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Using wearable technology to detect the autonomic signature of illness severity in schizophrenia

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ABSTRACT

Introduction: Research suggests that people with schizophrenia have autonomic dysfunctions. These have been linked to functioning problems, symptoms and considered a risk factor for illness chronicity. The aim of this study is to introduce a new Mobile Health (mHealth) method using wearable technology to assessing autonomic activity in people's everyday life. We aim to evaluate the new method acceptability and characterise the association between schizophrenia illness features and autonomic abnormalities.

Method: Thirty participants with schizophrenia and 25 controls were asked to wear a mHealth device measuring autonomic activity and movements during their normal everyday life. Measures of device use acceptability were collected from all participants. Participants with schizophrenia were also assessed for symptoms and functioning levels. Measures of heart rate variability (HRV), electrodermal activity (EDA) and movement were collected by the device and groups were compared. Correlation between physiological measures, functioning, symptoms and medication levels were assessed in people with schizophrenia.

Results: The mHealth device method proved to be acceptable and produced reliable measures of autonomic activity and behaviour. Compared to controls, people with schizophrenia showed lower levels of HRV, movement and functioning. In people with schizophrenia illness severity, particularly positive symptoms, was associated with parasympathetic deregulation.

Conclusions: Autonomic abnormalities can be detected using wearable technology from people's everyday life. These are in line with previous research and support the notion that autonomic deregulation are relevant illness features for mental and physical health in schizophrenia. This method may be developed as a monitoring system for well-being and relapse prevention.

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1. Introduction

People with schizophrenia experience a significant reduction in their functioning levels from illness onset (Cella et al., 2016; Reichenberg et al., 2014). Functioning problems are largely responsible for the long term consequences of the illness, poor life quality and much of the illness associated burden for sufferers, carers, the health care system and the society (Harvey, 2009; Jaaskelainen et al., 2013; Stouten et al., 2014). Much of the work done in this area has used interview based tools to assess the illness impact on social and occupational levels (Cella et al., 2016; Heinrichs et al., 2006; Schneider and Struening, 1983).

Challenges in the definition of functioning and its broad conceptualisation have made it difficult to study the biological markers associated

with this illness feature. One exception is research in the field of autonomic nervous system activity. Since the 80s autonomic system dysfunction have been consistently linked to functioning difficulties in people with schizophrenia (Brekke et al., 1997; Ohman et al., 1989; Tarrier and Barrowclough, 1990). Despite not always converging in identifying a specific biological system, the majority of the evidence supports the notion that autonomic deregulation may be implicated in functioning problems (Fujibayashi et al., 2009). Several studies suggest that reduce vagal tone and heart rate variability (HRV) are found in people with schizophrenia, and to a lesser degree in unaffected relatives (e.g. Bar et al., 2005; Ieda et al., 2014; Moon et al., 2013) and this is associated with lower scores on the Global Assessment of Functioning (Khandoker et al., 2010), illness chronicity (Toichi et al., 1999) and both positive and negative symptoms severity (Boettger et al., 2006; Kim et al., 2004). A recent meta-analysis suggested that this feature should be considered an endophenotype of schizophrenia (Clamor et al., 2016). Less convergent are findings from studies investigating sympathetic regulation. Some studies found people with schizophrenia displaying elevated event related phasic and tonic electrodermal

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activity, EDA, compared to controls (Zahn et al., 1997) while other studies found no differences (Castro et al., 2008; Hempel et al., 2005). Recently Montaquila et al. (2015) proposed that sympathetic deregulation in people with schizophrenia may be dependent on diminished parasympathetic activity and the consequent difficulties of the parasympathetic system to down-regulate sympathetic activity. This account may explain the incongruent sympathetic activation findings and explain why event-related activation is largely found in the normal range while there may be a selective difficulty in down-modulating this response. To date only a limited number of studies measured sympathetic and parasympathetic activity simultaneously and therefore this hypothesis has only partial empirical support.

Most of the studies available in the literature assess the relationship between autonomic activity and schizophrenia illness features using laboratory based paradigms. This method however does not allow assessing directly the relevance of autonomic events to functioning problems. Recent technological developments produced devices capable of recording autonomic activity from wearable devices. These are worn on such as regular cloths or watches and allow regular information gathering over extended time periods. This new prospect has made physiological research outside the laboratory accessible and allowed, for the first time, to study how autonomic deregulations contribute to mental health symptoms (Okruzek et al., 2016). This methodology is also beginning to be used for monitoring and prevention in neurological and cardiometabolic conditions (Corino et al., 2017; Picard et al., 2017; Sarkis et al., 2015).

The use of wearables and mobile health (mHealth) devices in people with schizophrenia may also be useful to support intervention to improve cardiometabolic health (Mitchell and De Hert, 2015). Recent research suggested that wearable devices may be useful to support weight loss and improve lifestyle in people with severe mental health condition (Naslund et al., 2016; Naslund et al., 2017).

This study has three aims. The first is to evaluate the acceptability and feasibility of the new mHealth technology in people with schizophrenia. The second is to compare sympathetic and parasympathetic activity between people with schizophrenia and healthy controls during everyday life. The third is to assess the association of possible autonomic abnormalities with functional difficulties and symptoms of schizophrenia.

2. Methods

2.1. Design

Cross-sectional comparing a group of people with schizophrenia with a control group.

2.2. Participants

Participants with schizophrenia were recruited from the National Health System, Community Mental Health Teams in South London (UK). Inclusion criteria were: (i) DSM-IV diagnosis of schizophrenia, (ii) aged 18–65, (iii) good command of English language. Exclusion criteria: (i) recent medication change (i.e. in the last month), (ii) poor literacy or learning disability, (iii) a DSM-IV diagnosis of substance dependence. Participants in the control group were healthy individuals recruited with advertisement from the local community to match the clinical group for age and gender. Inclusion criteria were set to allow appropriate group matching: age between 18 and 65 years, no history of DSM-IV diagnosis of schizophrenia or other mental disorder, no evidence of head injury/organic brain disorder, no learning disability and no diagnosis of substance dependence.

2.3. Measures

For all participants we collected demographic information (e.g. age, gender). For participants in the clinical group we collected information on their mental health history and current medication. Antipsychotic dosage was converted to chlorpromazine equivalents using guidelines from Woods (Woods, 2003).

2.4. Acceptability

The assessment acceptability was evaluated using an acceptability feedback questionnaire. The assessment questions were designed to be rated using a 7-point Likert scale. Questions enquired whether: i) the device disrupted participants' life; ii) stopped participants from doing usual activities; iii) it was embarrassing to wear the device around other people; iv) it was easy to remember to wear the device; v) it was enjoyable wearing the device as part of this study. This measure was used in a previous study involving people with schizophrenia and a similar mHealth device (Edwards et al., 2016).

2.5. Functioning

Functioning was assessed with the time use survey (Short, 2006). This is a semi-structured interview asking participants to retrospectively report the time spent in a variety of activities in the last month (e.g. work, education, socializing, sleep). Time spent in each activity is converted in number of hours per week. Time spent in structured activity is considered and index of function levels. Structured time includes activities such as work, volunteering, studying, socializing, travelling, hobbies, house chores, caring for others and looking after children. This measure was used in previous research with people with schizophrenia (Cella et al., 2016).

2.6. Symptoms

Symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This is a 30-item assessing symptom severity in the past week. For this study we considered five factors: Positive Symptoms (Pos), Negative Symptoms (Neg), Disorganised (Dis), Excited (Exc) and Negative Emotion Depressed (Emd) (Cella et al., 2014a; Wallwork et al., 2012).

2.7. Autonomic system

The measurement of the autonomic activation was conducted using a wearable device worn on the participant's wrist (i.e. Empatica E4) (Garbarino et al., 2014). The device has 3 sensors recording: i) *Electrodermal Activity (EDA)* via skin conductivity (this assesses overall responsiveness to external events by assessing sympathetic nervous system arousal); ii) *Blood volume pulse* with a photoplethysmography sensor. From this measure it is possible to extract time between heart beat peaks (inter-beat intervals IBI). From IBI data it is possible to extract heart rate variability (HRV); inter-beat intervals (RR); standard deviation of RR intervals (SDNN) and square root of the mean squared differences of successive RR intervals (RMSSD); iii) *Acceleration (ACC)* via a 3-axis accelerometer. Data from this sensor can be used to calculate activity levels.

2.8. Procedure

For the clinical group eligible participants who were considered suitable by their care team were approached and offered to take part in the study. Upon entering the study demographic and clinical information were collected from clinical records and during the initial assessment appointment all the study assessment measures were administered. Participants in the control group were screened for current and past

mental health problems using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). All participants were briefed on the use of the mHealth device and asked to wear it as much as possible for the following 6 days for the moment they wake up in the morning until bed time in the evening. Participants were asked to remove the mHealth device in case this could become wet (e.g. showering, swimming). Participants were contacted by phone twice during the assessment period by a study researcher for troubleshooting. Information collected by the wearable device was stored on the device memory and downloaded on the study server during face-to-face meetings. After the sixth day participants returned the device and completed the acceptability measures.

2.9. Data pre-processing

Participants returned recording segments of different length. We initially decided to exclude short recordings (i.e. <60 min) as some HRV parameters (e.g. SDNN) may be less informative over a shorter recording period. Further we opted to consider only longer recordings as these were considered more likely to include a different range of activities. After preliminary inspection we noticed that all participants had several continuous recording exceeding 8 h. We therefore decided to use only samples that had at least this length. All participants had at least two 8-h samples. During the six days in which they were asked to wear the device participants with schizophrenia completed on average 3.7 (SD1.3) - samples while controls 3.8 (SD1.2).

The EDA sensor collected data at a frequency of 4 Hz while the ACC sensor sampled at 32 Hz. The IBI sensor returned the time between heartbeat peaks. EDA data was handled using Ledalab for MATLAB to remove artefacts (Benedek and Kaernbach, 2010). Mean EDA amplitude was calculated for each sample. Heart rate variability parameters were calculated using IBI values from the Empatica Algorithm 1 and 2 (see Garbarino et al., 2014). Data was further processed with Kubios HRV (Tarvainen et al., 2014) to extract standard deviation of all normal RR intervals (SDNN) and root mean square of the successive differences of RR intervals (RMSSD) (Sollers et al., 2007).

From the ACC sensor we extracted an index of overall movement by means of standard Euclidean metric. This was computed for each of the 3-axis sensor at each sampling point and summed for the total recording sample length, thus producing an indicator of overall extent of movement during the recording period.

2.10. Data analysis

Data analysis was divided into three stages. Firstly the relationship between physiological variables was examined with Spearman rho correlation coefficient to assess the reliability of the parameter extracted. Secondly, we examined between group differences with a set of *t*-tests and univariate ANOVAs. Before this analysis we assessed distribution normality using the Shapiro–Wilk test. We follow-up any significant findings with a post-hoc analysis controlling for age, time spent in structured activities (from the time-use survey) and activity levels (as recorded by the accelerometer sensor). Finally, we assessed the relationship between the clinical and functional measures and physiological variables using Spearman rank correlations. For this analysis we controlled for multiple correlation and adjusted the significance threshold to a more conservative $p = 0.008$ (Benjamini and Hochberg, 1995). For all other analysis the significant threshold was set at $p < 0.05$.

3. Results

Table 1 shows the demographic characteristics for the two groups and the clinical characteristics for people with schizophrenia. The only significant difference was in the amount of time spent in structured activities.

Table 1

Shows the mean (SD) of the demographic and clinical characteristics of people with schizophrenia (SCZ) and healthy controls (HC).

	SCZ M [SD]	HC M [SD]	X ² or t
Gender	18 M/10 F	13 M/12 F	X ² = 0.8 n.s.
Age (years)	37.5 [10.8]	35.9 [12.5]	t = 0.5 n.s.
Illness Length (Yrs)	11.8 [4.1]		
PANSS5 Pos	9.8 [3.8]	–	
PANSS5 Neg	12.7 [5.8]	–	
PANSS5 Dis	7.7 [1.8]	–	
PANSS5 Exc	6.0 [2.6]	–	
PANSS5 Dep	9.9 [3.5]	–	
CPZ (mg)	367 [337]	–	
Structured Activity (hrs)	36 [21]	108 [39]	t = 8.6***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.1. Acceptability

All participants were able to use the watch according to the instructions received and completed the device acceptability questionnaire. The result showed very similar acceptability scores between the two groups. When asked about the acceptability of the research procedures and the mHealth device use, people with schizophrenia endorsed at least a good or excellent rating 81% of the times across all the items while controls endorsed the same ratings 80% of the times.

3.2. Physiological data validity

We calculated correlations between the physiological variables to assess validity. As expected HRV parameters showed strong and significant inter-correlations: mean RR correlated with SDNN ($\rho = 0.55$; $p < 0.001$) and with RMSSD ($\rho = 0.47$; $p < 0.001$), SDNN was correlated with RMSSD ($\rho = 0.77$; $p < 0.001$). Total movement levels were positively correlated with EDA ($\rho = 0.47$; $p = 0.002$) and RR RMSSD ($\rho = 0.29$; $p = 0.037$).

3.3. Group differences

Kolmogorov–Smirnov test revealed that EDA and ACC values were non-normally distributed. For these variables we repeated the analyses using non-parametric tests. There were no group differences in EDA (Mann–Whitney U = 126.0, n.s., see Fig. 1). Significant differences were found for SDNN ($F(1,52) = 6.4$, $p = 0.015$; SCZ: 102 ± 34 vs. HC: 129 ± 44) and RMSSD ($F(1,52) = 7.7$, $p = 0.008$; SCZ: 70 ± 25 vs. HC: 90 ± 27) and a trend toward significance for mean RR, $F(1,52) = 4.5$, $p = 0.07$; SCZ: 771 ± 121 vs. HC: 839 ± 147 (see Fig. 1). In all these measures, participants with schizophrenia had lower values. Group comparison on ACC data showed that people with schizophrenia had overall lower movement levels than controls, $F(1,52) = 5.3$, $p = 0.02$. As ACC data were skewed we replicated this result using non-parametric statistics (Mann–Whitney U = 470.5, $p = 0.03$).

Participants in the controls group had more hours of structured activity compared with people with schizophrenia, $F(1,52) = 74.4$, $p < 0.001$; SCZ: 36 ± 21 vs. HC: 108 ± 39 . This result was confirmed with non-parametric testing (Mann–Whitney U = 684, $p < 0.001$). We repeated all the analysis on physiological measures controlling for age, time-use structured activity and movement. The only significant difference still observed was in RR RMSSD, $F(1,49) = 4.6$; $p = 0.04$.

3.4. Correlations with clinical/functional measures

In people with schizophrenia RR SDNN negatively correlated with Positive symptoms ($\rho = -0.50$, $p = 0.007$) while movement negatively correlated with Negative symptoms ($\rho = -0.51$, $p = 0.006$). Number of weekly hours of structures activity correlated with movement levels ($\rho = 0.43$, $p = 0.02$) and negatively with mean RR ($\rho =$

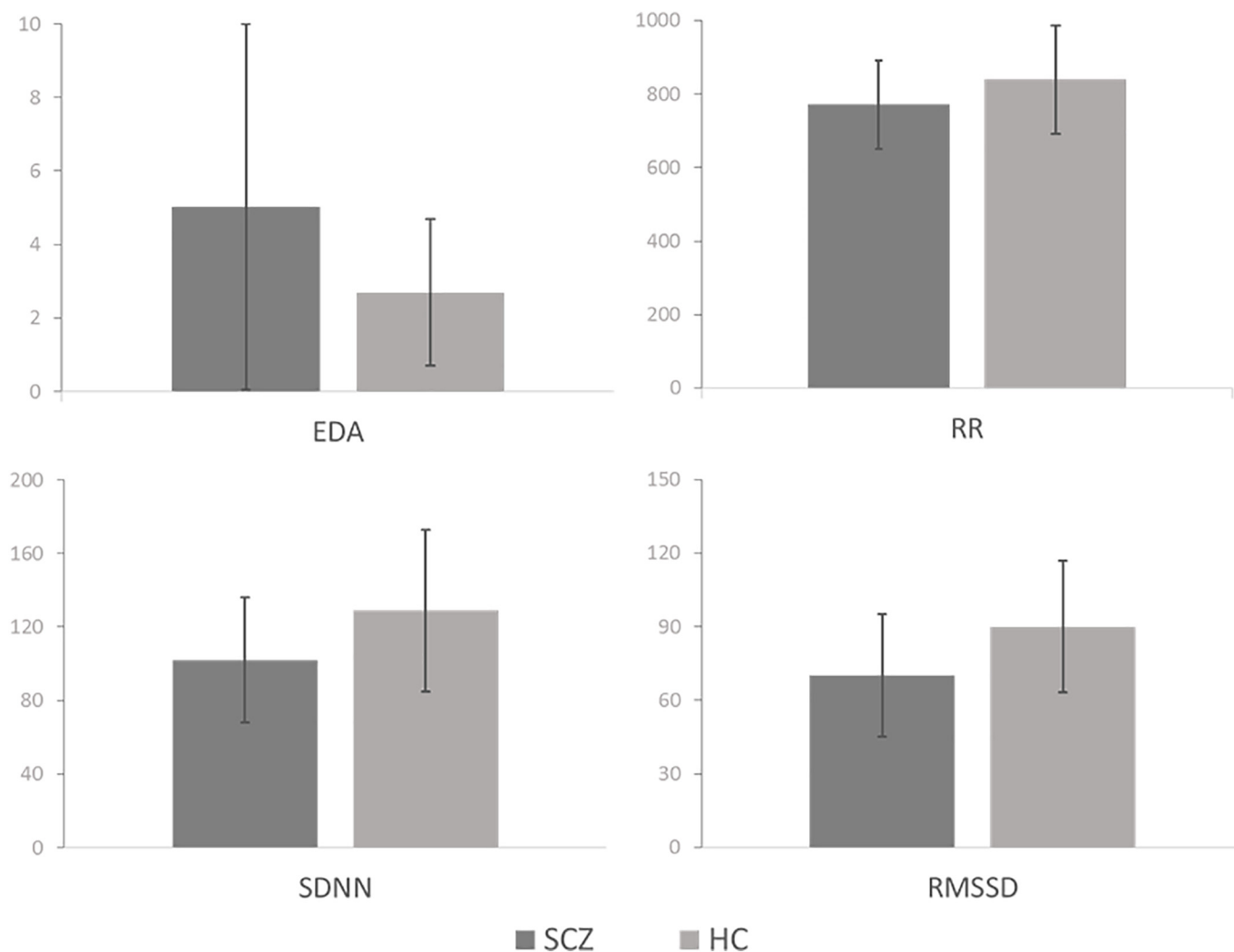


Fig. 1. Mean values of EDA (μS), RR (ms), SDNN (ms) and RMSSD (ms) for people with schizophrenia (SCZ) and healthy controls (HC). Error bars represent standard deviations.

–0.50, $p = 0.007$). We did not find association between medication and any of the autonomic parameters measured.

4. Discussion

In this study we evaluated the acceptability and feasibility of a new mHealth method assessing autonomic activity in everyday life in people with schizophrenia. We also compared measures of sympathetic and parasympathetic activity collected with this method from people's everyday life between people with schizophrenia and healthy controls. Finally we assessed the association between autonomic abnormalities, functional difficulties and symptoms of schizophrenia.

Our data on acceptability and feasibility suggest that this is a viable methodology for clinical studies. Evaluating these parameters is a necessary and important first step when testing new methodologies. mHealth devices present clinicians and researchers with an unprecedented opportunity to assess physiological parameters in real time and without interfering with people's lives. This may be particularly important for studies aiming to understand barriers to recovery in people with psychosis as autonomic deregulation has been found to be associated with different illness chronicity features (e.g. Bar et al., 2008; Chung et al., 2013; Kim et al., 2004; Valkonen-Korhonen et al., 2003).

In line with previous research our findings shows that people with schizophrenia have autonomic abnormalities, in particular reduced HRV (Bar et al., 2007; Iwamoto et al., 2012; Kim et al., 2004). Previous research suggests that HRV reduction may be associated with reduced

functioning (Fujibayashi et al., 2009; Valkonen-Korhonen et al., 2003). A number of hypotheses have been advanced on the role of autonomic deregulations and functioning in people with schizophrenia. Our findings suggest, in line with Montaquila et al., that autonomic abnormalities are mostly relevant for the parasympathetic branch of the autonomic system (Montaquila et al., 2015). This suggests that people with schizophrenia may have adequate reactivity to arousing stimuli but the parasympathetic system may fail to down-regulate this activation following habituation or stimulus removal. This study did not find abnormal EDA values in the clinical group and this may be dependent on the length of the recording period used (i.e. 8 h). Most of the studies showing abnormal sympathetic activity in people with schizophrenia use experimental designs evaluating event related activation on a much shorter timescale (e.g. Castro et al., 2008).

Lower parasympathetic activity in the group of people with schizophrenia was particularly evident for the standard deviation of RR intervals after controlling for age, functioning and movements levels. This index is considered more adequate for longer recordings as it measures HRV cycles over prolonged time periods and is relatively independent from activity levels therefore suggesting that HRV abnormalities may be related to other illness features such as symptoms (Thayer et al., 2012). This result did not entirely support the hypotheses that parasympathetic abnormalities are linked to functioning difficulties (Khandoker et al., 2010; Tarrier and Barrowclough, 1990; Toichi et al., 1999). However, it may be possible to reconcile these positions by considering how fundamental to schizophrenia both parasympathetic deregulation

and functioning problems are. It is likely that relevant moderating and mediating factors may intervene in modulating this relationship and perhaps contribute more decisively to explain this relationship. Our correlational analysis offers a potential candidate mediator for future study: positive symptoms. Previous studies have also found this symptom cluster to be associated with autonomic deregulation and functioning problems (Kim et al., 2004). It is also possible that poor functioning may be more influenced by other psychosocial aspects associated with psychoses such as limited opportunities and social contact, poor of self-esteem, social anxiety and low mood (Achim et al., 2011; Cella et al., 2014b; Saarni et al., 2010). The causal pathway to reduced HRV in psychosis remains uncertain and it is unclear if reduced HRV is the cause or the consequence of poor functioning.

This study has limitations. We did not exclude participants on the basis of their medication intake. It has been suggested in the literature that some drugs (e.g. anticholinergic medications) may have an effect on the parasympathetic systems (Agelink et al., 2001; Kim et al., 2013; Rechlin et al., 1994). However these studies have not been replicated and poorly adapt to the reality of clinical services where polypharmacy is common. We recorded chlorpromazine equivalent levels and controlled for it in the analysis; however we did not find medication having a significant influence on any of the physiological parameters recorded. A recent meta-analysis by Alvares et al. (2016) supports our finding and suggests that the impact of antipsychotic medication on HRV in people with schizophrenia is small and largely non-significant. Two of our participants in the clinical group were also prescribed with an antidepressant medication. Future studies should consider more systematically the role of depression and antidepressants as this may influence HRV (Brunoni et al., 2013). Aside of medication tobacco use should also be considered in future investigations as this may have an effect on the autonomic system. We did not record people's activity levels using self-assessed method (e.g. diary) as we wanted to record autonomic function without interfering with people's everyday life. As a result many participants reported that they were "forgetting" they were wearing a device. This is a positive aspect when considering future possible routine use of wearable devices however this meant that we were not able to monitor precisely people's activities. In the future studies should consider using, alongside wearable devices, Experience Sampling Methodology (ESM) (Nelson et al., 2017). This method has now been used extensively in people with psychosis (Edwards et al., 2016). Using ESM in combination with mobile autonomic monitoring will link more clearly how changes in mental health states affect people's autonomic system and give us the opportunity to devise precise and truly personalized monitoring systems.

The more routine use of mHealth device in people with psychosis may have important benefits. Several reports suggest that physical health is poor in people with psychosis (Stubbs et al., 2016; Vancampfort et al., 2015). Routine assessment of behavioural and physiological parameters such as activity levels and HRV could provide key information on people's wellbeing. Future interventions should capitalize on the possibility of tracking physiological parameters and monitoring these changes regularly.

Contributors

MC study idea and conducted preliminary analysis. LO, VZ, ZH, ML and MC prepared the database and conducted the final analysis. MC, LO and TW wrote the first draft of the paper. All authors contributed to the final version and have approved the final manuscript.

Role of the Funding Source

None specific to this project.

Conflict of interest

None.

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