EARLY SIGNS OF SCHIZOPHRENIA AND AUTONOMIC NERVOUS SYSTEM DYSREGULATION: A LITERATURE REVIEW

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Abstract

Objective: Recent research suggests that early signs of schizophrenia can be detected several years before its onset. Evidence suggests that the identification of at-risk individuals before the psychotic onset can significantly improve the course of the disorder. However, instruments employed for the detection of prodromal symptoms are far from being accurate in the prediction of a future transition to psychosis. The aim of the present review is to summarize literature on the early signs of schizophrenia and to identify physiological markers that may aid the identification of the disorder before psychotic transition.

Method: This critical review includes studies published between 1979 and 2018 that were indexed in major databases with the following keywords: schizophrenia, prodromal phase, basic symptoms, autonomic nervous system, heart rate variability.

Results: The examination of the relevant literature showed that, despite recent progress in the identification of at-risk states, the currently employed instruments do not allow an effective prediction of a future psychotic onset. Also, evidence suggests a significant association between alterations in the autonomic nervous system (ANS) functioning and psychotic disorders. However, literature on the association between ANS functioning and at-risk states for psychosis is still scarce. The addition of physiological risk indicators may represent a step forward in the detection of at-risk individuals.

Conclusions: Overall, the present literature review highlights that a future schizophrenic onset cannot be strongly predicted with current available measures. Given the established correlation between schizophrenia and autonomic dysregulation, an investigation of the ANS functioning in individuals who are at increased risk of developing schizophrenia may be particularly useful to improve the quality of the assessment, to identify at an early stage the dysregulated physiological patterns that have been linked with schizophrenia, and therefore to develop tailored interventions. Accordingly, it is crucial that future research investigates the presence of autonomic deficits in individuals at risk for psychosis.

Key words: schizophrenia, prodromal phase, basic symptoms, autonomic nervous system, heart rate variability

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Introduction

Schizophrenia is a mental disorder characterized by the persistent and invalidating presence of thought, perception, and behavioural symptoms, which result in major consequences for the global functioning of the individual on the cognitive, emotional and social level (Laurens et al. 2015, American Psychological Association 2013).

Schizophrenia often becomes a chronic condition (Belbasis et al. 2017) and its consequences are so negative that it has been considered as the most severe mental illness (Andreasen 2001). Research reports lifetime prevalence to be around 1%, varying from 0.4% to 1.5% according to the country of residence (Cannon 1996, McGrath et al. 2008, Yung and Nelson 2013). Less than half (20–40%) of patients diagnosed with schizophrenia have been found to show substantial clinical improvement after follow-up averaging 5–6 years (Hafner and der Heiden 2003, Lauronen et al. 2005), although the outcome in developing countries has been reported to be generally more favourable (Hopper 2000). The effects of schizophrenia on society are also considerable: in terms of the global burden of disease and

disability (Murray and Lopez 1996), schizophrenia ranks among the most invalidating disorders and is considered to be a major public health problem, along with cancer, heart disease and diabetes (Mathers and Loncar 2006). On the light of this evidence, a greater and more specific understanding of the causes and consequences of the disorder is essential in order to ensure the best possible outcome for the affected individuals through the identification of effective treatment. In this vein, research has recently deepened its investigation on potential physiological markers of schizophrenia. Accordingly, this critical review on early signs of schizophrenia and dysregulation of the autonomic nervous system includes studies published between 1979 and 2018 that were indexed in major databases, such as PubMed, Scopus, EBSCOhost, ProQuest Psychology Journal, PsycArticles, and PsycINFO, with the following keywords: schizophrenia, prodromal phase, basic symptoms, autonomic nervous system, heart rate variability.

Early signs of schizophrenia and risk for psychosis

At the end of the 20th century, schizophrenia research has begun to focus on the investigation of the prodromal phase of the disorder, with the intent of identifying a set of early signs to be detected before the acute onset (McGorry and Singh 1995, Yung et al. 1996, Yung and Nelson 2013, Schultze-Lutter 2009, Schultze-Lutter et al. 2015, Thompson et al. 2011). Research shows that the early signs of the disorder, including non-specific and externally non-visible symptoms, can be detected several years before the actual psychotic onset (Schultze-Lutter 2009, Yung and Nelson 2013). Nonetheless, prodromal symptoms are frequently underestimated by perceivers, their families and society, due to poor knowledge on their existence, alongside a lack of designated services for early interventions (Norman et al. 2005). This often leads to a delayed diagnosis and treatment and therefore to an increase in the Duration of Untreated Psychosis (DUP), described as the time elapsing between the first psychotic symptom and treatment initiation (Marshall et al. 2005). A long DUP has been shown to worsen the progress of the disorder: a systematic review investigating 26 studies has reported a significant association between longer DUP and worse outcome after 6 months, as demonstrated by a greater amount of symptoms, a diminished general functioning and a worsened quality of life (Marshall et al. 2005). Remission was also found significantly less likely to occur for individuals with a longer DUP. Similarly, a recent systematic review including 3493 studies and investigating the correlation between DUP and subsequent treatment outcome has reported that a longer DUP correlated significantly with poorer symptomatic and intervention outcome and with a lesser likelihood of remission (Penttilä et al. 2014). This suggests that reducing the timeframe between the first psychotic episode and treatment delivery can lead to a more favourable intervention outcome; therefore, an early intervention should be considered essential.

Research over the last 15 years has given birth to several sets of criteria and classification systems for the detection of schizophrenia's early signs. McGorry and Sing (1995) have outlined a group of specific symptoms considered to be predictive of psychotic onset and defined it in terms of "at risk mental state" (ARMS). These were further refined to become a symptomatic category called "Ultra High Risk" (UHR) for psychosis,

one of the currently most widely employed constructs in schizophrenia research (Yung and McGorry 1996, Yung et al. 2003, Yung et al. 2004).

UHR patients are detected investigating the presence of the following characteristics: (1) Attenuated Psychotic Symptoms (APS) — sub-threshold, attenuated forms of positive psychotic symptoms during the past year; (2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) — individuals who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; and (3) Trait and State Risk Factor (TSRF) — individuals who have a first-degree relative with a psychotic disorder or who have a schizotypal personality disorder, in addition to a significant decrease in functioning during the previous year (Nelson et al. 2011, Yung and Nelson 2013, Raballo et al. 2016).

Several studies have found that young individuals seeking treatment who also met UHR criteria were more likely to develop psychosis over a 1-2 years follow-up period (Cannon et al. 2008, Yung et al. 2003). Based on retrospective observations of the period determined as prodromal, there is a 30% to 40% chance of schizophrenia onset within the subsequent 2 years (Yung and Nelson 2011). Yung and colleagues (2003) investigated a sample of 49 subjects at UHR of transition to psychosis, finding that 40.8% of them developed a psychotic disorder within 12 months, with the majority of this subgroup (64.9%) developing schizophrenia. The variables found to significantly impact the transition to psychosis were a long duration of symptoms, poor functioning at intake, low-grade psychotic symptoms, depression and disorganization. Psychosis prediction by means of the UHR concept demonstrated a good sensitivity (86%), specificity (91%), positive predictive value (80%) and negative predictive value (94%) within 6 months. These results seem to suggest that the concept of UHR has a good predictive value within a relatively brief follow-up period. It should be noted, however, that the study was limited by its small sample size (*N*= 49), resulting in low statistical power.

Cannon et al. (2008) carried out a longitudinal study on a sample of 370 individuals. Subjects were administered the Structured Interview for Prodromal Syndromes (SIPS) at several points in time. Results demonstrated a risk of conversion to psychosis of 35% over a follow-up period of 2 ½ years, with a decelerating rate of transition (13% in the first 6 months, slows modestly to 9% from 7 to 12 months, slows to 5% per each 6-month epoch at 13 to 24 months, and then slows again to 2.7% from 25 to 30 months). Similarly, Ruhmann et al. (2003) have detected an estimate of 36.7% of UHR individuals who were not administered antipsychotic treatment and developed psychosis 1 year after meeting the criteria (Ruhrmann et al. 2003). Recently, transition rates from UHR to psychotic onset have been estimated to be around 19% (Schultze-Lutter et al. 2015).

It should be noted that concerns have been raised over the possibility that false positive ratings of transition may occur due to the "uncertain status of the transition concept" and due to the rapid changes in severity that are typical of the psychotic dimension "within and between individuals" (van Os and Guloksuz 2017 p 203). A study that has accounted for false positive ratings of transition through serial examination of individuals has reported significantly lower rates of transition (8%) compared to previous studies which did not account for this variable (Morrison et al. 2012).

According to the extant evidence, UHR symptoms are moderately successful in identifying individuals who

are close to a psychotic transition within a 1-year period from assessment. However, although this approach may reduce DUP, intervention at such a late state is unlikely to prevent the transition itself. It might be beneficial to intervene at an even earlier stage, with the aim of potentially preventing a future psychotic onset.

Basic Symptoms

An opportunity for an early detection of the prodromal phase might be to rely on the use of the complementary concept of *Basic Symptoms (BS),* as developed by Gerd Huber in the 1960s (Huber 1966). BS are described as disturbances in everyday activities, experienced by the individual and not necessarily noticeable by others. BS have been shown to negatively affect the life of the person who experiences them: a study on 118 subjects demonstrated a negative association between the presence of BS and the Global Assessment of Functioning (GAF), suggesting that subjects experiencing BS may have a reduced psychological, social and occupational functioning (Rocca et al. 2010).

The presence of BS was originally evaluated through the Bonn Scale for the Assessment of Basic Symptoms (BSABS), a semi-structured interview consisting of 92 items (Gross et al. 1987). BS can be identified in different forms in a timeframe between two months and 35 years before the psychotic onset (Gross et al. 1987). This suggests that the use of the BS construct may allow the detection of schizophrenia prodrome at an earlier stage as compared to the UHR concept. Cluster analysis has revealed six broad dimensions of BS showing good reliability and explaining a variance of 93%; the six dimensions also seem to persist across the different stages of the disorder (Schultze-Lutter et al. 2008).

On the line of BSBAS, a new assessment tool, the Schizophrenia Proneness Instrument (SPI), in its two versions for adults and children/adolescents (Adult, SPI-A, Schultze-Lutter et al. 2007 and Child and Youth, SPI-CY, Schultze-Lutter & Koch 2010) was more recently developed. SPI-A and SPI-CY are semi-structured interviews investigating four main areas of interest: adynamia, perceptual disorders, neuroticism and thought and action disorders. Differently from the BSABS, which only assesses the current state of the individual, SPI-A and SPI-CY allow to rate BS severity within the past 3 months (Schultze-Lutter et al. 2007).

The concept of BS seems to be accurate in excluding a potential future onset, while it has been found to be less likely to predict it: in the Cologne Early Recognition (CER) study, 160 patients were followed up prospectively for a mean follow-up period of 9.6 years, with a minimum of five years. Results revealed that 79 patients developed schizophrenia during the follow-up period and that only two of the patients who transitioned towards psychosis had not reported the presence of BS at first examination. On the other hand, 30% of individuals who did not report the presence of BS were subsequently diagnosed with schizophrenia; the overall presence *vs.* absence of BS correctly predicted subsequent transition to schizophrenia in 78.1% of cases (Klosterkötter et al. 2001).

Results of the CER study were further analysed, revealing two partially overlapping clusters of BS that showed a significantly higher predictive value as compared to the other symptoms. Indeed, these clusters were shown to be statistically more likely to predict an imminent psychotic breakdown as compared to the remaining BS (Schultze-Lutter et al. 2008, Schultze-Lutter et al. 2015). These have been therefore grouped into two highly predictive subgroups of risk criteria: the Cognitive-Perceptive BS criteria (COPER; see **table 1**) and the Cognitive basic symptoms criteria (COGDIS; see **table 2**) (Schultze-Lutter et al. 2015). Research suggests that the presence of symptoms belonging to the CODGIS group indicates a more imminent risk of psychotic onset and a greater risk of developing schizophrenia as compared to COPER (Schultze-Lutter et al. 2008; Klosterkötter et al. 2005; Schultze-Lutter et al. 2006, 2007); COGDIS symptoms have been found to be less effective in excluding the possibility of its onset (Klosterkötter et al. 2011, Ruhrmann et al. 2010ab). Similar results were reported following a prospective study administering SPI-A (Schulze-Lutter et al. 2007) on 146 subjects considered to be on a prodromal phase, with a 24 months follow-up; results revealed that 38% of individuals initially classified as at-risk developed a frank psychosis over a 12.1 months period (1-48, median= 9) according to COPER. Again, COGDIS appeared to be more specific than COPER. Differently from what previously reported, however, COPER did not seem to delineate a less imminent risk of psychosis as compared to COGDIS; rather, COPER symptoms appeared to be met in a group of prodromal subjects exhibiting less intense symptoms and therefore requiring special predictions (Schultze-Lutter et al. 2007). **Table 1** and **table 2** summarize COPER and COGDIS criteria, respectively.

As evident from the extant literature, despite the progress achieved throughout the last 15 years in the detection of at-risk individuals, the current instruments still produce a significant amount of false positive findings with regard to future psychotic onset; at the

Table 1. *High risk criteria for cognitive-perceptive (COPER) Basic Symptoms*

Presence of at least any one of the following ten basic symptoms with at least weekly occurrence (i.e., a SPI-A/SPI-CY score of ≥3) within the last three months and first occurrence at least 12 months ago (irrespective of frequency and persistence during this time):

1. **Thought interference**
2. **Thought perseveration**
3. **Thought pressure**
4. **Thought blockage**
5. **Disturbance of receptive speech**
6. **Decreased ability to discriminate between ideas and perception, fantasy and true memories**
7. **Unstable ideas of reference**
8. **Derealisation**
9. **Visual perception disturbances, excl. blurred vision and hypersensitivity to light**
10. **Acoustic perception disturbances, excl. hypersensitivity to sound**

Table 2. *High risk criteria for cognitive disturbances (COGDIS) Basic Symptoms*

Presence of at least any two of the following nine basic symptoms with at least weekly occurrence (i.e., a SPI-A/SPI-CY score of ≥3) within the last three months:

1.	**Inability to divide attention**
2.	**Thought interference**
3.	**Thought pressure**
4.	**Thought blockages**
5.	**Disturbance of receptive speech**
6.	**Disturbance of expressive speech**
7.	**Unstable ideas of reference**
8.	**Disturbances of abstract thinking**
9.	**Captivation of attention by details of the visual field**

same time, studies hardly exceed one year of follow-up, therefore raising the issue of potential "false false-positives", referring to those individuals who converted to psychosis after the end of the follow-up period and had therefore been wrongly considered false positive predictions. A further concern refers to treatment administration following the detection of at-risk individuals: subjects experiencing BS are likely to be treated in the attempt to avoid a psychotic transition and might therefore be less likely to develop a psychotic disorder. This may confound the results of follow-up studies.

Although research seems to agree on the necessity to accurately identify and treat at-risk states, as well as on the validity of the instruments implemented, no agreement has yet been reached on the therapeutic interventions proposed and on their effectiveness. Studies indicate that in 50% of cases the proposed psychotherapeutic interventions have been unable to avoid the transition towards a psychotic disorder up to the first 12 months post-treatment. Follow-up studies have shown that interventions were not able to modify the trajectory of the disorder towards psychosis after 2 years (Fusar-Poli 2017). This seems to suggest that, up to date, interventions are likely to postpone the onset of the disorder but are unable to prevent it.

The research findings summarized highlight the need to further investigate schizophrenia prodromal phase. Studies with longer follow-up periods and larger samples are needed in order to avoid the false-false positive confounder. The addition of physiological risk indicators may be useful in order to create a more specific understanding and to refine our ability to predict a future psychotic onset.

Schizophrenia and the Autonomic Nervous System (ANS)

The Autonomic Nervous System (ANS) is our "control system", whose main role is to regulate body homeostasis through the monitoring of bodily functions, among others heart rate, breathing rate and digestive system functioning (Schmidt and Thews 1989). The ANS is an implicit system; it operates independently from our conscious awareness and consists of two main branches. The first is the sympathetic nervous system (SNS), often defined as the "fight or flight" system, which serves the function of reacting in response to dangerous signals from the environment. The second is the parasympathetic nervous system (PNS), often

referred to as the "rest and digest" system, which allows the individual to relax and operate the normal bodily functions in absence of danger. The two branches of the ANS are activated or inhibited according to environmental needs.

Autonomic dysfunctions have been extensively investigated in relation to schizophrenia. Early studies relying on pupillometry in the investigation of parasympathetic activity have identified a "sluggish" parasympathetic function among schizophrenia patients in comparison to healthy controls (Spohn and Patterson 1989). Other studies have also investigated schizophrenic patients in relation to cholinergic activity, which had previously been associated with parasympathetic activity (Rubin 1974), finding a cholinergic deficiency in schizophrenic patients as compared to healthy controls (Singh and Kay 1985, Tandon and Greden 1989). This body of research has been interpreted as evidence suggesting a parasympathetic dysfunction in schizophrenia.

Early studies focusing on sympathetic activity also seem to suggest a dysfunctional sympathetic activation among schizophrenic patients (Zahn et al. 1979, Zahn et al. 1998, Walker et al. 2010, Walker et al. 2013). For example, Zahn et al. (1998) found that schizophrenic patients showed greater levels of skin conductance response. More recently, Walker et al. (2013) investigated cortisol levels in patients and controls and found an over-production of cortisol in schizophrenic patients. These results have been interpreted as evidence of a sympathetic deficit in schizophrenic individuals.

Recent literature, however, suggests that results of early studies on ANS functioning should be interpreted cautiously, as they focus exclusively on measurements of either sympathetic or parasympathetic activation. Authors investigating measures of ANS activity have warned that the contribution of sympathetic and parasympathetic functions should not be considered as operating in reciprocal control (Berntson et al. 2008) and that sympathetic activity should not be assumed examining parasympathetic activity and vice versa. In order to be reliable, studies should incorporate a measure that is able to simultaneously investigate sympathetic and parasympathetic activation. In its evaluation of autonomic models, Berntson and colleagues (2008) specify that sympathetic and parasympathetic dimensions are not fixed or invariant, and that it is flexibility in the alteration of these dimensions that allows the organism to deal with perturbations such as stress or physical activity and obtain "stability through change" (Sterling and Ever 1988 p 631).

Heart Rate Variability in Schizophrenia

Recently, research has been using the analysis of heart rate (HR) in order to assess ANS functions. Heart Rate Variability (HRV) in particular has been identified as the result of the ability of the ANS to modify intervals between heart beats according to physiological requirements. Therefore, the measurement of HRV has recently been employed for the investigation of autonomic balance (Berntson et al. 2008). This novel measure brings with itself the possibility to obtain data on sympathetic and parasympathetic activity simultaneously, allowing researchers to investigate the association between the two dimensions, and to detect any potential imbalance between them in individuals with mental disorders. In the analysis of HRV, authors have related high frequency (HF) to parasympathetic activity, while low frequency (LF) has been interpreted as a combination of parasympathetic and sympathetic activity. Therefore, the LF/HF ratio is used to interpret sympathovagal balance (Berntson et al. 2008).

Several studies have investigated the potential presence of a sympathovagal imbalance in individuals suffering from schizophrenia, often with contradictory findings. Rechlin et al. (1994) investigated HR in 20 unmedicated patients with paranoid schizophrenia and healthy controls, finding an elevated HR in schizophrenic patients (Rechlin et al. 1994). Inconsistently, however, authors also reported no significant differences in Cardiac Autonomic Functions (CAF) in the same patient groups as compared to the control subjects. This was also the case in the study carried out by Toichi et al. (1999), where the authors investigated CAF in hospitalized chronic schizophrenic patients and control subjects. CAF was evaluated based on the heartbeat intervals obtained from ECG monitoring. Results showed no significant differences in CAF between the two groups. It should be noted, however, that the patients recruited for the study were all under medication and had been hospitalized for at least 10 years; this might have had an effect on their ANS functioning. On the other hand, the authors found a direct influence of psychotic states on ANS, where the psychotic states restrained the parasympathetic but not the sympathetic function; according to the authors, "the presence of the psychotic state itself suppressed HRV" (Toichi et al. 1999 p 152). The authors concluded that the association between psychotic states and the ANS is mediated through the parasympathetic nervous system.

Recent studies seem to support this evidence. A substantial body of research suggests that a dysfunctional HRV in schizophrenia primarily results from a parasympathetic deficit, rather than from a sympathetic alteration. A study investigating a number of autonomic measures (i.e. HRV, baroflex sensitivity, cardiac output, left ventricular work index and total peripheral resistance) found a significantly reduced resting parasympathetic activity in schizophrenic patients as compared to healthy controls (Bär et al. 2007a). Interestingly, the LF/HF ratio was not significantly different between the two groups. These results seem to suggest that the sympathovagal imbalance in schizophrenic patients is a consequence of a reduction in parasympathetic parameters, rather than due to an increase in sympathetic activity (Bar et al. 2007b).

Ieda et al. (2014) measured salivary alpha-amylase (sAA) in 25 medicated schizophrenic patients *vs.* healthy controls. The sAA is the most abundant enzyme in saliva. Several studies have demonstrated sAA to be sensitive to stress-related changes and to be a reliable index of ANS dysregulation in individuals suffering from mental health disorders (Schumacher et al. 2013). The authors report that patients showed greater sAA levels as compared to controls, suggesting a sympathovagal imbalance. Having identified a diminished parasympathetic activity and no differences in SNS activity between the two groups, the authors concluded that the different sAA levels were due to parasympathetic activity suppression and a consequent SNS elevation (Ieda et al. 2014). They concluded that this results in a sympathetic nervous system dominance that is determined by a poor parasympathetic activity. It should be noted that most of the patients group (92%) was treated with different antipsychotics at the time of the examination; therefore, a significant effect of medications in the results obtained cannot be excluded.

Bär et al. (2007c) investigated the beat-to-beat QT interval variability in patients with schizophrenia in acute psychosis. The QT interval is a range of cardiac path and its functioning predicts the presence of malignant arrhythmias and the risk of sudden death. It is also used as a measure of cardiac activity and HRV. Twenty-five unmedicated patients in acute phase were subjected to high-resolution electrocardiographic recordings. The Scale for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS) was used to assess schizophrenic symptoms. Results of the study demonstrated an increased QT variability in patients as compared to controls and a greater sympathetic cardiac activity, which was interpreted as a consequence of a reduced complexity and decreased vagal tone (Bär et al. 2007c). Chang and colleagues (2009) also investigated measures of time frequency and complexity HRV domains in schizophrenic patients and controls, finding a decreased parasympathetic activity in patients as compared to healthy controls. The patients involved in this study had not taken antipsychotic medication in the past 28 days and depot antipsychotics in the past 24 weeks. Therefore, a role of medication on autonomic functioning can be excluded.

A body of evidence investigated the association between schizophrenia and ANS performance during the administration of a stress task. Castro and colleagues (2008) recorded HRV while administering an arithmetic stress task (participants were asked to subtract serial 7's starting from 700) in a sample of schizophrenic patients and controls. Results showed a similar autonomic response during the stress task between the two groups, but a deficit in recovering a HRV resting pattern when the task was over (Castro et al. 2008). Although a significant role of medication in autonomic deficits could not be excluded in the sample, the authors controlled the effects of treatment excluding individuals who had used medication with anticholinergic effects in the week preceding task administration; all patients recruited had also been on stable medication for the preceding two weeks.

The findings reported by Castro et al. (2008) were replicated in a study administering a social cognition task to 19 schizophrenic patients, 19 of their non-psychotic first-degree relatives and 19 control subjects: results revealed that patients, but not controls or first-degree relatives, exhibited a maintained autonomic pattern typical of stress exposure even after the cessation of the stimulus (Jauregui et al. 2011). These findings suggest that patients may display a normal sympathetic response to stress but experience greater difficulties in recovering from the stressor, leading to maintenance of sympathovagal imbalance. This may consequentially lead to a sympathetic

iper-arousal and a parasympathetic ipo-arousal. Akar et al. (2014) investigated HRV under stress in schizophrenia with the exposure to different types of noises. In the study, 19 unmedicated schizophrenic patients and 20 healthy subjects were exposed to white noise (WN), relaxing music or rest periods. HRV was investigated with the use of photoplethysmographic signals. Results exhibited lower HRV in patients as compared to controls throughout the different conditions, suggesting an ANS dysfunction in schizophrenic patients. Patients exhibited lower high-frequency power and higher low-frequency to high-frequency ratio. Furthermore, while WN was able to decrease parasympathetic activity in healthy subjects, this was not the case in schizophrenic patients, suggesting that individuals with schizophrenia were unable to obtain a decrease in low frequency HRV following the cessation of the auditory stimuli (Akar et al. 2015).

In summary, the evidence reviewed suggests that a dysfunctional PNS might be considered as the main contributor of the sympathovagal imbalance found in schizophrenia (Bär et al. 2007b). However, it should be noted that a few studies have reported contradictory findings in relation to the evidence presented above: some authors did not find evidence of sympathovagal imbalance in schizophrenic patients (Birkhofer et al. 2013, Rechlin et al. 1994, Henry et al. 2010). Also, Rachow et al. (2011) found an augmented sympathetic activity in schizophrenia. Finally, Lee et al. (2011) reported high values of both LF and HF HRV, indicating alterations both in sympathetic and in parasympathetic activity. Although the study reports a high statistical power, the authors were unable to control for the effects of antipsychotic medications, which have been shown to mediate autonomic response in schizophrenia.

The role of antipsychotic medication

A substantial body of research has been focusing on whether antipsychotic treatment may underlie the autonomic dysregulation associated with schizophrenia. Antipsychotic drugs have been shown to have anticholinergic effects; as a consequence, it has been argued that the reported association between HRV and schizophrenia could be a consequence of medication. In line with this perspective, studies seem to suggest that medicated schizophrenic patients exhibit a lower vagal activity as compared to healthy individuals (Kim et al. 2011). Interestingly, research has also suggested the possibility that HRV deficits in schizophrenia patients treated with antipsychotics could be exacerbated by medication (Mujica-Parodi et al. 2005).

Several other studies have reported a role of antipsychotic medication in the exacerbation of ANS dysfunctions among patients affected by schizophrenia. Birkhofer et al. (2013) carried out a study on a novel measure of HRV, called "deceleration capacity (DC)" on 40 schizophrenic medicated inpatients, 20 unmedicated patients and matched controls. Medicated patients were treated with olanzapine, risperidone, quetiapine, aripiprazole, amisulpride or lorazepam. Among treated patients, 29 were administered a single antipsychotic and 11 were on a combination of two antipsychotics. Although the authors did not account for treatment type, individuals on anticholinergic medication were excluded. Results of the study showed no significant differences in HRV measures between unmedicated schizophrenic patients and healthy controls; however, results demonstrated a reduction of DC in medicated patients. This evidence suggests that antipsychotics

may have a significant role in HRV deficits found in schizophrenia.

Iwamoto et al. (2012) also found a significant effect of antipsychotics on HRV functioning. Specifically, authors focused on the role of drug dosage on autonomic functioning. The study compared healthy controls with schizophrenic patients medicated with either chlorpromazine, biperiden or diazepam. Patients were divided into three groups according to their daily dose (high, medium, low). Results showed that the high-dose group exhibited a significantly lower HRV as compared to the medium-dose group and an even lower HRV than the low-dose group. The medium-dose group showed a significantly lower HRV than the control group, as did the high-dose group (Iwamoto et al. 2012). This finding suggests that antipsychotics may have a role in the reported autonomic dysregulation in schizophrenia.

Further evidence in support of the role of medication on the HRV-schizophrenia association derives from studies investigating and comparing the effect of different medications on HRV. Agelink and colleagues (2001) compared the effects of amisulpride, olanzapine, sertindole and clozapine, concluding that some drugs may have greater effects than others in HRV deficits found in schizophrenia patients. Specifically, evidence seems to suggest that clozapine may play a greater role on autonomic dysfunction, leading to lower levels of parasympathetic activity, as compared to other antipsychotic medications (Agelink et al. 2001, Mathewson et al. 2012). Tümüklü et al. (2008) explored the effects of clozapine on patients with schizophrenia measuring HRV before and after a 10 weeks treatment, finding a significantly decreased HRV following treatment; this seemed to be dependent on the dosage of clozapine administered. HRV changes were negatively correlated with clozapine's daily dose which seemed to be independent of autonomous side effects. The authors concluded that clozapine has a dose dependent effect on HRV (Tümüklü et al. 2008). Similar results were reported by Cohen et al. (2001). The authors carried out HR analysis in controls *vs.* schizophrenic patients treated with clozapine (N= 21), haloperidol (N= 18) and olanzapine (N= 17), finding that patients treated with clozapine had higher HR and lower HRV as compared to controls and patients treated with other medications, suggesting that clozapine may have a particularly significant role in the autonomic dysregulation typically found in schizophrenic patients (Cohen et al. 2001). Similarly, Wang et al. (2008) found that switching from olanzapine to amisulpride lead to improvements in parasympathetic activity, while the administration of risperidone affected the sympathovagal balance of previously unmedicated patients, leading to a parasympathetic dominance 6 weeks after treatment initiation (Chang et al. 2010). This evidence seems to suggest that antipsychotics may have a significant role in the vagal tone deficits in schizophrenia, and that some may have greater impact than others. However, a potential role of medication on HRV does not imply the inexistence of an unmediated relationship between schizophrenia and autonomic dysregulation. In Mujica-Parodi's study (2005), unmedicated patients exhibited statistically significant HRV deficits when compared to controls, independently of antipsychotic side effects. Symptom severity should also be considered as a confounding factor in the investigation of the role of medication, assuming that medicated patients are more likely to be suffering from a more severe illness. In support of this, Chang et al. study (2010), which reported a negative effect of risperidone on medicated schizophrenic's

parasympathetic activity, also reported a large effect of medication upon symptom severity, suggesting an inverse relationship between parasympathetic activity and symptom severity. In further support of a medication-independent correlation between HRV and schizophrenia, Bar et al. (2005) assessed HRV in 30 acute and unmedicated schizophrenic patients *vs.* matched controls. Patients were also assessed 2-4 days after the initiation of treatment in order to investigate the role and effects of antipsychotics in HRV. The study did not find any significant modification in HRV after administering antipsychotics to previously unmedicated patients, suggesting a loss of vagal efferent activity in schizophrenia which may be dose-independent. Similarly, Bar et al. (2008) investigated 15 healthy controls and 15 schizophrenic patients in acute phase before and after the administration of olanzapine treatment. Authors used several nonlinear parameters to investigate HRV (approximate entropy, compression entropy, fractal dimension) and QT variability. Similarly to what previously reported, untreated patients demonstrated a reduced complexity of heart rate regulation and an increase in QT-variability index as compared to healthy controls. Patients did not exhibit changes in QT following treatment.

Mann et al. (2004) investigated HRV during sleep in schizophrenic patients (*N*= 16) under two conditions (drug-free *vs.* 4 weeks olanzapine treatment). Results showed only slight changes in the sympathovagal balance, specifically in the sympathetic component; however, total HRV was not altered by medication (Mann et al. 2004). Malaspina et al. (2002) also found that reduced HRV in a sample of schizophrenic patients was independent of neuroleptic effect in a pilot double-blind, crossover study of placebo and haloperidol treatment linked with the analyses of the Holter electrocardiograms for high frequency HRV, calculated as the percent of successive normal inter-beat intervals greater than 50 milliseconds (PNN50). Results showed that patients had unchanged PNN50 between the haloperidol treatment and drug-free conditions.

It should be noted that limited evidence suggesting that antipsychotic medication may even have a positive effect on autonomic functioning exists: in one recent study, medicated patients exhibited a reduced cortisol secretion, index of a reduced hyperactivity of the HPA-axis (Mondelli et al. 2010). The reviewed evidence clearly indicates that the exact interplay of anti-psychotic medication and sympathovagal imbalance is in need of further studies. However, although the reported association between anti-psychotic medication and HRV deficits, current evidence also suggests that HRV dysfunctions in schizophrenia deserve to be considered beyond the mere effects of medication intake (Bar et al. 2005).

Severity of symptoms and HRV

A considerable body of research has investigated whether severity of psychotic symptoms plays a role in the correlation between HRV functioning and schizophrenia, beyond its association with a greater administration of antipsychotic medication. Kim et al. (2004) have investigated linear and non-linear measures of HRV in 50 clozapine-treated schizophrenic patients and 50 healthy controls. Symptom severity was assessed administering the Positive and Negative Syndrome Scale (PANSS). Results of the study demonstrated a positive correlation between psychotic symptoms severity and HRV measures (Kim et al.

2004). More recently, Kim et al. (2011) evaluated HRV and symptom severity in 21 patients treated with risperidone and 21 control subjects, finding that the severity of psychotic symptoms was negatively correlated with HRV after controlling for the effects of antipsychotic medications. In particular, symptoms which seemed to be particularly related to HRV deficits were the ones in the dimension of cognitive/disorganization; therefore, the authors hypothesized a potential role of a neuro-autonomic dysfunction in the pathophysiology of specific symptoms of schizophrenia (Kim et al. 2011). Further evidence comes from a study investigating ANS activity in schizophrenic patients and healthy controls, reporting a significantly lower ANS activity in schizophrenic patients with lower scores in the Global Assessment of Functioning (GAS) scale. These findings may have important implications, as they suggest that schizophrenic patients presenting a more severe symptomatology might have a more depressed ANS and greater HRV deficits; accordingly, they may encounter greater risks of cardiovascular events (Fujibayashi et al. 2009).

Similarly, Bar et al. (2012) assessed HRV, cardio-respiratory coupling and breathing rates and depth in acute patients, controls and first-degree relatives, finding that acute patients breathed significantly faster and shallower as compared to the other groups, and they also presented increased amounts of HRV fluctuations. The measures also positively correlated with symptom severity, corroborating previously reported findings (Bar et al. 2012, Fujibayashi et al. 2009). In line with this evidence, Chang et al. (2013) reported that patients with acute schizophrenia exhibited reduced HRV levels as compared to healthy controls, and that the severity of positive symptoms was negatively correlated with cardiac vagal control, so that a more severe symptomatology was associated with greater deficits in HRV.

Overall, most studies seem to suggest a significant correlation between HRV measures and schizophrenia. Although evidence appears to be mixed, this is probably due to small sample size and substantial heterogeneity of investigated indices and measurements used. A recent meta-analysis (Clamor et al. 2016) summarized the existing research on the association between HRV and schizophrenia. Results of the analysis suggest that HRV is significantly reduced in schizophrenia, independently of the considered measurements of vagal activity. Results remained significant independently of long-term or acute episodes, presence or absence of medication (all groups demonstrated reduced vagal activity). In the light of this evidence, the authors suggest that HRV is associated with schizophrenia, independently from severity, antipsychotic administration and disease phase (Clamor et al. 2016).

Autonomic Nervous System Dysregulation in at-risk for psychosis states

Evidence on the correlation between schizophrenia and ANS dysregulation is robust. Yet, literature investigating the presence of ANS deficits in the at-risk population is limited. Most studies investigating autonomic dysregulation in individuals considered to be at risk of psychotic transition focus on the assessment of unaffected first-degree relatives of individuals with psychosis, which are considered to be at significant risk of psychotic transition according to the Comprehensive Assessment of At Risk Mental States (CAARMS, Philips et al. 2005).

Bar et al. (2009) compared cardiac autonomic

functioning (CAF) in 36 patients suffering from paranoid schizophrenia, 36 of their unaffected first-degree relatives (*N*= 18 offsprings and *N*= 18 siblings) and 36 healthy controls. The three groups were subjected to ECG monitoring in order to investigate HRV, QT variability and baroflex sensitivity (BRS). Results revealed significantly reduced HRV and BRS and an increased QT variability in first-degree relatives of individuals affected by schizophrenia as compared to healthy controls (Bar et al. 2009). Interestingly, offsprings of schizophrenic patients demonstrated a particularly reduced HRV as compared to the siblings' group. This suggests that children of schizophrenic patients may be at a particular risk of developing the disorder (Bar et al. 2009). Liu et al. (2016) compared HRV in response to deep breathing in patients with schizophrenia, their first-degree relatives and matched healthy controls. Results revealed that deep breathing induced an increase in HRV following deep breathing; however, such a response was significantly reduced in both schizophrenic patients and their relatives, which suggests a reduced autonomic reactivity to deep breathing in these two groups. The authors concluded that HRV may be considered a genetic marker for schizophrenia (Liu et al. 2016).

A body of evidence investigated the association between ANS dysregulation and healthy first-degree relatives under stress conditions. Castro et al. (2009) administered a mental arithmetic stress task to schizophrenic patients and their unaffected relatives in order to investigate HRV under stress. Results revealed a similar HRV response to the stress test in healthy relatives as compared to the control group; however, the patients' relatives exhibited greater difficulties in the recovery of the HRV resting pattern following the cessation of the stimulus as compared to healthy controls. These results are in line with previous evidence reported by Castro et al. (2008), where schizophrenic patients exhibited a similar autonomic response as compared to healthy controls during the stress task but showed difficulties in recovering the HRV resting pattern when the task was over (Castro et al. 2008). In line with this evidence, in their literature review on cardiac dysfunctions in schizophrenic patients and their first-degree relatives, Bar et al. (2015) report a reduced efferent vagal activity, a decrease in HRV and complex and faster breathing rates in unmedicated patients and first-degree relatives. The presence of HRV deficits in unaffected first-degree relatives of individuals suffering from schizophrenia suggest that the autonomic dysregulation typically found in schizophrenic patients may be associated to a genetic predisposition. Therefore, a close monitoring of first-degree relatives of schizophrenic patients may be very valuable in order to take preventive measures both at a cardiovascular and at a psychopathological level.

Studies investigating autonomic dysregulation in the at-risk population without focusing on first-degree relatives of schizophrenic patients are extremely limited. A recent study has investigated the autonomic stress response of individuals grouped on the basis of their different liability to psychosis (Counotte et al. 2016). In the study, an experimental Virtual Reality design was used in order to examine the autonomic stress response to social exclusion of four groups of individuals: 55 patients who recently transitioned to psychosis, 20 UHR individuals, 42 healthy siblings of individuals suffering from schizophrenia and 53 healthy controls. Social stressors consisted in being virtually exposed to socially challenging situations, such as being part of a ethnic minority status, crowdedness and hostility. Results of the study revealed that the high

liability groups (UHR and psychotic patients) exhibited a diminished HRV as compared to the low liability groups (siblings of psychotic patients and healthy controls), both before and during the experiment. This evidence suggests that individuals who are at-risk for psychosis may also exhibit autonomic deficits.

The findings reported by Clamor et al. (2014) in a similar study seem to point to the opposite direction. The study investigated autonomic alterations in individuals with different degrees of vulnerability to psychosis. Specifically, the authors compared HRV measures among 23 psychotic patients, 21 unaffected first-degree relatives, 23 participants who experienced attenuated positive symptoms, a sample of 24 individuals who had been diagnosed with depression and 24 healthy controls. Results showed that the psychotic patients exhibited the greatest reduction in HRV as compared to the healthy controls. Unexpectedly, however, HRV did not significantly differ in the first-degree relatives and in the attenuated symptoms groups as compared to the healthy controls group. These results would suggest that autonomic dysregulation in schizophrenia may be specifically linked with the manifestation of the disorder itself, rather than being a vulnerability characteristic.

The few studies investigating autonomic dysregulation in samples of individuals at high risk of developing psychosis strongly support the view that future research should also investigate whether ANS dysregulation may be considered as a predictor of schizophrenia. Although limited, the available evidence prompts further research investigating ANS deficits as a marker for the development of psychotic disorders.

Discussion

The reviewed evidence suggests that schizophrenic patients are characterized by autonomic dysregulation, and in particular by a decreased HRV. Several studies have demonstrated an association between autonomic dysregulation and other pathologies, including increased body mass indexes, diastolic pressure, triglycerides, and other metabolic functions (Chung et al. 2013). A reduced complexity in HRV values also seems to be associated with increased complexity in respiration and cardiorespiratory coupling (CRC), leading to an increased risk of cardiovascular diseases (CVD) (Schultz et al. 2015). This could be one of the reasons why schizophrenic patients are at increased risk for cardiac mortality. Accordingly, further examination of the association between ANS functioning and schizophrenia may have crucial implications for the physical and mental health of patients. Given the greater risk of cardiac complications in this population, future research might consider autonomic dysregulation as an objective marker in the monitoring of their cardiovascular health. Further research is also needed in order to evaluate whether ANS dysfunctions can be detected during the prodromal phase of the disorder or whether autonomic deficits arise following the onset. Studies on the at-risk population are limited and have produced mixed findings (Counotte et al. 2016, Clamor et al. 2014), highlighting a clear need to expand this body of research. Follow-up and longitudinal studies are also needed to further investigate whether ANS alterations can be considered as potential risk factors for the development of psychotic disorders. If this was the case, ANS measures could be used alongside BS in the attempt to improve the detection of at-risk individuals before the psychotic transition and allow a more effective intervention.

Conclusions

Prodromal symptoms are often underestimated and dismissed by people who experience them and by society, unaware that they may be potential red flags on a possible future onset (Norman et al. 2005). In contrast, evidence seems to suggest that the prodromal phase of the disorder can be detected several years before the onset of the psychotic symptoms (Klosterkötter et al. 2001). Most importantly, evidence suggests that timeliness in the detection and treatment of BS may have a significant and positive impact in the future course of the disorder. On the basis of this evidence, the detection of at-risk individuals should be considered essential in order to avoid a long Duration of Untreated Psychosis, which has been shown to worsen the course of the disease (Penttilä et al. 2014). Research has developed several constructs in the attempt to recognise schizophrenia's prodromal phase before the onset of psychotic symptoms. However, evidence suggests that we are still far from being able to effectively identify a future schizophrenic onset.

The addition of an autonomically-informed perspective may be useful in order to accomplish the goal of a rapid recognition of the prodromal phase. The evidence summarized in the present work suggests a correlation between ANS functioning and schizophrenia (Clamor et al. 2016, Hamilton et al. 2014). On the light of this evidence, we suggest that future research may investigate measures of autonomic dysregulation in individuals at high risk of psychosis, hypothesizing that ANS abnormalities may be detected before the onset of the disorder and be considered a prodromal symptom. Given the role of social context and social interaction, both in autonomic functioning and schizophrenia, autonomic dysregulation may be investigated in future research during a social interaction task, in order to evaluate its mediating effect on the correlation between HRV and schizophrenia. Given the role of the ANS in stress-related changes, future research may also investigate autonomic deficits in at-risk individuals during a stress-inducing task and in the recovery phase following stress exposure.

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