 1 (for the section of the time series presented in Fig. 2 $K = 5$, for the time series of our empirical resting state BOLD signals $K = 49$). To ensure the robustness over several window sizes, the jump lengths from different window sizes were used to build the distribution (pooling). The range of window sizes (5 – 30 TRs) was split in half so that both fast and slow window ranges had approximately the same number of observations (note that you get more observations from smaller window sizes). This resulted in the pooling of fast window sizes (5 – 10 TRs) and slow window sizes (11 – 30 TRs).

As a summary statistic to compare these jump length distributions across sessions and subjects, we followed Battaglia et al. (2020) and Lombardo et al. (2020) and quantified the *median*⁴ *pooled jump length* $d = 0.815$ (red line in Fig. 2D). This quantity thus represents the *amount* of switching between network configurations which occurs *more often* per each subject. The median of the jump lengths can therefore be seen as a subject-specific measure of flexibility. The relatively large value of d indicates that the brain networks are generally not frozen but maintain a large degree of temporal variability. Technical details can be found in Supplement B. Note that the results were robust also for the majority of single window sizes, i.e., when the jump lengths from only one window size was used to build the distribution and to derive the median jump length (see Supplement E and F). For easier reading, we refer to the *median pooled jump length* simply as *jump length* from now on.

Based on the concept of similar network states lying close to each other in the state space and the potential landscape, we hypothesized that (1) patients would have smaller jump lengths than controls, (2) the jump lengths would be negatively correlated with symptom severity scores of OCD, depression, anxiety, and stress, and (3) the jump lengths would increase during psychotherapy.

2.4. Outlier detection

Outliers of the jump lengths were determined with the Matlab function *isoutlier* (MathWorks, 2020). Since the sample was normally distributed, the generalized extreme Studentized deviate (ESD) test was used as method (Barnett and Lewis, 1994). This test is considered advantageous in comparison to other tests, first because it allows to estimate the robustness by manually varying the threshold, and second overcomes the limitations of the Grubbs or the Tietjen-Moore test, which require pre-defining the number of outliers to be detected. The outlier detection was performed for thresholds between 0 and 1 in steps of 0.05. At a threshold of 0, only the most extreme outlier(s), if any, will be detected, while multiple outliers will be detected at a threshold of 1. For our sample, the result was robust over a range of the more conservative threshold values (0.2 to 0.35). We finally used the value 0.25, which resulted in the omission of one value of the first scan of a patient, and one value of the fourth scan of a control subject.

2.5. Statistical analyses

The Anderson-Darling test (function *adtest* in Matlab) confirmed that the jump length d was normally distributed amongst patients and controls, respectively, also for single sessions. (This should not be confused

⁴ Given the non-normal distribution of jump lengths, the median was chosen instead of the mean (Fig. 2D).

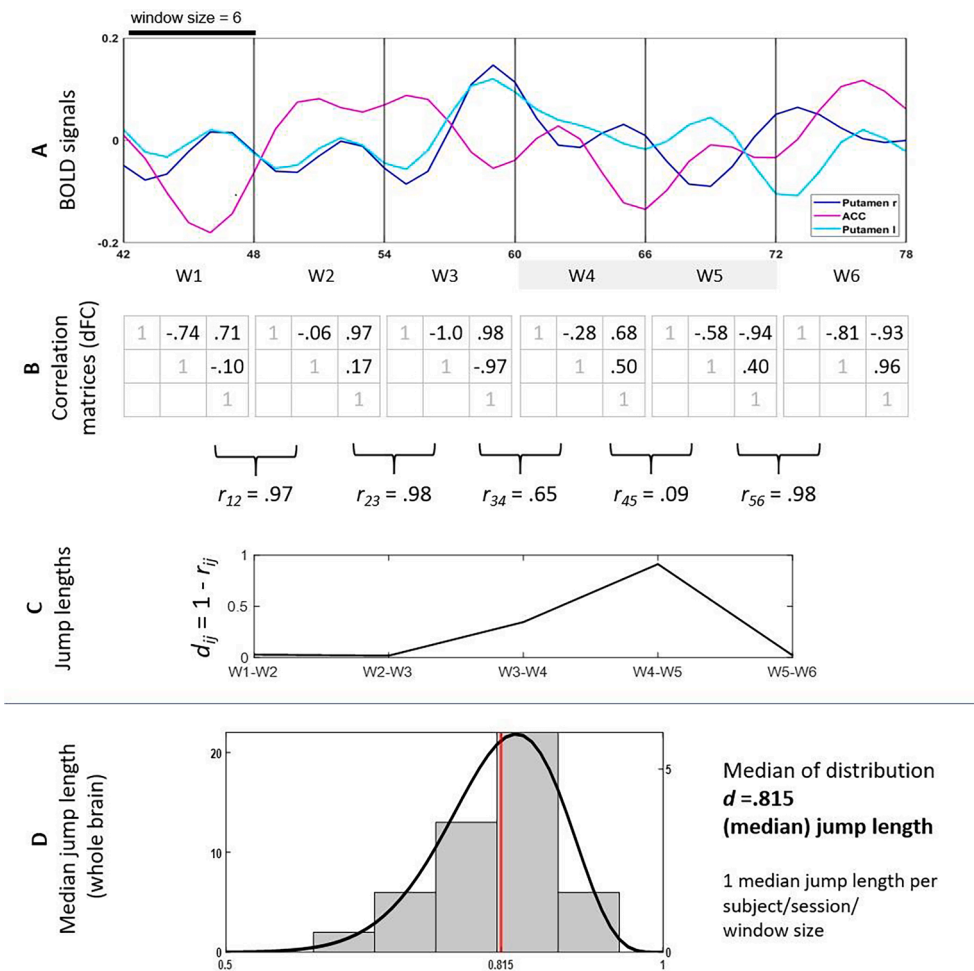


Fig. 2. Illustration of the time-variability of the functional connectivity (A), the assessment of the dynamic functional connectivity (dFC, B), and the calculation of the jump length d (C and D), which is used to measure flexibility. In (B), the correlation between the right putamen and the ACC can be found in the middle column of the first row of the matrices; the correlation between the left and the right putamen in the last column of the first row, and the correlation between the left putamen and the ACC in the last column of the second row. ACC: anterior cingulate cortex, Put: Putamen, W: window.

with the distributions of the jump lengths d_{ij} (Fig. 1D) within each subject that are *not* normally distributed.)

Correlations. Pearson correlation coefficients and their one-sided p -values were calculated between the six symptom severity scores and the jump lengths of all scans of the patients. Correlations were corrected for multiple comparisons (i.e., for the six psychological scores) by the false-discovery rate (FDR) algorithm (Benjamini and Hochberg, 1995) with a Matlab implementation of the R-function $p.adjust^5$. Note that three patients did not fill in the questionnaires corresponding to their last scans, resulting in $N = 73$ measurement points for the weekly assessed measures, and $N = 31$ for BDI-II and SCL-90, which were assessed at admission and discharge from the hospital. One-sided 95% confidence intervals were calculated with a bootstrapping approach (Matlab function *bootci*) with 1000 iterations. We also controlled for age and gender by adding the variable plus the interaction term to linear regression models, $d = \beta_0 + \beta_1 symptoms + \beta_2 age + \beta_3 gender + \beta_4 symptoms * age + \beta_5 symptoms * gender + \beta_6 age * gender + \epsilon$

Longitudinal assessment. A repeated measures ANOVA was set up in Matlab to investigate if patients showed a different trajectory than controls with “group” as the between-subject factor and “time” as the within-subject factor. The factor “group” consisted of two levels (“patients”, “controls”), the factor “time” of five levels (the five time points of the fMRI scans). The Mauchly test confirmed the sphericity of the data for all window sizes. To account for the fact that the F-test of the ANOVA is two-tailed, but our hypothesis is directed (one-tailed), the p -value was

corrected by applying the multiplication rule of probabilities. The probability of the ANOVA was thus divided by the chance to correctly guess the direction of the effect, which is $p = 1/2$. In other words, when two groups are compared in an ANOVA, the p -values can be divided by 2 to account for the directional hypothesis (Ley, 1979; Wuensch, 2006). In addition, the pre/post differences in jump lengths of the patients were calculated using a one-sided paired t -test with the first scan of each patient as the “pre” scan, and the last scan (3, 4, or 5, respectively) as the “post” scan. Effect sizes and their confidence intervals were calculated with the Matlab Toolbox by Hentschke & Stüttgen (2018).

Group differences. To assess the differences of jump lengths between groups, a two-sample t -test (one-sided) was calculated. For this, only the first scan of each subject was used ($N = 17$ for each group), since we expected a possible group difference to disappear during treatment, when patients were approaching a healthy range of functioning.

3. Results

A total of 132 fMRI scans were acquired by scanning 17 patients with obsessive-compulsive disorder and comorbid depression 3–5 times each in intervals of approximately 4 weeks during inpatient psychotherapy. 17 healthy controls were scanned at comparable time intervals. Six psychological symptom scales were applied: at their first and last fMRI scans, patients filled in the Beck Depression Inventory II (BDI-II) (Beck et al., 1996; Hautzinger et al., 2009), and the Symptom Checklist (SCL-90-R) (Derogatis et al., 1977; Glöckner-Rist and Stieglitz, 2012). In addition, the Depression-Anxiety-Stress Scale (DASS) (Lovibond and Lovibond, 1995; Nilges and Essau, 2015), and the Yale-Brown

⁵ <http://www.inside-r.org/r-doc/stats/p.adjust>

Obsessive-Compulsive Scale (Y-BOCS) (Goodman, 1989; Hand and Büttner-Westphal, 1991) were applied every week by an online-based real-time monitoring system (Synergetic Navigation System, SNS) (Schiepek et al., 2018).

3.1. High symptom scores are associated with small jump lengths (inflexibility)

Four of the 6 symptom severity scores were significantly correlated with the jump lengths d (Fig. 3). The correlation coefficients were highest for the BDI depression score and the SCL-90-R obsessive-compulsive score, i.e., those measures which were applied only pre and post treatment (Table 1). The correlation with stress was significant for the whole process with $N = 73$ measurements (three to five measurements for each of the 17 patients). The same trends were found for the anxiety and the depression score of the Depression-Anxiety-Stress Scale (DASS) and the Y-BOCS.

The effect of age and gender were assessed by adding these variables to a linear regression model (Supplement E). Neither the effect of age nor the effect of gender or any interactions were significant.

3.2. Jump length (flexibility) increases during psychotherapy

As hypothesized, the patients' jump lengths developed differently from controls during psychotherapy as shown by the $group \times time$ interaction term of the repeated measures ANOVA ($F(4,28) = 2.77, p = .025$). The effect size (partial eta squared) was in the medium range, $\eta_p^2 = 0.12$ with 95% confidence intervals = [0.06, 0.24]. The one-sided paired t -test, which was used as a post-hoc analysis, showed a significant increase of the jump lengths of the patients during psychotherapy ($p = 0.005, T = 3.00$, lower limit of the 95% confidence interval: 0.005). The effect size (Hedge's g) was large, $g = 1.00$ with 95% confidence intervals = [0.28, 1.79]. Fig. 4A depicts the increase of the jump lengths from a

Table 1

Correlation coefficients r , number of measurements N , lower (LL) and upper (UL) 95% confidence interval for r , and FDR-corrected p -values for the correlations between the symptom scores and the neural flexibility as assessed by the jump lengths of the brain network reconfiguration. Small window sizes refer to TRs 5 – 10 (~10 – 20 s), large window sizes refer to TRs 11 – 30 (~22 – 60 s).

	N	r	$r(LL)$	$r(UL)$	p	p_{corr}
Anxiety (DASS)	73					
small window sizes		-0.16	-0.39	0.11	0.085	0.128
large window sizes		0.11	-0.15	0.37	0.830	0.867
Stress (DASS)	73					
small window sizes		-0.26	-0.48	0.00	0.014*	0.030*
large window sizes		-0.02	-0.27	0.23	0.443	0.812
Depression (BDI-II)	31					
small window sizes		-0.46	-0.70	-0.02	0.005*	0.029*
large window sizes		0.02	-0.33	0.40	0.541	0.812
Depression (DASS)	73					
small window sizes		-0.12	-0.36	0.12	0.148	0.178
large window sizes		-0.02	-0.26	0.28	0.449	0.812
OCD (SCL-90-R)	31					
small window sizes		-0.40	-0.69	0.02	0.015*	0.030*
large window sizes		-0.03	-0.33	0.30	0.442	0.812
OCD (Y-BOCS)	73					
small window sizes		-0.07	-0.27	0.14	0.281	0.281
large window sizes		0.13	-0.11	0.35	0.867	0.867

* $p < .05$.

BDI-II: Beck Depression Inventory; DASS: Depression-Anxiety-Stress Scale; FDR: False Discovery Rate; OCD: obsessive-compulsive disorder; SCL: Symptom Checklist, Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

mean of $d = 0.804$ ($SD = 0.026$) to $d = 0.824$ ($SD = 0.009$). For the slow window sizes (TRs of 11 – 30), the results were not significant.

In line with our expectations, patients had a lower mean jump length at the beginning of psychotherapy, but the difference was not significant, possibly due to the relatively small sample size when using the first fMRI scan only.

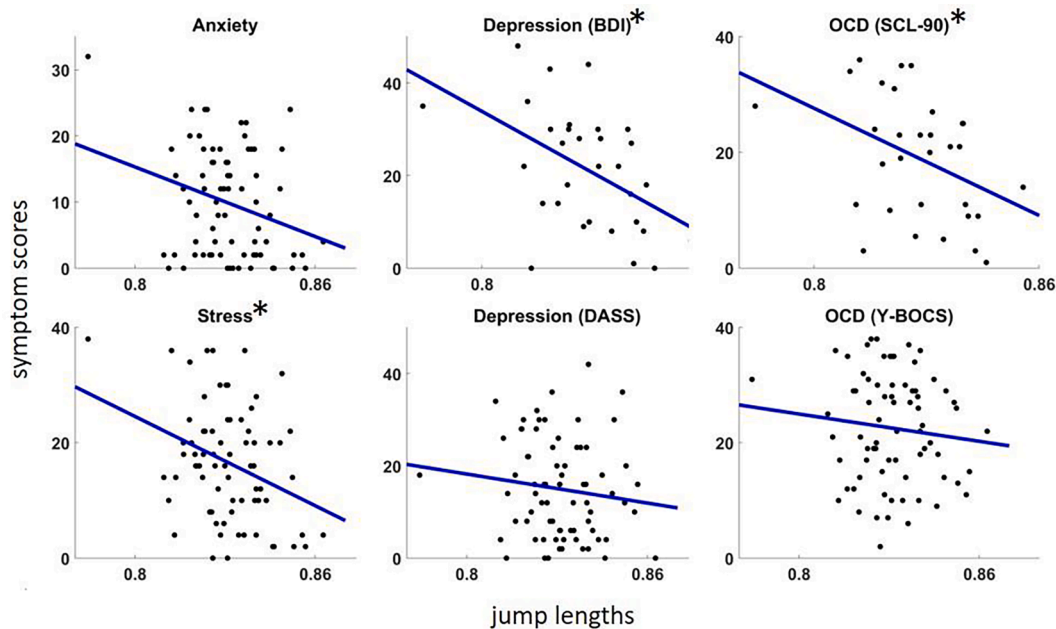
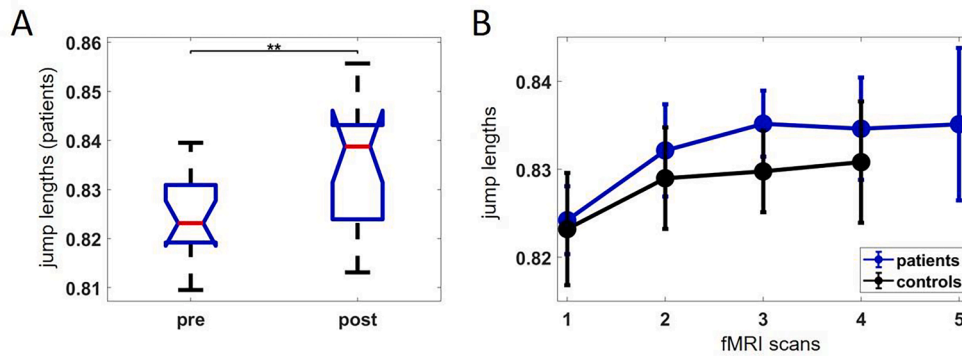


Fig. 3. Scatter plots of symptom scores and jump lengths for all patients and scans. The jump length, i.e., the difference between consecutive configurations of whole-brain functional connectivity ($1 - r$), decreases with higher symptom scores. In other words, psychological symptoms are associated with a reduced flexibility of brain network reconfigurations. The correlations were significant (*) for stress (measured by the Depression-Anxiety-Stress Scale, DASS), depression (measured by the Beck Depression Inventory, BDI-II) and obsessive-compulsive symptoms (measured by the Symptom Checklist, SCL-90-R). The correlations were not significant for anxiety, depression assessed by the Depression-Anxiety-Stress Scale (DASS), and for OCD symptoms assessed by the Y-BOCS (see discussion). Note the different sample sizes of measurements: while OCD (SCL-90-R) and depression (BDI-II) were assessed only at the beginning and at the end of treatment, the other scores were assessed at every fMRI scan during psychotherapy.



means and 95% confidence intervals of the controls. Note that there were only 7 patients with a 5th scan, indicated by the larger confidence interval. In the control group, only 2 participants had a 5th scan, which was omitted in the visualization but not in the calculations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Synergetics (Haken, 1982, 2006; Haken and Schiepek, 2010), one of the most prominent theories of self-organization, shows that many systems with complex interactions of a multitude of elements on the microscopic level can be described by a few macroscopic variables (order parameters). Extending this framework to Structured Flows on Manifolds (SFMs) allows formalizing the relation between behavior and neural activity (Jirsa, 2020; Pillai and Jirsa, 2017) and even hypothesizing on perspectives of brain resilience (Jirsa, 2020). We operationalized neural flexibility using the concepts of state space and multi-attractor dynamics. Representative states that are typically accessed by a subject (exploration of state space during fMRI resting state scans) were investigated. The dFC captures the organization of consecutive network configurations of brain regions (FC matrices) and was quantified by the jump lengths. The jump length assesses the amount of reconfiguration of brain networks and our findings suggest that it can be used as a measure of neural flexibility. This is in agreement with a wide literature using alternative characterizations of dFC that have revealed that enhanced flexibility in networks correlates with enhanced capacity to learn (Bassett et al., 2011), attentional levels (Kucy et al., 2017), executive control (Braun et al., 2015) and flexibility in several other cognitive and behavioral domains (Cohen, 2018; Jia et al., 2014), up to disposition to mindfulness (Lim et al., 2018).

When correlating the jump lengths with symptom severity scores, we found significant negative correlations for anxiety, stress, depression, and obsessive-compulsive symptoms. This confirmed our hypothesis that changes in dFC of brain signals reflect varying degrees of psychopathology, in particular low jump lengths (rigidity) being associated with high symptom severity. Also in line with our expectations, the jump lengths increased significantly over time (i.e., during psychotherapy) compared to controls. Therefore, we show here for the first time to our knowledge, that psychotherapy is able to increase neural flexibility.

4.1. Neural flexibility is impaired by general psychiatric symptoms

Depressive and obsessive-compulsive symptoms were both assessed by two different questionnaires: the BDI-II and the depression subscale of the DASS for depression, and the Y-BOCS and the OCD-subscale of the SCL-90-R for obsessive-compulsive symptoms. For both depression and OCD, significant negative correlations with neural flexibility were found with one of the measures only. When looking closer at the differences between the measures, it becomes clear that the significant correlations were found for those measures that assessed more general psychiatric impairments. In detail, the correlation with depression was significant for the Beck Depression Inventory (BDI-II), but not for the depression

Fig. 4. A) Increased jump lengths (flexibility) of the patients during treatment. The paired *t*-test between the jump lengths of the first scan and those of the last scan of each patient was significant at $p = .001$. The red line represents the median, the blue box the 2nd and 3rd quartile, and the whiskers the 1st and 4th quartiles. B) Comparison of the jump lengths between controls and patients over treatment time (fMRI scans 1–5). The trajectories of change assessed by a repeated measures ANOVA was significantly different between patients and controls ($p < .05$). The blue dots represent the mean jump length of the patients; the error bars represent the 95% confidence intervals per session (1-sided). The black dots and error bars represent

subscale of the Depression-Anxiety-Stress Scale (DASS-D). Nilges and Essau (2015) found a correlation coefficient of $r = 0.68$ between the two measures, which was similar in our sample ($r = 0.75$, Supplement E). Although the correlation between the measures is strong, the two scales do not measure the same aspects of depression. The BDI-II includes questions on weight loss, insomnia, somatic preoccupation, and irritability, which are not really discriminative for depression and appear in other psychiatric disorders, too. The BDI-II thus identifies symptoms as specific for depression that are attributed to the anxiety and stress subscales of the DASS. Assessing more general psychiatric symptoms and impairments, it is reasonable that the correlation of flexibility with the BDI-II is significant but not with the DASS-D.

The same is true for the results on the obsessive-compulsive symptom scores, which were assessed by the Yale Brown Obsessive Compulsive Scale (Y-BOCS) and the OCD subscale of the Symptom Checklist (SCL-90-R). Again, the significant negative correlation with flexibility was found for the questionnaire assessing more general symptoms (SCL-90-R). The OCD subscale of the SCL-90-R includes items like “your mind going blank”, “trouble remembering things”, and “trouble concentrating”, which cannot be seen as specific for obsessions and compulsions. In contrast, the Y-BOCS is asking for specific OCD-relevant thoughts and behaviors. The general correlation between Y-BOCS and OCD_SCL is moderate ($r = 0.41$) (Kim, Dysken, & Kuskowski, 1992), although it was strong in our sample ($r = 0.71$, Supplement E).

In the light of the significant correlation with stress, one might conclude that reduced flexibility is associated with general psychiatric impairment rather than specific symptoms of OCD or depression. This is not surprising since we assessed the neural flexibility of the whole brain. Investigations of sub-networks might yield more disease-specific results, along the lines of modular dFC speed analyses by Lombardo et al. (Lombardo et al., 2020). Nevertheless, our findings show how stress and strain alters the functioning of the brain. Given that flexibility is one of the key features of psychological functioning, it is reasonable to assume that it is affected by a variety of psychiatric disorders (Kashdan and Rottenberg, 2010).

4.2. Neural flexibility as a high-level measure of dynamic functional connectivity

Our results of reduced flexibility in patients with high symptom scores goes in line with the findings of Battaglia et al. (2020) and Lombardo et al. (2020). Both studies assessed the association between the jump lengths (called “speed” there) and cognitive abilities. Battaglia et al. (2020) report a significant decrease of jump lengths with age and an increase by trend with cognitive performance, i.e., young people with the highest scores of cognitive performance revealed the highest neural

flexibility. The relations found in this study were robust for a wide range of window sizes (6 to 210 s, corresponding to window sizes of 3–105 in our study) and for both resting state and task-related scans. Similarly, Lombardo et al. (2020) investigated subnetworks of brain regions functionally related to cognitive performance and found the same result. Furthermore, they report that flexibility was significantly reduced by 24 h of sleep deprivation. All measures that were assessed can be easily related to flexibility; indeed, flexibility might be the common denominator of aging, cognitive performance, and sleep deprivation. In this context, we would like to note that we were able to replicate the finding of reduced flexibility with age when using a wider range of window sizes comparable to those used by the authors (Supplement G). Although age was not a relevant factor in the window sizes used by us, the above-mentioned findings readily explain that no group difference in jump lengths was found in our sample. The comparable variability in the jump lengths of controls and patients may be explained by different cognitive abilities, sleepiness, and possibly a number of other factors of the healthy subjects. The psychiatric illness, however, seems to “override” those other influencing factors. More than age and other situational factors, cognitive-emotional impairments which are characteristic for psychiatric disorders are associated with reduced neural flexibility. In summary, our study adds to the growing evidence of the jump length being a reliable and meaningful high-level measure of dynamic functional connectivity.

4.3. Implications for treatment

Although evidence exists that psychotherapy is able to change brain function (Schiepek et al., 2013, 2011; Viol et al., 2020), neuroscience research has only marginally been able to give specific recommendations about how to improve the treatment of psychiatric disorders (van den Heuvel, 2015), because neither psychotherapy nor medication can directly alter the activity of specific brain regions, or specific connections between regions. In contrast, our findings provide the recommendation for psychotherapy to increase flexibility. The feasibility of influencing neural flexibility has been demonstrated by Bassett et al. (2011), as previously mentioned. The authors used a similar approach to ours by defining neural flexibility as the rate at which one brain region changes its involvement in network configurations and found that learning in general can increase neural flexibility. Successful psychotherapy implicitly addresses building blocks of cognitive flexibility like executive functioning, openness to experiences/salience detection and attention, self-control/inhibition, working memory, and switching (Dajani and Uddin, 2015; Kashdan and Rottenberg, 2010). For example, promoting an accepting, non-judging attitude with elements of Dialectic-Behavioral Therapy, Acceptance and Commitment Therapy, Mindfulness-based Therapy, or personalized psychotherapies based on specific case formulations (Schiepek, Stöger-Schmidinger, Aichhorn, Schöller, & Aas, 2016), can increase the openness to new experiences (Masuda et al., 2009). Similarly, successful interventions to increase emotional flexibility are available (e.g., Kotsou et al., 2011). Techniques that address behavioral flexibility are common components of behavioral therapy approaches (e.g., exposure with response prevention trainings). In addition, psychodrama and imaginary approaches have the potential to access new cognitive-affective states and can easily be integrated into existing therapeutic approaches (Singer, 2006). Consequently, treatment should aim at enhancing flexibility more explicitly as it is done so far, for example by destabilizing current dysfunctional patterns to allow order transitions as described and supported by the generic principles of human change (Haken and Schiepek, 2010). Our biomarkers, being purely imaging based, provide then a ground to assess how changes of “mind” flexibility are paralleled by changes of “brain” flexibility (at the level of its complex network dynamics).

An open question is if flexibility is desirable per se, even high levels of it, or if “too much” flexibility can be problematic. While it surely is a desirable therapeutic goal in the disorders we addressed here (OCD and

depression), other disorders like ADHD, bipolar disorder with rapid cycling, or emotionally unstable personality disorder are related to the instability of cognitive-emotional-behavioral states and undirected fleeting associations. The same can be assumed for the fluctuating and uncontrolled associations observed in schizophrenia. For these disorders, psychiatric impairment might be represented by being stuck in repetitive cycles of pathological affective and mental patterns. Most likely, optimal flexibility is reached when the building blocks constituting psychological flexibility are balanced, e.g., when the subject-specific level of openness is combined with an appropriate level of self-control. In this context, self-control requires a *meta*-consciousness about the undesirability of a current CEB pattern and the wish to switch to another state. Self-control would be represented as internal forces (top-down control) that allow neural state transitions – or, in the case of disorders with high volatility, its abidance.

4.4. Limitations and future research

The design of our study allows to describe the empirical manifestation of neural (in-)flexibility in relation to symptom scores, but does not allow any conclusions about the underlying mechanisms (Zarghami and Friston, 2020). Nevertheless, the findings fit well to theories of the brain working at (or close to) a critical point where small perturbations or even noise can trigger a transition into other states. Within this framework, one would conclude that psychiatric disorders correspond to a working point, where transitions are less likely (Deco et al., 2013). Psychotherapy aims to move mental and affective dynamics closer to an instability point. Indeed, transitions of cognitive-affective patterns and related increases of critical fluctuations of cognitive-affective dynamics are related to psychotherapy outcome (Haken & Schiepek, 2010; Olthof et al., 2020; Olthof et al., 2019; Schiepek, Tominschek, & Heinzl, 2014).

Since no data on the cognitive abilities of our patients are available, we could not test the influence of this factor on our sample, which might – along with the symptom scores – further explain the individual jump lengths. This can be tested easily in future studies. Furthermore, studies that use a sample under either psychotherapeutic or medication treatment could separate the influence of the two therapeutic approaches on neural flexibility. It would be interesting to investigate which aspect of the disorder (e.g., chronicity, specific symptoms, general stress) most influences the flexibility of the brain, and if the correlations hold also for other psychiatric disorders. As an important side note, we would like to stress that flexibility refers to neural switching of the brain only, and cannot per se be translated to emotional, cognitive and/or behavioral flexibility. The link is so far only indirect via the known fact that psychopathology of OCD corresponds to inflexible CEB-patterns (see introduction). Future studies should test the hypothesis that the jump lengths is indeed correlated to measures of CEB-flexibility. This would, however, require to measure the flexibility of cognition and emotion during the resting state scan, which is a challenge to be addressed by future studies. In this context, it would also be interesting to investigate other methods that capture dynamic aspects of functional connectivity, e.g. Multiplication of Temporal Derivatives (Shine et al., 2015), Weighted Average of Shared Trajectory (Faghiri et al., 2020), and Instantaneous Phase Synchronization (Glerean et al., 2012).

On the methodological side, fMRI scans with higher temporal resolution (TR below 1 s) would allow more sampling points per window (given the idea that capturing one peak of the BOLD signal is the most appropriate window size) and thus improve the power and robustness of the correlations between the BOLD time series per window. However, it should be mentioned again that our results, even though they were done with 6 sampling points per window only, were robust over several window sizes.

The framework of dynamic functional connectivity allows to investigate a rich variety of research questions that are related to flexibility. For example, it has been hypothesized that (some) psychiatric disorders

like depression are characterized by dysfunctional synchronization (Haken and Schiepek, 2010; Helm et al., 2018), similar to those observed in neurological diseases (Parkinson, tinnitus, epilepsy) (Popovych et al., 2008; Tass et al., 2012). Pathological oversynchronization could, for example, be assessed by the correlation between connections (*meta-connectivity*) (Battaglia et al., 2020). Finally, these research questions might in the long run provide guidance (e.g., stimulated desynchronization like the Coordinated Reset method in the case of tinnitus, Tass et al., 2012) on how neuromodulation could be developed as a complementary treatment for psychiatric disorders.

5. Author notes

No acknowledgements to be made.

VJ has received funding from the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3). All other authors received no specific funding for this project.

All authors declare no conflict of interest.

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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.2021.102844>.

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