

Anhedonia in Schizophrenia



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Abstract Anhedonia has long been considered a cardinal symptom of schizophrenia. This symptom is strongly associated with poor functional outcome, and limited

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treatment options are available. While originally conceptualized as an inability to experience pleasure, recent work has consistently shown that individuals with schizophrenia have an intact capacity to experience pleasure in-the-moment. Adjacent work in basic affective neuroscience has broadened the conceptualization of anhedonia to include not only the capacity to experience pleasure but highlights important temporal affective dynamics and decision-making processes that go awry in schizophrenia. Here we detail these mechanisms for emotional and motivational impairment in people with schizophrenia including: (1) initial response to reward; (2) reward anticipation; (3) reward learning; (4) effort-cost decision-making; (5) working memory and cognitive control. We will review studies that utilized various types of rewards (e.g., monetary, social), in order to draw conclusions regarding whether findings vary by reward type. We will then discuss how modern assessment methods may best incorporate each of the mechanisms, to provide a more fine-grained understanding of anhedonia in individuals with schizophrenia. We will close by providing a discussion of relevant future directions.

Keywords Anhedonia · Motivation · Reward · Schizophrenia

1 Anhedonia as a Cardinal Symptom of Schizophrenia

Anhedonia, traditionally defined as the diminished capacity to experience pleasure, has long been considered a core clinical feature of schizophrenia (SZ) and is associated with poor functional outcomes (e.g., Mueser et al. 1991). There are limited treatment options for targeting this critical symptom, partially because the mechanisms driving anhedonia in SZ are not yet fully understood. As such, both the field of SZ research broadly and the Research Domain Criteria (RDoC) initiative have recognized the centrality of examining emotional experience, motivation and incentive processing to better understand mechanisms at play. More specifically, the RDoC Matrix includes a “positive valence” systems (PVS) domain (Insel et al. 2010) outlining several constructs that may be critical to understanding mechanisms of anhedonia and motivational impairments in SZ. We describe various components of the RDoC PVS below.

2 A Heuristic Model of the Motivation-Action-Outcome Pathway

The RDoC PVS contains three superordinate constructs: Reward responsiveness, reward learning, and reward valuation. Reward responsiveness includes sub-constructs of initial response to reward, reward anticipation, and reward satiation. Reward learning includes sub-constructs of habit, probabilistic and

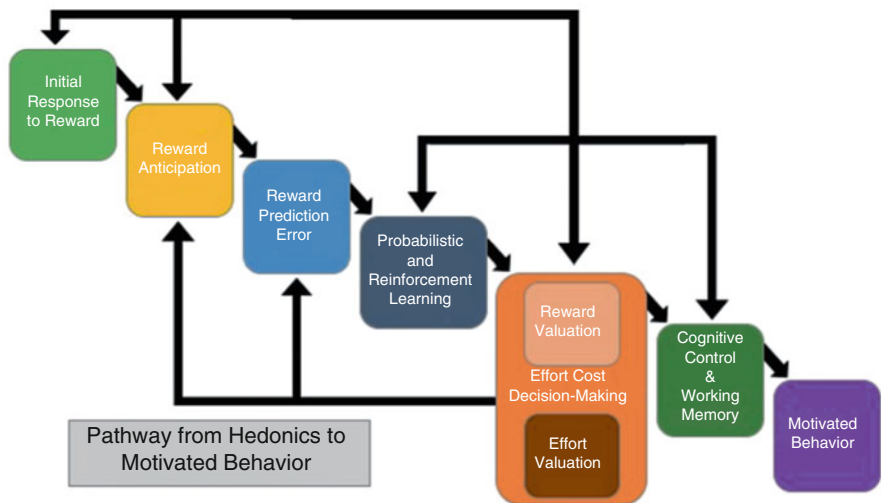


Fig. 1 Pathway from hedonics to motivated behavior

reinforcement learning, and reward prediction error. Reward valuation includes sub-constructs of probability, delay, and effort. Our group has used a complementary model to link experienced or anticipated rewards with the action plans that need to be generated and maintained to obtain these rewards (Kring and Barch 2014). Below, we describe the components within this model, which are thought to be of critical importance when conceptualizing anhedonia in SZ.

In our model (see Fig. 1), the first component is initial response to reward (a subconstruct of reward responsiveness in the RDoC PVS), but has also been referred to as hedonics or liking. Initial response to reward captures the ability to “enjoy” a stimulus or event in the moment, and is what is most closely linked to historical definitions of anhedonia. The second component is reward anticipation (a subconstruct of reward responsiveness in the RDoC PVS) and has also been described as wanting. The third component, probabilistic and reinforcement learning (a subconstruct of reward learning in the RDoC PVS), involves how individuals associate rewarding or punishing outcomes with particular actions (i.e., reward learning). Importantly, such learning can be either implicit (i.e., outside of conscious awareness) or explicit (i.e., including the use of explicit representations about potential reward associations). The fourth component is reward valuation in the RDoC PVS. There are a number of components to reward valuation, including integrating information about the intrinsic hedonic properties of a stimulus, the current state of the organism (Rolls et al. 1989), delay until a reward can occur (Rudebeck et al. 2006), the probability that a reward will occur (Cools et al. 2002), and other potential rewards that are available in the environment. The fifth component in our model is the ability to compute effort relative to reward value (a subconstruct of reward valuation in the RDoC PVS), or what we refer to as effort-cost decision-making (ECDM). ECDM refers to determining the cost of

engaging in actions necessary to obtain a desired outcome and determining how much of that cost you are willing to undertake, or how much effort you are willing to allocate. Finally, the sixth component in our model, cognitive control and working memory (constructs in the cognitive systems RDoC), involves the ability to generate and execute goal-directed action plans necessary to achieve the valued outcome. While not in the RDoC PVS, we consider this component to be an important mechanism for understanding anhedonia as it is necessary to integrate reward information (e.g., anticipatory response, value of reward) while utilizing cognitive systems to generate and maintain internal representations of potential reward to guide behavior. Below we summarize previous research that has examined components of our model in people with SZ.

3 Mechanisms

3.1 *Initial Response to Reward*

A majority of studies show that people with SZ report similar levels of positive emotion in the presence of evocative stimuli (e.g., pictures, film clips, food) relative to controls (see Cohen and Minor 2010 for review). This intact experience of pleasure in response to evocative stimuli has been shown via self-report and psychophysiologic measures (see Kring and Moran 2008 for review). Similarly, neuroimaging studies examining striatal responses to the receipt of monetary rewards in SZ have shown a consistent pattern of intact responses, with robust ventral striatal responses to the receipt of money in patients (see Radua et al. 2015 for review). However, some of these studies did report abnormal cortical responses to reward receipt. For example, prior work has noted reduced reward-related responses in medial prefrontal cortex (PFC) (Schlagenhauf et al. 2009), abnormal responses in both medial and lateral PFC (Waltz et al. 2010), and reduced salience coding in ventrolateral PFC in SZ (Waltz et al. 2010). Additionally, while some have not found evidence of reduced response to positive stimuli in the ventral striatum, this reduced activation was associated with higher anhedonia ratings in SZ (Dowd and Barch 2010).

While asociality, a limited desire to spend time with others, may suggest a reduction in pleasure in social situations, the research is mixed on pleasure in response to social rewards in SZ. Ecological momentary assessment (EMA) literature suggests that while people with SZ report a preference for being alone, they report greater positive emotion when around others than when alone and similar levels of positive emotion when around others relative to controls (see Mote and Fulford 2020 for review). Similarly, individuals with SZ have similar levels of positive emotion during social role play tasks relative to controls (Aghevli et al. 2003; Blanchard et al. 2015). However, while there were no group differences in positive affect following social interactions, higher negative symptoms in SZ were related to less positive affect in response to interactions (Blanchard et al. 2015).

Further, other work suggests that individuals with SZ find smiles less rewarding than controls (Catalano et al. 2018) and show reduced activation for social rewards in the ventral striatum, anterior cingulate, and ventromedial PFC relative to controls (Lee et al. 2019). Thus, across studies there is consistent evidence that people with SZ report experiencing pleasure in response to rewards such as pictures/film clips, monetary rewards, and while spending time with others. This extends to neuroimaging studies showing intact striatal responses to positive pictures (Ursu et al. 2011) or monetary reward (e.g., Dowd and Barch 2012). However, there is also evidence of reduced sensitivity to social reward cues such as a smiling face or cooperative social behavior and this reduced sensitivity may be related to negative symptoms and anhedonia in particular.

3.2 Reward Anticipation and Reinforcement Learning

3.2.1 Reward Anticipation

There is a mixed literature on anticipated pleasure in SZ. For example, some studies assessing anticipatory pleasure via retrospective self-report measures (Gard et al. 2007) and anticipation to evocative stimuli (e.g., pictures) show reduced anticipated pleasure relative to controls (e.g., Moran and Kring 2018). Further, some studies have found that decreased anticipatory responses have been shown to be related to negative symptoms including anhedonia (e.g., Gard et al. 2007). However, other studies do not find a difference in self-reported anticipatory pleasure (Frost and Strauss 2016). While there are relatively few behavioral studies directly measuring reward anticipation/prediction in SZ, these studies show evidence for reduced anticipation (Heerey and Gold 2007; Moran and Kring 2018). Much of the focus instead has been on neuroimaging studies, which have reported reduced ventral striatum activity to cues predicting food (Grimm et al. 2012) or monetary reward in SZ relative to controls (for review, see Radua et al. 2015). These results have been found in unmedicated individuals with SZ (Nielsen et al. 2018) and medicated individuals with SZ (Moran et al. 2019). However, these deficits may not be present in individuals taking atypical medication (Juckel et al. 2006). Other work has noted reduced ventral striatal responses to anticipation cues in antipsychotic-naïve SZ patients, which improved following atypical antipsychotic treatment (Nielsen et al. 2012). In addition, disruptions in ventral striatal activity during anticipation of reward has been associated with anhedonia in SZ (e.g., Dowd and Barch 2012).

Only a handful of studies assessed anticipation of social interactions, with findings suggesting reduced anticipatory pleasure for social interactions/rewards. Laboratory social interaction studies have found that people with SZ anticipated more negative emotion during a social inclusion task (Engel et al. 2016) and anticipate less pleasure for social interactions with smiling partners (Campellone and Kring 2018). Similar to studies examining anticipation of monetary reward, when anticipating a social reward, individuals with SZ showed blunting of striatal

regions relative to controls (Schwarz et al. 2020). And further, an EMA study found a trend in people with SZ anticipating social activities as being less enjoyable than controls (Gard et al. 2014). Thus, consistent with literature showing disrupted anticipatory responses in SZ in response to evocative stimuli and monetary rewards, research suggests disrupted anticipatory responses to social rewards; however, more research is needed to further clarify how and when anticipation for social interactions is disrupted and its relationship to anhedonia.

3.2.2 Reinforcement Learning and Prediction Error

Intriguingly, several behavioral studies have suggested that reinforcement learning in response to monetary gain is intact in SZ when learning is fairly implicit (e.g., Barch et al. 2017). Similarly, several studies using the Weather Prediction task have shown a relatively intact learning rate, but impaired asymptotic performance, which provides mixed evidence for striatal learning impairments (Kéri et al. 2005). When the paradigms become more difficult and require the explicit use of representations about stimulus-reward contingencies, individuals with SZ show more consistent evidence of impaired reinforcement learning (e.g., Culbreth et al. 2016a). Interestingly, these impairments may be greater when individuals with SZ must learn from reward versus from punishment and have consistently been related to anhedonia and motivational impairments in SZ (e.g., Gold et al. 2012). A number of studies have also shown altered prediction error responses (e.g., differences between expected and observed outcomes) in SZ (Radua et al. 2015), both in terms of reductions in responses to unpredicted rewards and larger than expected responses to predicted rewards (Reinen et al. 2016). However, this finding does not appear to be consistent across all patients as other studies have found intact prediction error responses in the striatum among medicated individuals (Culbreth et al. 2017), and even evidence for increased prediction error responses in medicated patients (White et al. 2015). Thus, further work is needed to understand under what conditions prediction error responses are intact in SZ in order to further understand the specific computational mechanisms that may underlie aberrant reinforcement learning.

While the majority of reinforcement learning literature has focused on learning via monetary reward, a growing literature has shown that learning from social rewards (e.g., a smiling face, trusting behavior) follows a similar pattern of learning and activates similar neural circuitry including the ventral striatal and orbital frontal cortex (e.g., Jones et al. 2011). Only a handful of studies have assessed social reinforcement learning in SZ, usually via social trust laboratory tasks. In a series of behavioral trust experiments, people with SZ failed to use social feedback to adapt their trusting behavior, thus suggesting a reduced ability to learn from social rewards relative to controls (Fett et al. 2012; Hanssen et al. 2020). Similarly, another study found that people with SZ showed less trust in smiling partners relative to controls, but were sensitive to negative social outcomes (e.g., scowling face) (Campellone et al. 2016). Thus similar to learning from monetary reward, SZ may be sensitive to

learning from negative but not positive (gaining money, or smiling faces) outcomes but more work is needed on social learning and its symptom correlates in SZ.

3.3 *Effort Valuation*

The last decade has seen a burgeoning of research on effort allocation and its relationship to anhedonia and motivation processing. Physical effort to receive monetary reward studies has found relatively consistent evidence for impairment in SZ (e.g., Reddy et al. 2015). The majority of studies found that the degree of reduction in effort allocation was associated with either negative symptoms (e.g., Gold et al. 2013) or functional status (Barch et al. 2014). Several recent studies have also examined cognitive effort allocation for monetary reward in SZ. One study using a progressive ratio task found evidence for reduced effort allocation in SZ (Wolf et al. 2014). Further, recent work utilizing a cognitive effort paradigm that assesses discounting of rewards as a function of effort found impaired cognitive effort allocation in SZ (Culbreth et al. 2016b). In contrast, others have found little evidence of reduced cognitive effort in SZ, though these studies did suggest that individuals with SZ had difficulty detecting variations in cognitive effort among conditions (Gold et al. 2015).

Only a few studies have examined the neural correlates of aberrant effort-based decision-making in SZ. Our group showed that BOLD activation while making decisions about cognitive effort was similar in controls and SZ participants. However, reduced BOLD activation in the ventral striatum was associated with negative symptoms (Culbreth et al. 2020). Similarly, an additional study showed greater BOLD activation in the ventral striatum during effort-based choice was associated with greater willingness to exert physical effort across both individuals with SZ and control (Huang et al. 2016). Another study showed somewhat surprisingly greater activation of the caudate for individuals with SZ compared to controls as a function of effort. However, this task did not include a choice, but rather required individuals to perform either a hard or easy option, thus it is not clear if these findings relate to the larger effort-based decision-making literature. Based on this small number of studies, the literature suggests potential contributions to effort-based decision-making deficits in SZ from the ventral striatum and that these deficits are related to negative symptoms, though clearly more work is needed in this domain.

To the best of our knowledge, there has only been one study that has examined effort-based decision-making for social rewards in SZ. Participants with SZ and controls completed a button pressing effort task under a social encouragement (e.g., a confederate cheered the participant on) and a neutral condition (e.g., a confederate sat quietly). Both groups showed increased vigor (i.e., more rapid button pressing) during the social encouragement condition, suggesting that people with SZ show normative levels of effort exertion in the context of social encouragement (Fulford et al. 2018). Further, clinician rated social withdrawal was associated with reduced effort across both social and non-social conditions. Thus, while one study suggests

social encouragement has a similar effect on people with and without SZ, further work is needed to understand effort-based decision-making in social contexts and its relationship to anhedonia.

3.4 Cognitive Control and Goal-Directed Action

Numerous reviews have outlined the evidence for impairments in goal representation and cognitive control in SZ (e.g., Barch and Ceaser 2012), as well as the evidence for altered activation, connectivity, and structure of brain regions such as the dorsolateral prefrontal cortex (DLPFC) (e.g., Minzenberg et al. 2009). Several studies suggest that individuals with SZ are not able to improve their performance on cognitive tasks when offered monetary incentives (e.g., Rassovsky et al. 2005). A study examining whether or not individuals with SZ could improve cognitive control on a response inhibition task found that patients were able to speed their responses when presented with specific cues about winning money, and to a certain extent could speed their responses on trials in the reward “context” even when they could not earn money, an effect thought to reflect the maintenance of reward information through proactive control mechanisms. However, individuals with SZ showed a significantly smaller incentive context effect than controls (Mann et al. 2013). In an fMRI study examining whether monetary incentives modulate DLPFC activity during a cognitive control task in SZ, results found no behavioral differences between patients and controls and found a somewhat intact pattern of increased sustained DLPFC activity during rewarded blocks in individuals with SZ as a group. However, individual differences in anhedonia symptom severity were associated with reduced sustained DLPFC activation in the same region that showed overall increased activity as a function of reward (Chung and Barch 2016).

The bulk of research examining the use of rewards to improve cognitive task performance has focused on monetary rewards. However, there is a growing literature examining other forms of rewards such as liquids and social stimuli in healthy populations. In controls, research has found that performance on a cognitive control task was greater on positively valenced liquid feedback trials relative to neutral valenced liquid feedback (e.g., Yee et al. 2016). Work examining social reward’s influence on cognitive control found that social stimuli (i.e., short dynamic facial responses) did not significantly improve cognitive control performance in controls; however, it did relate to greater positive affect suggesting that social feedback was interpreted but may not be as powerful as rewards such as juice or money (Crawford et al. 2020). To the best of our knowledge, no studies have examined social rewards impact on cognitive task performance in SZ but it will be important for future work to examine whether the benefits seen in utilizing monetary rewards to boost cognitive performance extend to other reward types such as liquid or social reward types.

There has also been a myriad of work describing interactions between cognitive control/working memory and reinforcement learning processes in SZ. For example, Collins and colleagues published a series of studies suggesting that working memory

impairments may make a significant contribution to reinforcement learning deficits in SZ (Collins et al. 2017). In addition, there is a literature reporting altered activity in cortical regions involved in cognitive control during anticipation/prediction error (Gilleen et al. 2015) and during reinforcement learning (e.g., Culbreth et al. 2016a). These results are consistent with the literature documenting altered cognitive control function in SZ, and point to a need to examine interactions between these control systems and dopamine-mediated reinforcement learning systems.

4 Using Technology to Assess Anhedonia in Daily Life

Research examining anhedonia in SZ has typically involved relating experimental measures, thought to probe the aforementioned mechanisms of anhedonia, to interview-based assessments of anhedonia. Newer interview-based measures have been developed that better reflect our current understanding of anhedonia in SZ (e.g., Brief Negative Symptom Scale (BNSS) Kirkpatrick et al. 2010; Clinical Assessment Interview for Negative Symptoms (CAINS) Kring et al. 2013), allowing for a more accurate way to examine relationships between experimental tasks and clinical interviews. An adjacent literature has taken advantage of technological advances to assess anhedonia in daily life using mobile-based applications (see Fig. 2). Mobile assessments can capture emotional experience and motivated behavior in a variety of contexts as they unfold (i.e., public settings, with other vs. alone), and these contexts may be integral to understanding anhedonia. Below, we discuss current work in this area and areas for future investigation.

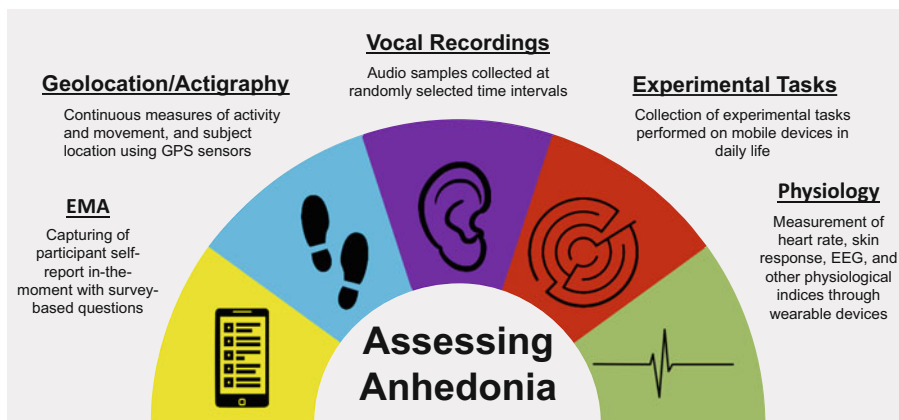


Fig. 2 Methods of assessing anhedonia utilizing mobile technology

4.1 *Ecological Momentary Assessment*

Ecological Momentary Assessment (EMA) utilizes smartphone technology to capture experiences as they occur in daily life (Stone and Shiffman 1994). A number of studies have used EMA to help better understand the emotion and motivation in the daily lives of people with SZ. Studies assessing emotion in daily life typically find that individuals with SZ report less positive and more negative affect when compared to controls (see Cho et al. 2017 for review). While this result may seem to contrast with previously described experimental work suggesting intact hedonic capacity in SZ, it is important to consider that ratings of positive and negative affect via EMA are not necessarily linked to a particular experience or behavior, let alone an experience or behavior that is standardized across participants (e.g., tasting a cookie, receiving money). Thus, EMA helps to extend our understanding of anhedonia in SZ to suggest that while the capacity to experience pleasure in the moment may be intact, the actual experience of pleasure throughout their daily lives may be reduced relative to controls.

EMA studies have also yielded important contextual information by clarifying emotional experience in specific contexts. As reviewed above, in social situations people with SZ report greater levels of positive affect with others compared to being alone, suggesting that social context is important for emotional experience (Mote and Fulford 2020). Further, EMA has aided mechanistic understanding of anhedonia. For example, regarding experience of effort in daily life, one study showed that people with SZ reported engaging in less effortful behaviors and setting less effortful goals than controls (Gard et al. 2014). Taken together, recent EMA studies have begun to delineate how anhedonia may manifest in the daily lives of people with SZ and point to important contexts for future study.

Several recent studies have attempted to integrate EMA methods with experimental tasks to link mechanisms relevant to anhedonia in SZ with measures of daily emotional experience. Our group found that poorer performance on a reward learning task and reduced willingness to expend effort on a physical effort task were related to decreased enjoyment and motivation in daily life (Moran et al. 2017). Similarly, another study linked better performance on a reward learning task to greater dopamine activity in striatal, caudate, and putamen during reward learning and to more reward-related behavior in daily life (Kasanova et al. 2017). Further, another study showed that people with SZ who reported greater anticipatory pleasure in daily life showed greater BOLD activation of putamen, caudate insula, and cingulate when anticipating future reward (Moran et al. 2019). These studies highlight that tasks and clinical assessments thought to tap into mechanisms relevant to EMA are relating to emotional experiences in daily life, thus giving us evidence supporting models developed based on laboratory tests and providing future directions for improved understanding.

4.2 *Mobile Sensing Applications*

A more recent literature is looking to get a snapshot of people outside the laboratory utilizing passive sensing data. Passive sensing allows collection of data outside of self-report to get a sense of a person's functioning across a variety of measures, without burdening the participant with frequent questions. Passive sensing can involve a number of different measures assessed via mobile technology including such things as social behavior (e.g., calls received, text messages sent), physical activity (number of steps taken, GPS location, accelerometer), environmental surroundings (e.g., ambient light, ambient noise), phone usage (e.g., apps used, number of phone pickups), physiologic recordings (e.g., heart rate variability), and sleep (e.g., Ben-Zeev et al. 2016).

Perhaps the most frequently studied metric for passive data in SZ thus far are measures of movement. In terms of actigraphy, lower levels of motor activity have been associated with higher levels of negative symptoms (including anhedonia) in people with SZ (see Wee et al. 2019 for review). Further, multiple GPS studies have found that people with SZ exhibit lower average distance traveled, distance traveled from home, and a higher rate of samples at home when compared to controls (e.g., Depp et al. 2019; Raugh et al. 2020). Importantly, these GPS measures are related to symptoms, such that patients experiencing the greatest severity of anhedonia have the greatest reduction in GPS measures. Thus, participants with SZ demonstrate reduced measures of mobility compared to controls. To date, studies in SZ have not attempted to integrate experimental task with measures of participant mobility, nor have many studies contextualized EMA self-report of daily experience through simultaneous collection of GPS or actigraphy measures. Such analyses represent a critical next step as researchers attempt to understand how anhedonia manifests in the daily lives of SZ patients and attempt to link objective measures of movement to particular experimental task variables. Finally, to the best of our knowledge, only a handful of studies have examined physiologic measures such as electrodermal activity or heart rate variability in psychosis outside of the lab, however, there are a number of exciting avenues for future work (Reinertsen and Clifford 2018). One study did find that combining physiologic measures with EMA outside the lab was feasible in a psychosis population and that variables such as electrodermal activity were significantly related to symptoms reported via EMA (Cella et al. 2019).

In regard to social experience, a few studies have sought to better understand social experience in people with SZ utilizing passive data. For example, one study found that stability in social activity measured via sensing data (e.g., frequency of calls and text messages) was associated with reduced symptoms in a SZ population (He-Yueya et al. 2020). Recent research has also used a collection of short audio or video recordings collected at randomly selected time intervals. These recordings can then be coded for a variety of different social metrics (e.g., number of voices, participant engagement in conversation, vocal intonation, facial expression). For example, one study using this method found that people with SZ interacted with others at similar rates as controls but the quality of the interaction was reduced

relative to controls (Abel et al. 2021). Another study coded these random audio recordings for social interactions and found that they were moderately correlated with measures of clinician rated social functioning measures in SZ, however showed little relationship with EMA ratings of social interaction in daily life (Abel and Minor 2021). A study of vocal and facial features found that both vocal and facial features were significantly related to social engagement and clinician rated negative symptoms (Cohen et al. 2020). Thus, findings suggest that passive sensing data such as audio, video, and phone usage metrics collected in daily life may be a useful way of gaining additional insight into the social functioning and negative symptoms in people with SZ. Future work is needed to continue to clarify what these various data streams relate to and how to code them for questions of interest.

4.3 Deploying Experimental Tasks on Mobile Devices

A small number of studies have begun deploying experimental tasks, similar to those described in the aforementioned sections, onto mobile phones as a means to understand the temporal dynamics of task performance as well as how specific contexts may affect task performance (e.g., Moore et al. 2017; Weizenbaum et al. 2020). For example, one study in elderly participants found that performance on a memory and semantic reasoning task improved following intellectually stimulating activity (Allard et al. 2014). In the domain of reinforcement learning, one study collected repeated tasks assessments on a mobile phone in non-psychiatric healthy controls and found evidence of both slow and fast learning processes over the course of a week (Eldar et al. 2018). However, studies using such methods to probe temporal dynamics and contextual effects of processes relevant to anhedonia in SZ have not been conducted to date, representing an important avenue for future research.

5 Summary

Anhedonia has long been considered a cardinal symptom of SZ, which is strongly associated with poor functional outcome. Throughout this chapter, we have provided evidence for a heuristic model of anhedonia in SZ, wherein disruption of various component processes (e.g., reward anticipation, effort valuation) results in alterations in emotional experience and reductions in motivated behavior. We argue that future research is needed to better clarify the temporal dynamics of such component processes, the contexts in which they extend (e.g., social and monetary rewards) as well as how these processes unfold and manifest in daily life.

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