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BRIEF REPORT

Blending active and passive digital technology methods to improve symptom monitoring in early psychosis

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Aims: Psychotic symptoms fluctuate over time and effective and regular monitoring may contribute to relapse prevention and improve long-term outcomes. In this proof-of-concept study we test the feasibility, acceptability and potential usefulness of a novel digital method assessing the association between physiological signals and psychotic symptom distress.

Methods: Fifteen participants with first episode psychosis were asked to use a self-assessment mobile phone application for psychotic symptom monitoring for 10 days while using a wrist worn device continuously recording heart rate variability (HRV) and electrodermal activity (EDA). We compared physiological activity when participants reported experiencing distressing and non-distressing psychotic symptoms.

Results: Participants completed on average 76% of the mobile phone symptom assessments. When reporting distressing hallucinations and delusions participants had significantly higher EDA levels and non-significant lower HRV values compared to when these symptoms were non-distressing.

Conclusions: This study provides further evidence linking psychotic symptom's distress, as experienced in everyday life, and autonomic deregulation. This proof-of-concept study may lead to further longer-term efforts to identify relapse biosignatures using automated methods based on passive monitoring. This method may allow for earlier interventions, contribute to improve relapse prevention and reduce symptoms interfering with recovery.

KEYWORDS

autonomic, eHealth, mHealth, psychosis, schizophrenia, wearable

1 | INTRODUCTION

Relapse after the first episode of psychosis is common (Robinson et al., 1999) and it is associated with poorer recovery, increased distress, depression and suicidal thoughts (Birchwood & Spencer, 2001; Birchwood, Todd, & Jackson, 1998). Relapse prevention is therefore a highly desired outcome. Early warning signs of relapse usually comprise dysphoria and the emergence of attenuated but distressing psychotic symptoms (eg, hearing voices), appearing over a period of typically 5 days (Brown, Kim, Mitchell, & Inskip, 2010; Cella, Cooper, Dymond, & Reed, 2008; Gleeson, Rawlings, Jackson, & McGorry, 2005). Evidence using ambulatory methods for tracking symptoms suggests that high levels of symptom related distress and poor coping abilities are amongst the most important factors contributing to relapse (Lardinois et al., 2007).

There is consensus that regular symptom monitoring may improve early intervention and relapse prevention, but it is not clear how often this should occur (Spaniel et al., 2008). Regular monitoring conducted by clinicians is also resource intensive and may be difficult to implement for early intervention services. It has been suggested that mobile health (mHealth) technologies could help to achieve frequent monitoring in the context of limited resources (Kumar et al., 2013; Narayan & Manji, 2016). However, most mHealth current monitoring tools for psychosis require symptom self-assessment which may be deliberately avoided when individuals are experiencing more severe or distressing symptoms. Passive remote monitoring (pRMT) might provide a

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solution if it is associated with information on symptoms fluctuation and it is well tolerated.

There is evidence that people with psychosis have autonomic abnormalities and these are associated with psychotic symptoms and lower functioning levels (Bar et al., 2005; Clamor, Lincoln, Thayer, & Koenig, 2016; Fujibayashi et al., 2009). Studies suggest that people with psychosis have reduced vagal tone and heart rate variability (HRV) (Bar et al., 2005; Moon, Lee, Kim, & Hwang, 2013) and this is associated with illness chronicity (Toichi et al., 1999), low scores on the Global Assessment of Functioning (GAF) (Khandoker, Fujibayashi, Moritani, & Palaniswami, 2010), and symptoms severity (Kim et al., 2004). Studies investigating sympathetic regulation found that people with psychosis have elevated levels of electrodermal activity (EDA) (Zahn et al., 1997), and these are thought to be dependent from a limited parasympathetic capacity to down-regulate sympathetic activity (Montaquila, Trachik, & Bedwell, 2015).

Until recently most studies assessed the association between symptoms and physiological abnormalities under laboratory conditions. Developments in mHealth devices have now made it possible to measure autonomic parameters using non-invasive wearable devices and there is evidence of their acceptability in people with psychosis (eg, Cella et al., 2018). Given the association between autonomic deregulation and psychotic symptoms, pRMT might help to identify increases in symptom related distress which may be of use in averting extreme symptom worsening and relapse.

This proof-of-concept study combines active and passive monitoring methods to explore the association between psychotic symptoms distress fluctuations and changes in autonomic parameters in a group of individuals with first episode psychosis. According to Montaquila et al. (2015) we hypothesize that high levels of distress associated with hallucinations and delusions will be associated with low Heart Rate Variability (HRV) and high Electrodermal Activity (EDA).

2 | METHODS

2.1 | Participants

We recruited individuals under the care of early intervention teams in the South London and Maudsley Foundation Trust part of the UK National Health System. The inclusion criteria were: (a) having experienced a psychotic episode, (b) aged between 18 and 35 years; (c) onset of psychosis within the last 12 months; (d) able to provide written informed consent.

2.2 | Measures

Participants completed an assessment of symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) and functioning using the GAF (Hall, 1995). Clinical and medication information was extracted from participants' electronic health records. Mean chlorpromazine equivalent levels for antipsychotic medications were calculated according to Woods (Woods, 2003). Then participants were instructed on how to use a wrist worn device, the Empatica E4 (https://www.empatica.com/en-gb/research/e4/). This device has sensors recording physiological and behavioural measures including heart rate, motion, EDA and skin temperature. Participants were asked to wear the device during day time (ie, from when they wake up in the morning until they went to bed in the evening). Alongside the wrist device, participants were asked to use a mobile phone app(lication) for symptom self-assessment, called ClinTouch, developed specifically for people with psychosis (Palmier-Claus et al., 2012; Palmier-Claus et al., 2013). This app prompts participants at four pseudo-random times per day (between 11 AM and 9 PM) to answer symptoms rating questions (eg, "Have you heard a voice telling you that you are worthless today?"; "I have felt like I could read other people's thoughts"). Each participant rates up to 12 symptoms validated against the PANSS (Palmier-Claus et al., 2012) in addition to personally relevant early warning signs using scores ranging from 1 (not present) to 7 (present). These included ratings of: anxiety, hallucinations, suspiciousness, depression, somatic concern, social withdrawal, hostility, conceptual disorganization but not only. The mobile phone app allows for personalization so that only relevant symptom rating prompts are sent to participants. For each symptom rated as present the app prompts participants to rate the associated distress level ranging from 1 to 7. A rating above three was considered indicative of a distressing symptom. All the participants in this study experienced hallucinations and delusions and each ClinTouch assessment asked to rate these symptoms. Participants were asked to use simultaneously the ClinTouch mobile phone app and the E4 device for 10 consecutive days. Devices acceptability was evaluated using a questionnaire including questions on the device level of disruption to participants' life, if the device was easy to use or stopped participants to do activities, and whether the experience of using the device was enjoyable or caused any embarrassment. This measure was used in previous studies involving people with psychosis and similar mHealth devices (eg, Edwards, Cella, Tarrier, & Wykes, 2016).

2.3 | Analysis

For analysis we considered samples of physiological recording collected at the time participants completed the mobile phone symptom self-assessment survey. We considered physiological recording samples of 20 minutes, from 10 minutes before the symptoms self-assessment survey trigger to 10 minutes after.

The EDA data was pre-processed for artefact using Ledalab 3.2.2 toolbox from Matlab (Benedek & Kaernbach, 2010). For each sample we used this software to extract EDA mean magnitude. HRV was computed from inter-beat intervals values using Kubios HRV software (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014). For HRV analysis we considered the standard deviation of all normal heart beat peak intervals (SDNN). This measure is considered more accurate over shorter samples (ie, less than 1 hour) (Okruszek, Dolan, Lawrence, & Cella, 2017; Sollers, Buchanan, Mowrer, Hill, & Thayer, 2007). The E4 device also collected information on movement using a 3-axis accelerometer. From this information we computed an overall activity measure by means of a standard Euclidean metric. We used this measure as a covariate in the analysis. This is because EDA and HRV parameters are affected by the body metabolic state and controlling for activity helps to exclude physiological changes dependent on exercise and physical exertion.

We assessed the acceptability of the procedures employed in this study by considering the proportion of participants endorsing a positive rating on the acceptability feedback questionnaire items (ie, endorsing agree on strongly agree).

We used multi-level logistic modelling with participant, our cluster variable, considered as a random-effect, whereas the effects of the predictors (ie, SDNN and EDA) on the outcome variable (ie, symptoms distress present or absent) were described as fixed effects. Analysis was conducted using the XTMELOGIT command in Stata (Version 15) (StataCorp, 2017) in line with similar studies (eg, Edwards, Cella, Emsley, Tarrier, & Wykes, 2018; Kimhy, Myin-Germeys, Palmier-Claus, & Swendsen, 2012). The effect of predictors on the outcome, representing the regression coefficients, is expressed as Z scores and odd ratios.

3 | RESULTS

Of the 15 participants recruited, 14 completed the whole study. One participant withdrew after a sudden family bereavement. The participants were predominantly men (80%) with a mean age of 28.1 (SD 3.8) and were all prescribed antipsychotic medications (mean chlorpromazine equivalent 238.7 [SD 174.1]). The mean PANSS positive score was 17.2 (SD 4.5), the negative was 17.9 (SD 4.7) and the general was 35.7 (SD 10.1). The GAF mean score was 48.8 (SD 9.3).

Participants completed an average of 76% of the ClinTouch assessments over the study period (ie, on average three out of four assessments per day). All participants used the watch according to the instructions received and completed the device acceptability questionnaire. Results from the acceptability questionnaire showed that both devices were easy to use and did not have significant side-effects with over 80% of the participants rating the app and the wearable device as easy to use and non-disruptive and the experience of using the devices as enjoyable.

Overall, we were able to combine data from ClinTouch and the E4 device for 157 symptoms surveys (each assessing both hallucinations and delusions). Of the completed surveys we had 47% with hallucinations rated as distressing and 45% with delusions rated as distressing. Participants rated a minimum of 6 and a maximum of 16 surveys with no significant differences in completion levels.

The model performed on delusion (Wald $X^2[2] = 8.75$, $P = 0.013$) showed that EDA values were higher when experiencing distressing ($z = 2.98$, $P = 0.003$; OR [odds ratio] = 1.05; 95% confidence interval [CI] 1.02-1.08) compared to experiencing not-distressing delusion but there was no significant difference in SDNN values ($z = -0.97$, $P = 0.3$; OR = 0.99; 95% CI 0.98-1.02). A similar model performed on hallucination (Wald $X^2[2] = 8.01$, $P = 0.02$) showed that EDA values were higher when experiencing distressing ($z = 2.88$, $P = 0.004$; OR = 1.06; 95% CI 1.02-1.09) compared to non-distressing hallucinations but there was no significant difference in SDNN ($z = -0.95$, $P = 0.34$; OR = 0.99; 95% CI 0.98-1.02) (see Figure 1).

4 | DISCUSSION

This proof-of-concept study tested the combination of active and passive monitoring methods for symptom monitoring with the longer-term aim to develop a method that can use predominantly passive information to improve symptom monitoring and contribute towards relapse prevention in people with psychosis. We tested mHealth devices in people with first episode psychosis for the first time, and an aim of this study was to assess acceptability and ease of use of these devices. The results support a high level of uptake and acceptability of the wearable device used and high completion levels for the mobile phone surveys.

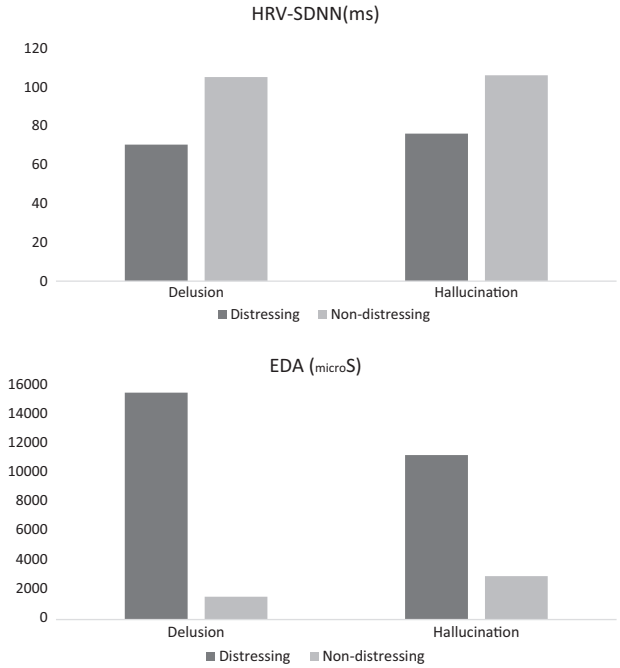

FIGURE 1 Show mean heart rate variability (SDNN-in milliseconds) and electrodermal activity (EDA in microsiemens) for samples where hallucination and delusion were reported as distressing and non-distressing

Our results also suggest that when reporting distressing hallucinations and delusions participants had significantly higher EDA levels values compared to when these symptoms were not distressing. Associations between HRV and symptom distress were in the expected direction but did not reach a statistically significant threshold. These results replicate laboratory studies of physiological abnormalities (Kim et al., 2004) and emerging evidence associating these abnormalities with positive symptom fluctuations (Kimhy et al., 2017). Further studies consolidating the evidence on the biosignature of positive symptoms may have important implications for delivering improved and cost-effective outcomes.

With new wearable technology allowing for effortless physiological recording in real-time this study suggests that it may be possible to measure a reliable biosignature of symptom exacerbation and potentially relapse risk. With these indicators linked to a clinical service the prospect of prevention and rapid response to symptom worsening may improve substantially. However, achieving this ambitious target will require further efforts to develop data handling algorithms and machine learning tools that can produce personalized and meaningful alerts for service users and clinicians (Iniesta, Stahl, & McGuffin, 2016). Limitations of this study are the small number of service users, potential selection bias at recruitment for those more familiar with

technology use, the potential confounding role of medication and variability in cardio-metabolic fitness which is difficult to control for in the analysis. However, a recent review suggests that medication is unlikely to have a strong effect on autonomic activity (Alvares, Quintana, Hickie, & Guastella, 2016).

There are other issues the field of mHealth and pRMT should consider including data handling, confidentiality and potential stigma associated with device use (Simblett et al., 2018). However, it is likely that the benefits of this technology will exceed these potential difficulties, especially in high-risk group such as people with first episode psychosis.

With increasing evidence suggesting that mHealth devices are acceptable and easy to use the focus of research now should shift to develop accurate systems for prediction based predominantly on passive monitoring information. Efforts should also be made for building the necessary evidence for devices to be recommended and used as part of routine care.

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