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Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia

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ABSTRACT

Background: Apathy can be defined as a reduction of goal-directed behavior and is a strong predictor for poor functional outcome in schizophrenia. However, no objective measure of apathy has been identified and assessment is limited to retrospective interview-based ratings. Here we aimed to identify more precise objective readouts of apathy for translational research and clinical practice.
Methods: We employed a combined approach including interview-based ratings of the two negative symptom factors apathy and diminished expression, actigraphy based measures of spontaneous motor activity and the evaluation of daily activities using ecological momentary assessment. Furthermore, a functional magnetic resonance imaging task for reward anticipation was applied to investigate shared and divergent neural correlates of interview-based and behaviorally measured apathy.
Results: We found in 18 schizophrenia patients with high interview-based apathy levels that motor activity was negatively correlated with apathy but not with diminished expression. In contrast, measures of daily activities were not associated with apathy. Neural activation during reward anticipation revealed an association between hypoactivation of the ventral striatum and interview-based apathy as well as hypoactivation of the inferior frontal gyrus and motor activity level.
Conclusions: Spontaneous motor activity is an objective readout of apathy, which was specific and not present for diminished expression. On a neural level, interview-based and objective measures of apathy showed divergent neural correlates in the cortical-striatal network, which suggests dissociable neural processes. Finally, motor activity provides a promising readout for quantifying apathy in both translational research and clinical practice.

1. Introduction

Negative symptoms of psychotic disorders refer to the absence or diminution of normal functions and consist of the dimensions diminished expression and apathy (Bischof et al., 2016; Blanchard and Cohen, 2006). The negative symptom dimension apathy has been defined as a quantitative reduction in goal-directed behavior (Levy and Dubois, 2006). Importantly, apathy is a strong predictor of clinically relevant outcomes such as independent living, work outcomes and quality of life (Foussias et al., 2011; Mucci et al., 2016; Ventura et al., 2015).

Current assessment methods for apathy rely mostly on retrospective interview-based self-reports, which might not reflect the actual activities and motivational states during the time period being assessed (Green et al., 2015). It is a matter of debate whether these interview-based measures need to be supplemented by objective measures to provide suitable clinical trial endpoints. In addition, translation between human and animal research would benefit from more objective measures (Cathomas et al., 2015). Ideally, an objective measure would provide a complete assessment of behavior across the time period of interest. However, only few studies have combined clinical ratings with observed behavior (Trémeau et al., 2012).

In this study we aim to explore possible behavioral measures of apathy that provide an online sampling of behavior. In humans, actigraphy allows for objective recording of spontaneous motor activity through a portable device (Teicher, 1995). Initial results suggested that negative symptoms are associated with reduced motor activity (Walther et al., 2009). However, actigraphy fails to distinguish between goal-directed and random motor behavior. Therefore, we complemented actigraphy with online descriptions of patient activities in regular intervals through modern portable diary systems, i.e. ecological momentary assessment

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(EMA) (Kimhy et al., 2006). Previous EMA studies have mostly focused on subjective experience and have provided valuable evidence regarding patterns of both positive and negative symptoms, but have not specifically addressed the association between interview-based apathy and daily activities quantified by EMA (Gard et al., 2014; Hennig and Lincoln, 2017; Moran et al., 2017; Oorschot et al., 2013, 2012). In contrast, we employ the method to sample self-reported activities during the period of observation, which can later be separated into goal-directed and non-goal-directed activities. Therefore, both actigraphy and EMA allow continuous sampling of behavior during the observation period that can then be related to interview-based retrospective assessment of apathy.

More direct behavioral assessments of apathy would promote monitoring in clinical trials and enable studying the neurobiology of apathy. Previous literature strongly suggests abnormalities within the fronto-striatal circuitry as neural substrate for apathy in schizophrenia (Kos et al., 2016; Kring and Barch, 2014). In patients with schizophrenia, one of the most consistent finding is the association of ventral striatal hypoactivation during reward anticipation and negative symptoms (Radua et al., 2015), which seems to be specific to apathy/amotivation (Kirschner et al., 2015; Simon et al., 2015, 2010; Wolf et al., 2014). Furthermore, alterations in the prefrontal cortex may underly disrupted cognitive processes including action planning and action initiation (Levy and Dubois, 2006). Thus, it would be of high interest to assess whether similar neural correlates are associated with interview-based and behavioral measures of apathy.

Our main hypotheses were that activity level and the amount of self-reported daily activities, reported through EMA, are associated with interview-based apathy. Furthermore, we expected shared neural correlates of interview-based apathy and activity level/self-report, reflected by hypoactivation in the ventral striatum (VS) and the prefrontal cortex (PFC) during a reward anticipation task.

2. Methods and materials

2.1. Participants

The sample consisted of 18 patients with schizophrenia ($n = 14$) or schizoaffective disorder ($n = 4$). Participants were recruited from the outpatient departments of the Psychiatric University Hospital of Zurich and an organisation providing subsidized work programs. Diagnosis was confirmed in a structured Mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998). We excluded participants with any other DSM-IV axis I disorder, former or current drug abuse, medication with lorazepam higher than 1 mg, florid psychotic symptoms, i.e. any positive subscale item score higher than four as measured with the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987). Further exclusion criteria were pronounced akathisia levels (>3 on the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and a history of head trauma or other neurological illness. All participants provided written informed consent to participate in the study, which was approved by the local Ethics committee.

2.2. Study design

The study consisted of two sessions and daily activity recording on four days in between. In the first session participants received a diagnostic interview, a psychopathological assessment and a detailed oral and written instruction about the usage of the electronic diary. Subsequently, daily activity data were sampled on four subsequent days. In session two, functional magnetic resonance imaging of the reward system was performed. Participants were compensated with 20 Swiss francs (CHF) for the diagnostic interview and the psychopathological assessment. Additional financial compensation was provided dependent on participant's response rate during the collection of the daily life data and the task-performance during the fMRI.

2.3. Actigraphy

The tri-axial-accelometer, integrated in to Pro-Diary® ("PRO-Diary Overview - CamNtech", 2016), was used to measure motor activity and diary records simultaneously. Participants were instructed to wear Pro-Diary on the nondominant hand (Middelkoop et al., 1997). The Pro-Diary device uses the same sensor to measure motor activity as the previous Actiwatch device (Cambridge Neurotechnology, Inc., Cambridge, UK), which has been used in several studies investigating motor activity levels in patients with schizophrenia (e.g. (Bracht et al., 2013; Docx et al., 2013; Walther et al., 2017, 2014; Wichniak et al., 2011). The movement counts were stored consecutively in 30s intervals during the complete period of four days. We excluded periods of nighttime sleep as indicated in a sleep protocol from the analysis. Participants had to remove Pro-Diary during bath or shower. They marked these periods in the Pro-Diary and they were removed from the raw data. Actigraphy data was processed using Pro-Diary Software and Excel®. Activity level (AL) expressed as counts per hour provided a measure of global amount of spontaneous motor activity and was used as the primary readout of the actigraphic data. The overall acceptance of the Pro-Diary was very high. In particular, our actigraphy data revealed that 15 patients wore the Pro-Diary on all four days, two patients forgot it on one day and one patient forgot to wear it on two days.

2.4. Daily activity measures

Daily life data was collected using a preprogramed wrist-worn electronic diary (Pro-Diary®). Diary recordings were conducted according to current literature for EMA in schizophrenia and severe mental disorders (Bos and Schoevers, 2015; Myin-Germeys et al., 2009). Ten times a day on four consecutive days (two weekdays and two weekend days) the watch emitted a signal at unpredictable moments. The time range of the signal was set according to the individual awake periods of the day. After each beep participants filled out a short questionnaire, which assessed (1) behavior 15 min before the signal, (2) the affective state associated with the behavior, (3) the social context and (4) whether participant initiated the activity by himself or not. Participants could choose from the predefined list of activities provided in the electronic questionnaire or type their own description of the activity (see Table S1). Participants were instructed to respond immediately after the signal and only recordings within 15 min were allowed. Participants received 2 CHF for each completed questionnaire. For further data analysis reported activities were classified into "goal-directed" and "non-goal-directed" defined a previous independent assessment and rating from six experts (see Supplementary methods). Goal-directed activities implicated pursuing explicit goals (working, doing sports, cooking, paying bills, personal hygiene, cleaning up etc.), whereas non goal-directed behaviors were associated with non-explicit goals (i.e. hanging around, watching TV, eating).

2.5. Interview-based psychopathological assessment

Psychopathological assessment included Brief Negative Symptom Scale (BNSS; (Strauss et al., 2012)), PANSS, Global Assessment of Functioning scale (GAF; (Frances et al., 1994)), Personal and Social Performance Scale (PSP; (Juckel et al., 2008)) and Calgary Depression Scale (CDS; (Addington et al., 1990)). The apathy factor was defined as the sum of the global ratings for avolition, anhedonia and asociality subscales on the BNSS. Furthermore, comprehensive rating scales of motor symptoms were applied, including the Modified Simpson-Angus Scale (MSAS), the Barnes Akathisia Rating Scale (BAS) (Barnes, 1989) and the Modified Rogers Scale (MRS) (Lund et al., 1991).

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