Aus dem Zentralinstitut für Seelische Gesundheit
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(Direktor: Prof. Dr. med. Andreas Meyer-Lindenberg)

Ambulatory Assessment of Solitude and its Implications for Mental Health

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Anastasia Benedyk
aus
Odessa, Ukraine
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Dekan: Prof. Dr. med. Sergij Goerdt

Referentin: Prof. Dr. med. Dr. phil. Heike Tost

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PREFACE

This cumulative dissertation presents a compilation of research endeavors that have contributed to the exploration of solitude and its ramifications for mental well-being. The listed publications, encompass a longitudinal study investigating responses to the COVID-19 pandemic (Publication 1), and a study exploring physical activity as a mitigating factor for social isolation (Publication 2). Further details are listed below.

Publication 1: **Benedyk A**, Moldavski A, Reichert M, Reinhard I, Lohr SL, Schwarz K, Berhe O, Höflich A, Lautenbach S, von der Goltz C, Ebner-Priemer U, Zipf A, Tost H, Meyer-Lindenberg A: Initial response to the COVID-19 pandemic on real-life well-being, social contact and roaming behavior in patients with schizophrenia, major depression and healthy controls: A longitudinal ecological momentary assessment study. Eur Neuropsychopharmacol. 2023 69:79-83. Epub 2023 Feb 2.

Publication 2: Benedyk A*, Reichert M*, Giurgiu M, Timm I, Reinhard I, Nigg C, Berhe O, Moldavski A, von der Goltz C, Braun U, Ebner-Priemer U, Meyer-Lindenberg A, Tost H: Physical activity as a compensatory mechanism for social isolation: Real-life behavioral and neural circuit markers (Nature Mental Health: accepted, in press)

***These authors contributed equally**

Arbeitsschritte	**Publikation 1**	**Publikation 2**
Konzeption (%)	100	50
Literaturrecherche (%)	90	50
Ethikantrag (%)	50	0
Tierversuchsantrag (%)	N/A	N/A
Datenerhebung (%)	90	50
Datenauswertung (%)	100	70
Ergebnisinterpretation (%)	70	50
Verfassen des Manuskripttextes (%)	80	70
Revision (%)	70	70
Geben Sie an, welche Abbildungen / Abbildungstafeln aus Ihrer Doktorarbeit entstanden sind	All figures of the main manuscript and supplement of this article arose from the dissertation work of A. Benedyk	All figures of the main manuscript and supplement of this article arose from the dissertation work of A. Benedyk
Geben Sie im Einzelnen an, welche Daten/Zahlen/Tabellen auf Forschungsergebnissen von anderen beruhen.	N/A	N/A

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ABBREVIATIONS

AA	Ambulatory Assessment
BIS	Barrat Impulsivity Scale
BMI	Body-Mass-Index
BOLD	Blood-oxygen-level dependent
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impression
CI	Confidence intervall
COVID	Coronavirus disease
CSF	Cerebrospinal fluid
CTQ	Childhood Trauma Questionnaire
DF	Degrees of freedom
DMN	Default mode network
EMA	Ecological Momentary Assessment
EMI	Ecological Momentary Interventions
ERQ	Emotion Regulation Questionnaire
ESM	Experience sampling method
FOV	Field of view
FWHM	Full Width Half Maximum
GIS	Geographic Information System
GPS	Global Positioning System
HC	Healthy controls
ICC	Intraclass correlation coefficient
JITAI	Just-in-time adaptive interventions
LPA	Light physical activity
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major depressive disorder
MDMQ	Multidimensional Mood Questionnaire
MEMS	Micro electro-mechanical systems
MET	Metabolic equivalent of task
MHR	Mental health risk
Mini-DIPS	Diagnostisches Kurz-Interview bei psychischen Störungen
MLM	Multilevel modeling
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient-Echo
MRI	Magnetic resonance imaging
NEO-FFI	NEO Five-Factor Inventory
OR	Odds ratio
PA	Physical activity
PANAS	Positive and Negative Affect Scale
PANSS	Positive and Negative Symptom Scale
PCA	Principal component analysis
PDSD	Perceived desired social distance
RFID	Radio-Frequency Identification
ROI	Region of interest
SCID	Structured Clinical Interview for DSM-IV

SD	Standard deviation
SES	Socioeconomic status
SMI	Severe mental illness
SNS	Self-report of Negative Symptoms
SPQ	Schizotypal Personality Questionnaire
SQL	Structured Query Language
STAI	State-Trait Anxiety Inventory
SZ	Schizophrenia
TE	Echo time
TR	Repetition time
UCLA	University of California Loneliness Scale

All the lonely people, where do they all come from?

The Beatles. 1966.

1 INTRODUCTION

Human beings are social creatures that fundamentally thrive on interpersonal interaction. Despite the inherently social nature, solitude, i.e., being alone without social contact is a ubiquitous and essential component of daily life. Notably, healthy adults spend on average around one third, older people even over 50% of their waking time alone (Danvers et al., 2023; Larson, 1990). Being alone is not only perceived differently over the lifespan (Long & Averill, 2003), but may also have varying impact on mental health depending on lifestyle, environment, and social context (Birditt et al., 2019).
In fact, the lack of meaningful social contact can result in elevated stress levels, feelings of loneliness, and even depression and anxiety (Wolters et al., 2023; Campagne, 2019). Consequently, clinicians consider being alone a serious health risk, especially for emotionally vulnerable individuals (Green, 2023; Riddle, 2021). It is therefore all the worse that those with preexisting severe mental illness (SMI), such as schizophrenia or major depression, are often facing social exclusion, even though they have the same social needs as the general public, including the desire for satisfying relationships and feeling useful (Boardman, 2011; Davidson et al., 2001). With time, prolonged solitude can become a way of life, resulting in social deficits as well as stigmatization (Hareven et al., 2023; Torales et al., 2023; Elmer et al., 2020; Kwapil et al., 2013; Linz & Sturm, 2013). Social deficits, in turn, often lead to inappropriate repetitive social behaviors, causing individuals to withdraw even further from social interactions, creating a vicious circle of permanent isolation (Figure 1.1; Porcelli et al., 2019).

1.1 Social isolation and social withdrawal

In recent years, social isolation has emerged as a growing concern, significantly affecting mental well-being in the general population (Leigh-Hunt et al., 2017). This development is mainly driven by societal and technological changes, not least through social media platforms which, ironically, were originally created to enhance social connections, but have unintentionally contributed to increased social isolation (Primack et al., 2017).
Social isolation is associated with several negative health consequences, including various mental health issues and cardiovascular diseases (Rico-Uribe et al., 2018). Particularly concerning, it affects both mental and physical health, thereby posing a substantial burden which is comparable to well-established and detrimental risk factors

like smoking or high blood pressure (Pantell et al., 2013) and significantly increases premature mortality (Holt-Lunstad et al., 2015; Cornwell & Waite, 2009). Furthermore, social isolation can impair social skills, hinder the development of social competence, and lead to decreased empathy and reduced self-esteem (Preston & Rew, 2022; Porcelli et al., 2019; Leary et al., 2003).

Patients with mental illnesses often face challenges in multiple social dimensions, including reduced social network size (Houtjes et al., 2014; Gayer-Anderson & Morgan, 2013), social anhedonia (Barkus, 2021; Blanchard et al., 2011) as well as impairments in social skills (Robertson et al., 2014; Tse & Bond, 2004) and social motivation (Fulford et al., 2018). This in turn may result in pronounced loneliness and lead to more social withdrawal (Okruszek et al., 2023; Wu et al., 2020; Erzen & Çikrikci, 2018; Lim et al., 2018). In addition, spending extended periods of their time alone at home can often result in exacerbated symptoms, heightened depression, and increased feelings of loneliness (Nagata et al., 2020; de Sousa et al., 2015; Linz & Sturm, 2013). In schizophrenia, social isolation mediates the relationship between symptoms, depression, and suicidal ideation, and increases suicide risk by fostering feelings of exclusion and rejection (Bornheimer et al., 2020; Roy & Pompili, 2009; Horan et al., 2006). Moreover, seclusion can also lead to sensory isolation and trigger psychotic symptoms and formal thought disorder (Daniel & Mason, 2015; de Sousa et al., 2015).

While social isolation is primarily the result of external circumstances, social withdrawal is a more intentional and self-imposed behavioral response. It refers to a behavioral pattern characterized by a deliberate and intentional retreat from social interactions and engagements (Linz & Sturm, 2013). It can therefore arise from factors like social anxiety, where individuals avoid social interactions due to fear of embarrassment, or social anhedonia, where they distance themselves from others because they do not like social company (McEnery et al., 2019; Michail & Birchwood, 2013; Blanchard et al., 2011; Silvia & Kwapil, 2011; Kwapil, 1998). In psychiatric patients, social withdrawal is often linked to negative symptoms like reduced emotional expression, decreased motivation, and impaired social functioning, perpetuating a cycle of isolation, intensifying feelings of loneliness, and exacerbating mental health symptoms (Figure 1.1; Strauss & Cohen, 2017; Lysaker et al., 2012).

Figure 1.1. The vicious circle of social isolation and its implications for mental health

Prolonged solitude, concomitant with reduced social contact, may result in social deficits, which in turn, often lead to social withdrawal, intensifying feelings of loneliness, and exacerbating mental health symptoms.

1.1.1 Loneliness due to social isolation

Throughout history, loneliness has been regarded as a global human phenomenon (Mushtaq et al., 2014), being such a prevalent concern that the United Kingdom even appointed a “minister of Loneliness” in 2018 (Campagne, 2019).

Loneliness, also referred to as perceived social isolation, is characterized by a negative emotional state, stemming from dissatisfaction with the gap between desired and actual social relationships (Campagne, 2019; Coplan & Bowker, 2014). Notably, it does not necessarily depend on a particular level of social connectedness. Individuals may feel lonely in a crowd, with their family, or all by themselves. As Campagne (2019) emphasizes: "alone" is a fact and "lonely" is a feeling. Furthermore, loneliness has significant implications for both mental and physical health and is associated with psychiatric disorders such as depression, anxiety, or substance use, as well as reduced physical activity and adverse physical conditions such as diabetes and cardiovascular diseases (Zhang & Dong, 2022; Mushtaq et al., 2014; van Beljouw et al., 2014).

Understanding the factors and traits associated with experiencing loneliness or cherishing solitude is gaining importance for overall health and well-being across all age groups from adolescents to the elderly (van Beljouw et al., 2014). The complexity of daily life's environmental factors makes it difficult to accurately capture and measure the uniqueness of social contexts and the subjective experience of loneliness within controlled laboratory settings and structured social tasks. This underscores the pressing need for innovative, ecologically valid, and reliable assessment methods capable of addressing these essential dimensions.

1.2 Ambulatory Assessment

Accurate and comprehensive data assessment is crucial in psychiatric research and clinical practice, allowing for the evaluation and understanding of symptoms, treatment outcomes, and individual differences. A novel approach promises to overcome the challenges faced by traditional psychiatric settings, providing a more comprehensive and dynamic understanding of psychiatric conditions in daily life (Reichert et al., 2021; Raugh et al., 2019; Ebner-Priemer & Trull, 2009a; Odgers et al., 2009).

Ambulatory Assessment (AA), akin to portable continuous blood pressure assessment, enables to capture real-time data on patients' experiences, symptoms, and behaviors in their natural environment through brief, repeated assessments over time using mobile and wearable devices (Shiffman et al., 2008). Several limitations of traditional measures can be transcended and valuable insights into the real-life fluctuations and contextual factors influencing mental health gained by integrating AA methods in psychiatric research.

First, the occurrence of the white coat effect (Pickering et al., 1988), where patients may exhibit different behaviors or symptoms due to a clinical setting, can lead to an inaccurate assessment of their true mental health. By assessing individuals in a real-world setting, AA enhances ecological validity and captures momentary variations and contextual factors, such as environmental triggers or social interactions, that contribute to psychiatric symptoms, providing a more comprehensive understanding of their determinants (Myin-Germeys, Birchwood & Kwapil 2011; Ebner-Priemer and Trull 2009b). Second, clinical retrospective assessments rely on patients' recall of past experiences, which can be prone to biases and inaccuracies, leading to incomplete or distorted information (Solhan et al., 2009). AA allows to record momentary feelings by prompting participants to report their experiences and behaviors in real-time or at predetermined intervals, reducing reliance on memory (Shiffman et al., 2008). Third, questionnaires and interviews typically assess symptoms over extended periods, yielding aggregated data that are limited in temporal resolution (Federico et al., 2013). AA on the other hand allows for brief and repeated data assessment, resulting in a high amount of data points that can help to investigate the dynamic nature of mood and psychiatric symptoms as well as their potential changes over time. Fourth, participants may alter their responses due to social desirability concerns, leading to response bias and limited insight into genuine experiences and behaviors (Bispo Júnior, 2022; Beins, 2013). The AA approach allows measurement of the natural environments, providing a more accurate reflection of feelings and behavior in individuals' daily life.

A final notable advantage is the potential for a more individualized, idiographic approach to psychiatric research (Fisher et al., 2018). AA captures person-specific experiences and processes related to symptoms (Zuidersma et al., 2020), which contrasts with traditional nomothetic research that often compares averaged data of patient groups to healthy individuals (Robinson, 2011). Given the significant heterogeneity in the presentation of psychopathology, the need for personalized models in both research and clinical practice has been emphasized, as there is no "average" individual, and treatments effective for some may not work for others, (Habtewold et al., 2020; Wright & Woods, 2020; Fried & Nesse, 2015; Molenaar, 2004).

As a result of the mentioned advantages, AA has gained increasing popularity as both a research methodology and a clinical self-monitoring tool, and has already been utilized to enhance the comprehension of symptoms, mood variability, and contextual influences on psychopathology, encompassing a wide range of mental disorders (Bell et al., 2017; Engel et al., 2016; Walz et al., 2014; Aan Het Rot et al., 2012; Shiffman, 2009).

Active and passive data assessment

Ambulatory Assessment can principally be categorized into two distinct forms, active and passive assessment, each offering unique advantages and insights (Figure 1.2). Active assessment, such as ecological momentary assessment (EMA; Shiffman et al., 2008), also known as experience sampling method (ESM; Larson & Csikszentmihalyi, 1983), involves patients' active engagement in reporting their experiences, symptoms, and behaviors. It allows for the collection of detailed subjective data, capturing present mood and situational context. On the other hand, passive assessment utilizes technology, such as wearable devices or smartphone sensors, to collect objective data without requiring patients' active involvement. This approach provides continuous monitoring of physiological responses, physical activity patterns, and environmental factors (Mestdagh & Dejonckheere, 2021). By combining these techniques, researchers can gain a comprehensive and multidimensional understanding of symptoms related behavior, such as social withdrawal, including subjective experiences, behavioral patterns, and contextual factors (Nisenson et al., 2021; Raugh et al., 2020; Reichert et al., 2021).

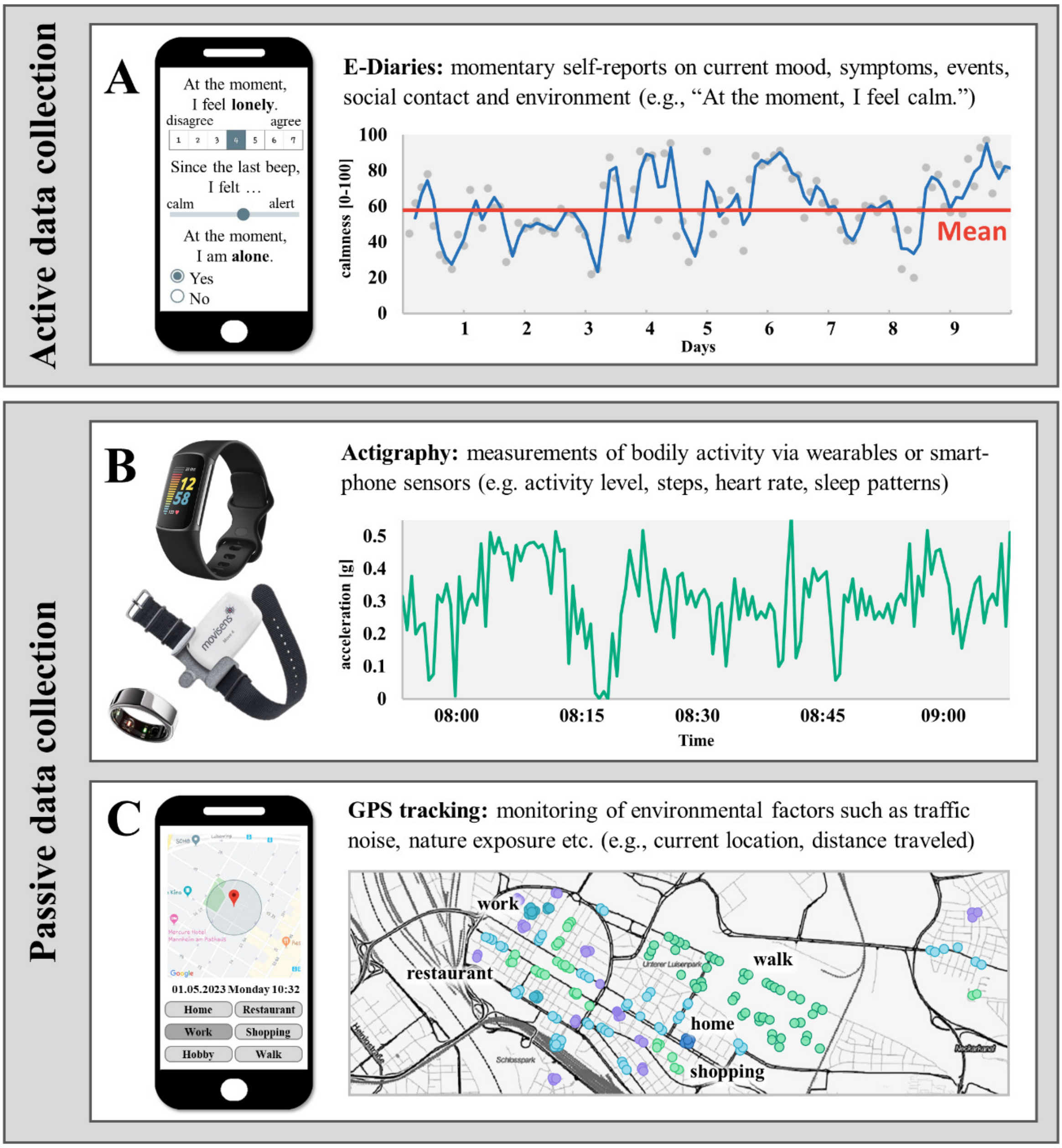

Figure 1.2. Ambulatory Assessment techniques for active and passive data collection

A: Smartphone-based e-diaries gather real-time data through predefined questions, capturing momentary self-reports on mood, thoughts, symptoms, and situational context. Left: A smartphone displaying exemplary daily questions recorded through e-diaries. Right: Illustration of daily mood fluctuations, with orange line indicating the mean value of the displayed period, emphasizing that traditional retrospective assessment can overlook daily variations in emotional states.

B: Wearable sensors enable continuous actigraphy monitoring of physical activity, steps, heart rate, and sleep patterns. Left: Examples of various wearable sensors with integrated accelerometers for daily use. Right: Displaying one-hour movement acceleration data from a wrist-worn accelerometer, which can complement e-diaries in studying physical activity in social settings.

C: Geolocation tracking via GPS provides continuous monitoring of current location and environmental factors like traffic noise and green spaces. Left: Visualization of the labeling procedure used to categorize visited locations. Right: A map displaying visited places and the spatial movement trajectory, providing a comprehensive view of the individual's mobility patterns.

Smartphone image ElisaRiva (http://www.pixabay.com). Map image by © OpenStreetMap contributors (https://www.openstreetmap.org). Displayed sensors: fitbit Charge 5 (https://healthsolutions.fitbit.com), movisens Move 4 (https://www.movisens.com), Oura ring (https://ouraring.com).

1.2.1 Ecological Momentary Assessment: E-diary

Since the widespread affordability of smartphones in the general population, electronic diaries (e-diaries) with predefined questions have facilitated convenient access to daily self-reports on mood, thoughts, activities, and environment. Here, participants respond to queries at predetermined intervals (multiple times per day) that are either prompted (e.g., at fixed or random time points) or self-initiated. Questions, response formats, and sampling strategies highly depend on the research question and the studied population (Bourmand, 2023; Palmier-Claus et al., 2011; Ebner-Priemer & Sawitzki, 2007). The most common sampling schemes are triggered based on specific times, locations or events, including a diverse range of questions which are either rated on a scale (e.g., visual analogue scale: 0 = “not at all”, 100 = “very much”; 7-point Likert scale) or provided with a single or multiple choice format. In the field of psychiatry, questions often relate to symptoms such as feelings of loneliness, anxiety, avolition, or auditory hallucinations. Currently, while most EMA studies last approximately 1-2 weeks (Vachon et al., 2019), the importance of longitudinal assessments is becoming more prominent (Reichert et al., 2021; Raugh et al., 2019).

E-diary studies have shown that processes once thought to be stable can exhibit significant day-to-day variations, challenging previous assumptions (Reichert et al., 2021; Buck et al., 2019). For instance, research revealed remarkable fluctuations of emotions, and affective states (Santangelo et al., 2014; Chepenik et al., 2006) or more intense and variable negative emotions in schizophrenia than in healthy controls (Myin-Germeys, Delespaul, & de Vries 2000). These findings underscore the dynamic nature of psychological processes and the relevance of capturing real-life fluctuations in understanding mental health conditions.

Moreover, e-diaries have emerged as valuable tools to capture and investigate social context in psychiatric patient populations, providing real-time insights into, e.g., social interactions, support networks, and perceived social connectedness. Numerous EMA studies have already investigated social functioning in the daily life of patients with schizophrenia and depression by assessing their preferences and amount of time spending alone, involvement in interactions, or the influence of the presence of others (Mote & Fulford, 2020; Colombo et al., 2019; Liu et al., 2019).

1.2.2 Mobile Sensing: Actigraphy and geolocation tracking

Passive data collection of contextual factors through smart devices has emerged as an objective and less obtrusive approach for individuals with psychiatric disorders, offering advantages over traditional self-reports such as continuous monitoring, instant feedback, and increased accuracy (Mestdagh & Dejonckheere, 2021; Cornet & Holden, 2018; Aung et al., 2017). Contextual factors play a pivotal role in shaping human behavior, emotions, and thoughts. For instance, the presence or absence of others can significantly influence individuals' feelings and behaviors, whether they are with their partner, a group of strangers, or alone. Similarly, different settings such as home, work, public, or clinical visits elicit distinct emotional and behavioral responses (Reichert et al., 2021).

Currently, researchers are recognizing the potential of passive smartphone sensing in mental health research for evaluating well-being, understanding mental illness, maintaining mental health, and exploring relationships between sensor parameters and psychiatric psychopathology (Cornet & Holden, 2018; Aung et al., 2017). Passive monitoring offers advantages not only by circumventing self-report pitfalls like active self-evaluation, but is also potentially detecting responses individuals are not consciously aware of (Difrancesco et al., 2019; Carpenter et al., 2016; Doberenz et al., 2011). Moreover, passive collection allows for a high number of variables, meaning that more measures can be collected without increasing participant burden (Raugh et al., 2019). Mobile sensing offers various approaches and technologies to track social interactions, such as Bluetooth and Radio-Frequency Identification (RFID) for detecting nearby devices, with ongoing developments in this field (Reichert et al., 2021). For example, a portable electronically activated recorder (EAR) periodically records snippets of ambient sounds from participants' momentary experience, facilitating the assessment and understanding of audible aspects of social environments and interactions (Mehl, 2017). Another objective and easy-to-use smartwatch-based social sensor, SocialBit, is under development and validation, with an algorithm capable of distinguishing speakers and conversation partners, enabling passive identification of ongoing social interactions (White et al., 2023).

Furthermore, various passive digital phenotyping variables can be gathered, which could have implications for social behavior. These variables include data of phone usage (e.g., call/text logs, Bluetooth connectivity), physical activity (e.g., exercise), social media usage (e.g., time spent on Facebook), geolocation information (GPS coordinates; e.g., specific locations), and speech samples obtained from ambient sound. Digital activity, such as phone call duration or social media usage, not only predict changes in affective state, illness severity and relapses but also provide insights into social behavior of psychiatric patients (Miller et al., 2022; Ebner-Priemer et al., 2020; Barnett et al., 2018). Studies have shown that in bipolar disorder, increased digital activity is linked to mania, while reduced outgoing texts are associated with depression (Beiwinkel et al., 2016; Faurholt-Jepsen et al., 2014). Furthermore, Lüscher et al. (2019) employed a blend of self-reports and multimodal affect recognition methods, including speech transcriptions, to investigate how social support and communication influence dyadic diabetes management in couples' daily lives, potentially offering a transferable approach to assessing the significance of social support in the field of psychiatry, where it holds similar importance.

In the further course, I will concentrate on two passive methods for assessing behavioral and environmental parameters using actigraphy and geolocation tracking.

Actigraphy

Recent advancements in integrated smartphone and wearable sensors, such as accelerometers, have opened up an exciting opportunity for continuous monitoring of participants' activity patterns with minimal burden. Accelerometers, such as micro electro-mechanical systems (MEMS), enable objective tracking of physical activity in daily live. They measure changes in acceleration in three axes (horizontal right-left (X), vertical (Y), and horizontal front-back (Z)), including both static forces, such as the earth's gravity, and dynamic forces resulting from movement.

Commonly used in sports science, these devices can be effectively used to investigate severe mental illness in various daily contexts, offering the potential for greater accuracy than self-reports (Kruisdijk et al., 2017). They have been recommended as valuable tools for assessing physical activity, including sedentary behavior and daily step counts, in various patient populations with different symptoms (Strauss et al., 2022; Strassnig, Harvey, et al., 2021; Collier et al., 2018; Reichert et al., 2015; Burton et al., 2013). Previous research has shown that activity patterns cannot only distinguish between different disorders but also between specific mood states, such as mania and depression (Krane-Gartiser et al., 2014; Burton et al., 2013).

Furthermore, studies employing actigraphy have successfully identified psychomotor retardation (Roberts et al., 2020; Vahia & Sewell, 2016; Reichert et al., 2015; Krane-

Gartiser et al., 2014) and disrupted sleep patterns associated with mental illnesses (Wainberg et al., 2021). Moreover, daily activity can be remotely assessed via combined heart rate and movement sensors to monitor activity energy expenditure across various psychiatric disorders (Maatoug et al., 2022; Miller et al., 2022; Liang et al., 2019; Faurholt-Jepsen et al., 2016). Remarkably, patients show a high level of acceptance and demonstrate good compliance with these methods (Raugh et al., 2021; Kruisdijk et al., 2017; Naslund, Aschbrenner, & Bartels, 2016).

By providing detailed information on patients' daily functioning and movement patterns, accelerometry has further the potential to support the investigation of mental health conditions (Miller et al., 2022; Reichert et al., 2021).

Geolocation tracking

In our daily lives, humans are exposed to a wide range of environmental influences that can significantly affect their mental well-being, with some factors like green spaces and social interactions known to enhance resilience, while others, such as air pollutants and traffic noises, have been linked to an elevated risk of psychiatric disorders (Reichert & Braun et al., 2020; Tost et al., 2019). GPS (Global Positioning System) and magnetometer technologies, along with barometers for weather assessment, enable precise geolocation tracking and offer insights into individuals' movements, spatial behavior, activity patterns, and environmental exposure.

While commonly used across various fields, these technologies have also found application in psychiatry for monitoring and comprehending the daily activities and mobility patterns of individuals with mental health conditions. Geolocation tracking is a powerful approach for objectively assessing social interactions, engagement, and isolation by capturing individuals' real-time locations and movements, contributing to a comprehensive understanding of the social context in psychiatric patients. This combination, coupled with EMA self-reports, has shown promise as a more accurate predictor of symptoms (Raugh et al., 2020), offering valuable insights into mental health conditions and aiding in the development of informed interventions and treatment strategies (Depp et al., 2019).

Studies using GPS monitoring have revealed that individuals with schizophrenia tend to travel shorter distances and spend more time at home (Depp et al., 2019). Geolocation data may offer an objective tool for assessing negative symptoms, with GPS showing stronger correlations with behavioral aspects of asociality, avolition, and anhedonia in individuals with schizophrenia and bipolar disorder (Raugh et al., 2020).

Notably, shorter travel distances and proximity to home are associated with decreased motivation and greater negative symptom severity (Depp et al., 2019).

By objectively capturing patients' spatial behavior, activity patterns, and self-reports, mobile sensing may provide a deeper understanding of how social interactions influence daily functioning, activity participation, and overall well-being of psychiatric patients.

2 EMPIRICAL STUDIES

2.1 Research questions and hypotheses

Conventional experiments usually take place under laboratory conditions. However, since we are interested in the role of social contact on daily well-being, it is important to collect data from an ecologically valid, everyday environment. Therefore, we investigated how AA can be used in different populations, from healthy subjects to psychiatric patients, to measure everyday mood and environmental context. Here, we examine different everyday factors, such as well-being, loneliness, and social contact, which were assessed under the COVID-19 related restrictions, in psychiatric populations. We also looked into the influence of social company on well-being and how physical activity can be used to compensate for social interactions that are currently lacking.

In study 1, we investigated the impact of the COVID-19 pandemic on the daily-life experiences of individuals with preexisting severe mental illnesses, specifically schizophrenia and major depression, compared to healthy participants. Here, we used longitudinal EMA and mobile sensing data before and during the beginning of the first and second pandemic waves in Germany. The primary hypothesis was that psychiatric patients might experience a worsening of well-being during the pandemic due to factors such as loneliness, anxiety, and social isolation.

In study 2, we aimed to explore the effect of momentary solitude and physical activity on the mood and loneliness of healthy young adults using intensive longitudinal real-life and neuroimaging data. The main goal was to examine the potential of physical activity as an accessible and effective resilience strategy to mitigate the negative affective impact of social isolation on mental health and to investigate whether some individuals benefit more than others. Since social isolation and loneliness pose major societal challenges whose global spread has been accelerated by the COVID-19 pandemic, a sample of healthy adults collected during this period was also investigated.

Please note that several parts of this thesis have already been published (Study 1: Benedyk et al., 2023) or are about to be published (Study 2: Benedyk & Reichert et al., 2024, in press at Nature Mental Health) by the doctoral candidate as a shared first author. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications.

2.2 Study 1. Initial response to the COVID-19 pandemic on real-life affective well-being, social contact and roaming behavior in patients with schizophrenia, major depression and healthy controls

2.2.1 Abstract

The COVID-19 pandemic strongly impacted people's daily lives. However, it remains unknown how the pandemic situation affects daily-life experiences of individuals with preexisting severe mental illnesses (SMI). In this real-life longitudinal study, the acute onset of the COVID-19 pandemic in Germany did not cause the already low everyday affective well-being of patients with schizophrenia (SZ) or major depression (MDD) to decrease further. On the contrary, healthy participants' well-being, anxiety, social isolation, and mobility worsened, especially in healthy individuals at risk for mental disorder, but remained above the levels seen in patients. Despite being stressful for healthy individuals at risk for mental disorder, the COVID-19 pandemic had little additional influence on daily-life well-being in psychiatric patients with SMI. This highlights the need for preventive action and targeted support of this vulnerable population.

2.2.2 Introduction

The COVID-19 pandemic has a pervasive impact on people's daily lives (Haleem, Javaid et al. 2020). While many psychiatrists were especially concerned about a potential worsening of symptoms in individuals already suffering from severe mental illnesses (SMI; Unützer et al., 2020; Yao et al., 2020) stress caused by the social isolation and other life restrictions resulting from the COVID-19 pandemic can also lead to significant mental health impairments in healthy individuals, especially those at risk for mental disorder (Berhe et al., 2023). This is suggested by a worldwide increase in fear (Brülhart et al., 2021; Betsch, 2020) and a slight and transient increase in symptoms, especially related to depression, during the first pandemic phase in the general population (Robinson et al., 2022).

Here, we therefore aimed to investigate how initial pandemic-driven events affected well-being of patients with schizophrenia spectrum disorder (SZ) or major depression (MDD) as well as healthy controls (HC) with different levels of mental health risk, using longitudinal ecological momentary assessment (EMA) and mobile sensing data before (preacute) and during (acute) the first and second waves of the COVID-19 pandemic in Germany (Figure 2.1A).

2.2.3 Materials and Methods

Participants provided written informed consent approved by the institutional review board of Heidelberg University, Germany. Three groups of participants (n = 20 [SZ], n = 24 [MDD] and n = 21 [HC]) were subjected to an EMA protocol (smartphone-based self-ratings, step counter, real-life GPS location tracking) and psychological inventories (Figure 2.1B) across 24 weeks. Participants reported twice a day on their daily-life well-being (valence, energy, calmness), social context (loneliness, being alone) and anxiety level (fearfulness) using e-diaries (details in supplement).

First, to test whether patients' e-diary ratings differed from HC, we evaluated the full sample (n=65) across the whole measurement period (February-November 2020, including both infection waves).

Second, to investigate the effect of the COVID-19 pandemic on participants' daily experiences, we considered two independent samples during the first (n = 23; 02/01/20 – 03/31/20) and second (n=31; 09/14/20 – 10/30/20) infection waves separately. For each wave, we divided the relevant time period into two non-overlapping phases. Here, we defined preacute (6 weeks) and acute (2 weeks) phases, representing time periods before and during the peak of a given wave, respectively (Figure 2.1A). Outcome measures, representing relevant aspects of daily-life that were potentially influenced by the pandemic situation, i.e., well-being, anxiety, social isolation and mobility (Figure 2.2), were analyzed using multilevel models with group (SZ, MDD, HC) and phase (preacute, acute) as predictors, and time of day, time of day squared (level 1), and sex (level 2) as covariates.

Third, we compared ratings of HC before the first and second waves. Finally, we explored whether healthy individuals that are at risk for mental disorder (indexed by, e.g., pathological personality traits) are particularly vulnerable to the COVID-19 pandemic. For this, we included a mental health risk factor (MHR), derived from a principal component analysis of mental health risk measures, as a moderator in our multilevel models (see supplement, Table 2.3).

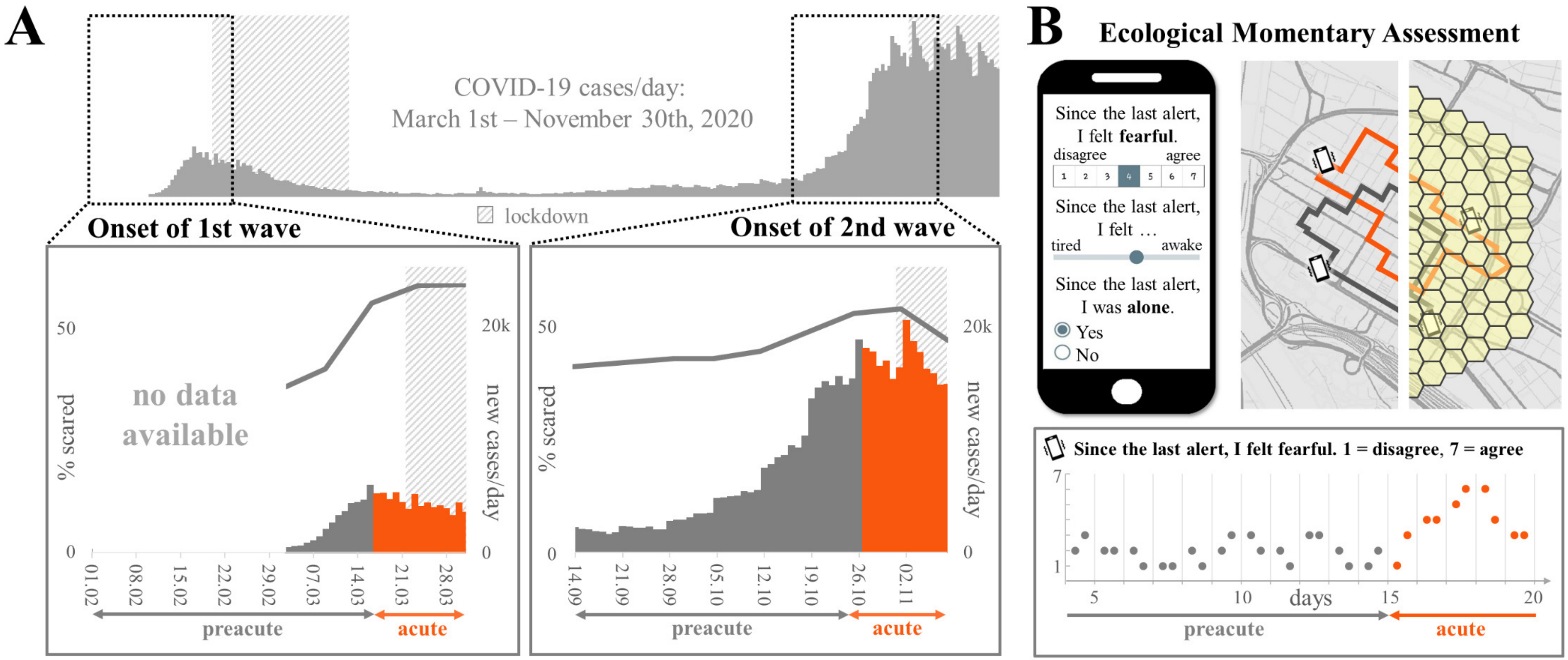

Figure 2.1. Definition of time phases and methods

A: Preacute and acute phases based on the course of two waves of increasing COVID-19 infection cases per day from 1st March – 30th November 2020 in Germany (right y axis; provided by Robert Koch Institute, https://rki.de). Dashed areas indicate government-mandated lockdowns in Germany, including restrictions of social contacts and stay-at-home recommendations. Fear ratings in the general population assessed in a weekly survey among 1000 participants (left y-axis; https://projekte.uni-erfurt.de/cosmo2020/web/).

B: Ecological Momentary Assessment: Descriptive illustration of smartphone-based daily-life assessments with simulated e-diary items (left), ratings (smartphone trigger points) and spatial movement trajectory overlayed by equilar hexagons (cells). Smartphone image by ElisaRiva (http://www.pixabay.com), map image by © OpenStreetMap contributors (https://www.openstreetmap.org/).

2.2.4 Results

Consistent with prior literature (Schneider et al., 2017; Myin-Germeys et al., 2003), both patient groups reported reduced well-being (SZ: valence: $p \leq 0.040$, MDD: valence, energy, calmness: p-values < 0.001), increased anxiety level (SZ and MDD: fearful $p \leq 0.004$), and social isolation (SZ: lonely, alone: p-values ≤ 0.025; MDD: lonely: $p < 0.002$) as compared to HC across the whole sample and measurement period. SZ patients engaged in more physical activity (i.e.,steps) compared to MDD patients ($p = 0.038$), but spatial mobility was not different between groups (cells: $p > 0.07$).

During the first wave (Figure 2.2B), we observed a decrease in well-being (valence, calmness: p-values < 0.001) as well as an increase in anxiety (fearful: $p < 0.001$) among HC. In contrast, patients showed a slight improvement (SZ: valence, energy, calmness, fearful: p-values < 0.010, MDD: calmness, fearful: p-values < 0.038) or no change in affective ratings (MDD: valence, energy: p-values > 0.05). In line with governmental stay-at-home recommendations, MDD and HC groups spent more time alone (alone: $p \leq 0.026$) and all groups took fewer steps (steps: $p \leq 0.003$).

During the second wave (Figure 2.2C), we observed a similar improvement in the well-being of SZ patients as during the first wave (valence, energy: p-values < 0.017), with a slight increase in fearfulness (fearful: $p < 0.001$). MDD patients' well-being remained stably low (all p-values > 0.05), while fearfulness and loneliness improved (fearful, lonely: p-values < 0.008). Time spent alone, the number of steps, and spatial roaming did not change in any group.

Interestingly, the HC tended to show decreased well-being (valence: $p = 0.052$, energy: $p = 0.056$, calmness: $p = 0.042$) before the second wave compared to ratings of HC before the first wave (Figure 2.3A). Moreover, HC showed no changes in any rating during the second wave (all p-values > 0.05; Figure 2.2C).

Finally, our analysis revealed a significant moderating role of a general mental health risk factor in rating changes from preacute to acute phases of the first wave. Here, HC with median to high MHR showed the strongest negative change in ratings (valence, calmness, fearful: p-values < 0.001; Figure 2.3B).

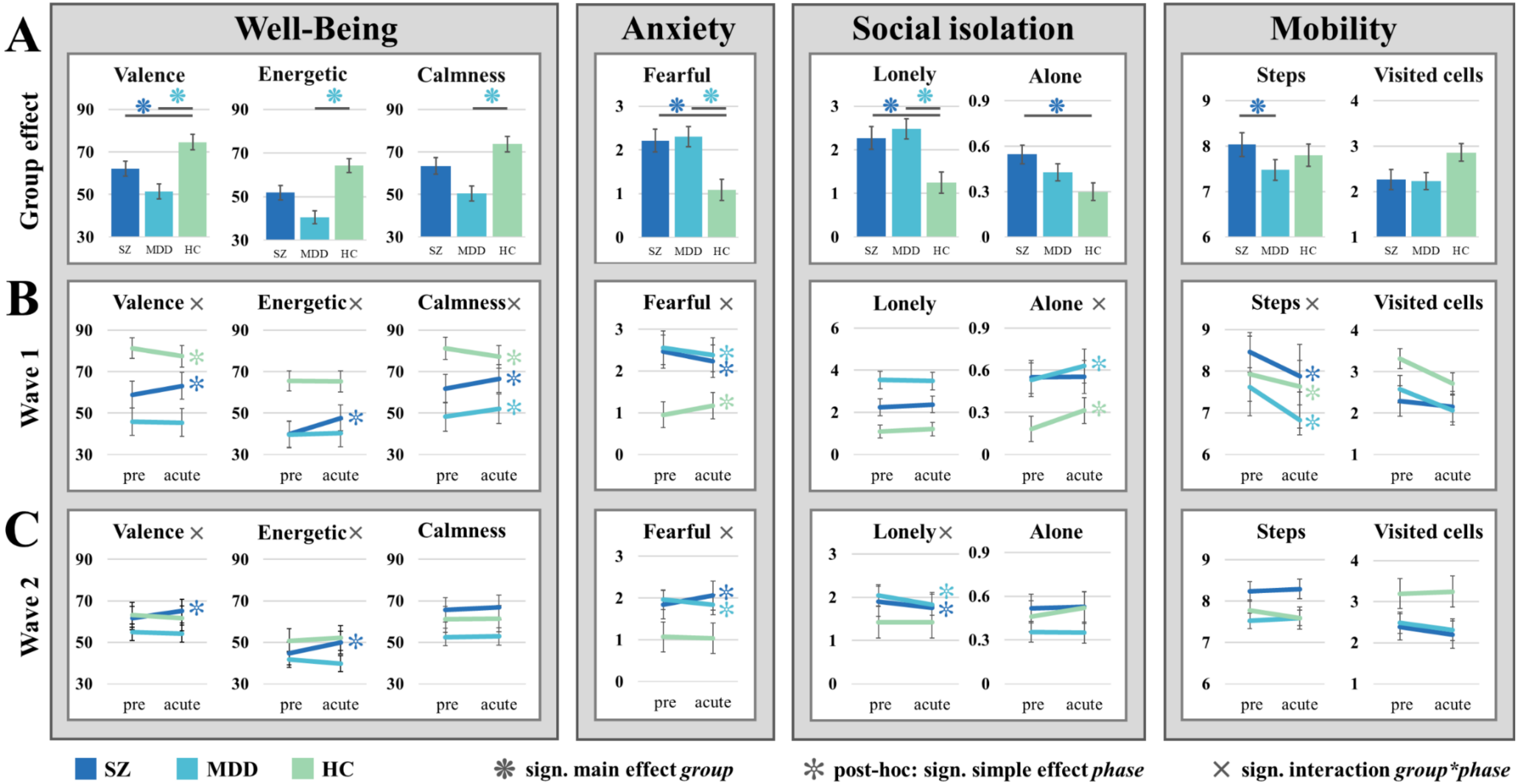

Figure 2.2. Effects of group and wave

A: General differences between patient groups and healthy controls (n=65) in each e-diary item. Significant group effects are marked with an asterisk ∗.

B: Comparison of e-diary ratings during preacute (02/01/20 – 03/17/20) and acute phases (03/18/20 – 03/31/20) of the first wave (n=23) of increasing COVID-19 infection cases.

C: Comparison of e-diary ratings during preacute (09/14/20 – 10/26/20) and acute phases (10/27/20 – 11/10/20) of the second wave (n=31) of increasing COVID-19 infection cases. Significant group*phase interactions are marked with a cross ×. Significant post-hoc tests preacute vs. acute are marked with an asterisk ✻. All p-values are Bonferroni-Holm corrected.

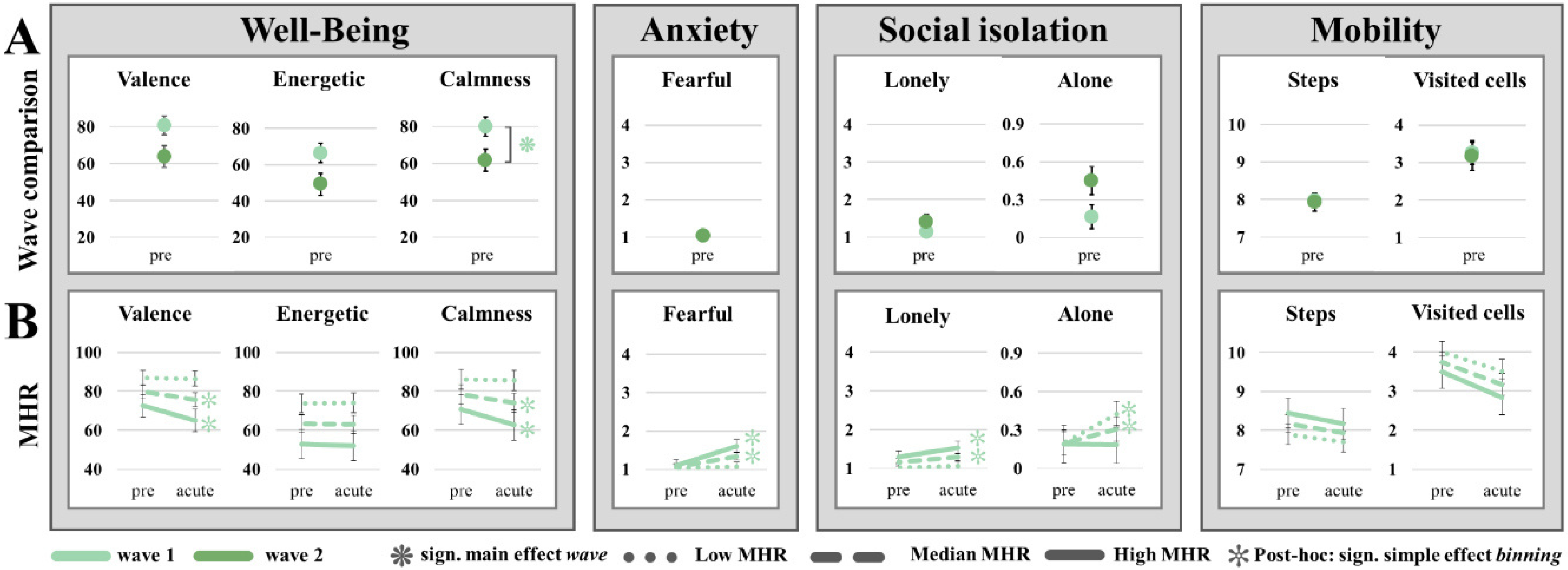

Figure 2.3. Wave comparison and mental health risk in healthy controls

A: Comparison of HC ratings before wave 1 and wave 2. Significant wave effect is marked with an asterisk ∗.

B: Interaction effects phase*MHR (mental health risk) in HC during the first wave divided by groups and 25 percentile (low MHR), median and 75 percentile (high MHR) of subjective MHR loadings. Significant post-hoc tests preacute vs. acute are marked with an asterisk ✻.

2.2.5 Discussion

Despite the initial concern of many psychiatrists about a mental health deterioration of psychiatric patients during the pandemic (Unützer et al., 2020; H. Yao et al., 2020), we found no evidence for a negative impact of the pandemic situation on daily-life well-being in our patient samples beyond the highly significant reduction in well-being associated with diagnosis. This stability could be attributed to various factors. First, almost all patients had access to mental health services, including medication (SZ: n = 15; MDD: n = 18) which might have buffered the adverse impact of the pandemic. Second, avoidance strategies (e.g., social withdrawal), normally maladaptive, temporarily transformed into beneficial and socially accepted coping behavior during pandemic restrictions. Third, the reduction in everyday stressors during the stay-at-home period (Pirkis et al., 2021) may have outweighed the negative impact of isolation for this population. Finally, the stigma of loneliness may have eased during a time where social isolation was proscribed.

Among healthy controls, however, we found a change in ratings during the acute phase of the first wave, which corresponds to the increase in fear, concern, and worry in the general population (Betsch, 2020; Shi et al., 2020). Interestingly, HC entered the second wave with an already reduced well-being (as compared to the first wave), which remained stable at a low level during the acute phase.

Moreover, an initial increase in anxiety and a reduction in well-being during the first wave was most pronounced in healthy individuals with high MHR load. This suggests that at-risk individuals among the healthy were especially prone to pandemic-related stressors. Vulnerability-stress models, such as the hopelessness theory (Alloy et al., 1988), may explain the increasing prevalence in mental health problems among previously healthy individuals who experienced negative pandemic related conditions.

While we are aware that a small sample size may affect statistical power, the number of prompts provided within (level 1) and across (level 2) all participants was quite high. Thus, there was sufficient power assumed to detect general differences across and between groups (SZ, MDD, HC), phases (preacute, acute), and waves (first, second). Moreover, the reported results in psychiatric patients resemble clinical characteristics of previously reported large cohorts (Fountoulakis et al., 2019; van Noorden et al., 2012).

In summary, the prospective design of this study and the prepandemic real-time data in SMI patients and HC offer the opportunity to observe effects of the pandemic onset as they unfold on an intra-individual level. As shown, stressful events, such as the COVID-19 pandemic, have a more pronounced negative influence on the mental states of at-risk healthy individuals rather than patients suffering from SMI. This highlights the need for preventive action as well as targeted support of this vulnerable population. Nonetheless, further investigations are needed to better understand the specific effects of threatening circumstances, such as pandemic outbreaks, on the mental health of both patients and healthy individuals.

2.2.6 Supplementary Material

Participants and study procedures

A group of 65 participants (20 patients with schizophrenia (SZ), 24 patients with major depressive disorder (MDD) and 21 healthy controls (HC)) were recruited as part of a longitudinal naturalistic study for multimodal characterization of negative symptoms with a total assessment period of 24 weeks. Of those participants, 23 subjects were enrolled prior to 03/17/2020, i.e., before the first wave of COVID-19 related infection cases and 32 subjects were enrolled prior to 10/03/2020, i.e., before the second wave of COVID-19 related infection cases in Germany.

Participants were included in the study if they were between 18 and 60 years of age and matched no standard MRI exclusion criteria (e.g., pregnancy, claustrophobia, pacemaker etc.). Patients with a confirmed diagnosis of SZ or MDD with at least mild to moderate negative symptoms and without current alcohol or drug dependence were recruited from inpatient and outpatient treatment facilities at the Central Institute of Mental Health (CIMH), in Mannheim, Germany. HCs were recruited from the local community by advertisement. Psychiatric diagnoses were confirmed by trained clinical interviewers using the Mini-DIPS Neuropsychiatric Interview (Margraf et al., 2017) for both patient groups. Exclusion criteria for HC included a lifetime history of significant general medical, psychiatric, or neurological illness, prior psychotropic pharmacological treatment or head trauma. All participants provided written informed consent for protocols approved by the institutional review boards of the Medical Faculty Mannheim of the University of Heidelberg. This study was approved by the Medical Ethics Committee II of the Medical Faculty Mannheim at the Ruprecht-Karls-University in Heidelberg, Germany.

Table 2.1. Demographic and clinical characteristics

Measure	Group						Group comparison		
	Schizophrenia Group (SZ)		Major Depression Group (MDD)		Healthy Controls Group (HC)				
n = 65	**n = 20**		**n = 24**		**n = 21**				
	Mean	**SD[1]**	**Mean**	**SD[1]**	**Mean**	**SD[1]**	**F or χ^2 value**	**p-value**	
Demographic variables									
Age [years]	34.6	10.3	38.0	13.5	38.5	11.1	0.69 (2; 62)	0.503	
Gender (male/female)	15/5		9/15		11/10		6.2 (2)	**0.045***	**SZ ≠ MDD**
Psychological variables									
PANSS pos.	13.4	5.6	8.2	1.2	7.1	0.3	22.96 (2; 62)	**<0.001***	**SZ ≠ HC, SZ ≠ MDD**
PANSS neg.	19.1	6.6	11.3	3.5	7.4	0.9	40.24 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC, SZ ≠ MDD**
PANSS gen.	31.7	9.6	27.3	5.1	16.3	0.7	33.70 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
PANSS total	64.2	18.8	46.8	7.6	30.9	1.3	43.33 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC, SZ ≠ MDD**
MADRS	12.7	7.1	15.3	5.9	0.6	1.2	46.28 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
CGI	4.3	0.9	3.8	0.9	1.0	0	124.42 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
SNS	15.0	8.0	17.9	4.7	3.5	3.7	39.51 (2; 62)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
Premorbid intelligence	106.8	12.8	116.1	13.5	111.6	12.6	2.78 (2; 60)	0.070	
Ambulatory Assessment									
Prompts (n)	4073		5239		5013		0.93 (2; 62)	0.400	
Compliance [%]	76.2	16.8	74.6	17.5	80.7	14.2	1.56 (2; 62)	0.219	
Wave 1 (n = 23)	**n = 7**		**n = 6**		**n = 10**				
	Mean	**SD[1]**	**Mean**	**SD[1]**	**Mean**	**SD[1]**	**F or χ^2 value**	**p-value**	
Demographic variables									
Age [years]	35.4	12.1	38.8	15.5	36.4	9.6	0.14 (2;20)	0.874	
Gender (male/female)	7/0		1/5		3/7		11.24 (2)	**0.004***	**SZ ≠ HC, SZ ≠ MDD**
Psychological variables									
PANSS pos.	14.1	5.9	8.5	0.8	7.2	0.3	9.78 (2; 20)	**0.001***	**SZ ≠ HC, SZ ≠ MDD**
PANSS neg.	17.0	4.2	13.0	3.3	7.4	0.7	23.53 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC, SZ ≠ MDD**
PANSS gen.	31.4	10.3	29.7	2.9	16.4	0.8	16.76 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
PANSS total	62.6	16.0	51.2	4.8	31.0	1.3	25.99 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC, SZ ≠ MDD**
MADRS	11.1	8.0	17.0	5.4	1.0	1.6	18.81 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
CGI	4.1	0.9	4.3	1.0	1.0	0.0	58.01 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
SNS	13.1	10.5	18.5	2.4	3.6	4.2	13.87 (2; 20)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
Premorbid intelligence	106.4	9.0	126.3	14.4	107.9	9.6	6.71 (2; 19)	**0.006***	**MDD ≠ HC, SZ ≠ MDD**
Ambulatory Assessment									
Prompts (n)	470		463		869		0.7 (2; 20)	0.510	
Compliance [%]	76.1	20.0	64.4	16.9	78.2	15.4	1.61 (2; 20)	0.220	
Wave 2 (n = 31)	**n = 8**		**n = 16**		**n = 7**				
	Mean	**SD[1]**	**Mean**	**SD[1]**	**Mean**	**SD[1]**	**F or χ^2 value**	**p-value**	
Demographic variables									
Age [years]	34.6	6.0	37.2	13.0	40.6	12.9	0.49 (2;28)	0.617	
Gender (male/female)	5/3		7/9		4/3		0.86 (2)	0.650	
Psychological variables									
PANSS pos.	12.1	5.2	8.0	1.2	7.0	0	8.13 (2; 28)	**0.002***	**SZ ≠ HC, SZ ≠ MDD**
PANSS neg.	17.1	5.9	11.0	3.6	7.7	1.3	11.0 (2; 28)	**<0.001***	**SZ ≠ HC, SZ ≠ MDD**
PANSS gen.	27.9	9.1	27.1	5.6	16.4	0.8	8.68 (2; 28)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
PANSS total	57.1	18.4	46.1	8.0	31.1	1.5	10.62 (2; 28)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
MADRS	13.0	7.0	15.6	6.0	0.3	0.5	18.30 (2; 28)	**<0.001***	**SZ ≠ HC MDD ≠ HC**
CGI	4.0	0.8	3.6	0.8	1.0	0	42.49 (2; 28)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
SNS	16.8	6.8	17.6	5.6	3.4	4.0	16.60 (2; 28)	**<0.001***	**SZ ≠ HC, MDD ≠ HC**
Premorbid intelligence	105.5	11.3	112.9	12.3	115.4	17.5	1.19 (2; 28)	0.320	
Ambulatory Assessment									
Prompts (n)	740		1302		729		0.06 (2; 28)	0.945	
Compliance [%]	80.1	11.7	77.8	16.4	83.0	13.7	0.19 (2; 28)	0.828	

[1] SD = Standard deviation
[2] (df1; df2)
* Significant values ($p < 0.05$) are marked with an asterisk

Demographic and clinical characteristics

Current symptom severity was assessed in all groups using Positive and Negative Symptom Scale (PANSS; Kay et al., 1987), Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1977) and Self-evaluation of Negative Symptoms (SNS; Dollfus et al., 2016). In addition, general disorder severity was rated using the Clinical Global Impression Scale (CGI; Guy, 1976).

To determine potential differences between the three groups, a one-way analyses of variance (ANOVA) were performed, followed by Tukey post-hoc tests to identify differences between each pair of groups as well as $\chi 2$-tests for the categorical variables, with significance level set to $\alpha = 0.05$. Significant demographic differences were included in the multilevel model as covariates of no interest.
Demographic details and clinical sample characteristics are presented in Table 2.1.

Assessment procedures and measures

All participants completed a standard battery of questionnaires and self-ratings at their first study appointment and were subjected to an Ecological Momentary Assessment (EMA) protocol including smartphone-based e-diaries, step counter and real-life location tracking across 24 weeks.

Ecological Momentary Assessment (EMA)

Symptomatology/psychological variables (active EMA data)

Participants were asked to provide EMA on their symptomatology/psychological variables on e-diaries implemented either on participants' own smartphones or on study smartphones (Nokia 6.2 or Nokia 7.2) using a custom experience sampling software developed by the movisens GmbH, named INDICATE-N application (movisensXS). Assessments were obtained at fixed times. i.e., twice a day at 09:00 AM and 09:00 PM in participants' everyday life. E-diary prompts could be postponed for up to 30 minutes. At the beginning of the study, all participants were thoroughly instructed on how to use the INDICATE-N application and a demonstration of exemplified e-diary ratings was presented to all participants for training purposes. While participants were also subjected to an intense sampling schema (i.e., 3 intense phases with six daily prompts for 10 days each), the starting day of each intense phase was randomized. However, this high-resolution sampling was not relevant to the research question on long-term effects of COVID-19 related restrictions on participants well-being.
At each assessment participants were asked to rate their mood, affect, and their social context by answering 21 e-diary items. From these, a set of 6 relevant items (for more details see Table 2.2) was chosen for the current COVID-19 analyses, assessing loneliness and fearfulness (taken from the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996; Watson et al., 1988)), valence, energetic arousal, and calmness (taken from the Multidimensional Mood Questionnaire (MDMQ; Wilhelm & Schoebi, 2007), as well as social contact (being alone vs. being with others). The items were rated either using a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree)

or visual analog scale with a score range from 0 to 100. To quantify social contact, an established binary scale was used to assess whether or not the participants had been in company since the last alert (Collip et al., 2013; Myin-Germeys et al., 2001).

To assess mood, a six-item short scale based on the Multidimensional Mood Questionnaire (Wilhelm & Schoebi, 2007) was used. In particular, two bipolar items were assessed for each of the three basic affective dimensions (Valence: unwell to well (unwohl-wohl) and discontent to content (unzufrieden-zufrieden); Energetic arousal: no energy to full energy (energielos-energiegeladen) and tired to awake (müde-wach); Calmness: tense to relaxed (angespannt-entspannt) and agitated to calm (unruhig-ruhig)). The bipolar items were presented in mixed order and reversed polarity.

Mobile sensing (passive EMA data)

Modern smartphones come equipped with multiple build-in sensors, which can be used to sense different aspects of environmental parameters. The number of steps was determined by integrated accelerometry smartphone sensors across the whole study duration.

To track participants' spatial roaming patterns, we used a sophisticated custom-developed algorithm combining Global Positioning System, Wireless Local Area Network, and (Global System Mobile Communication signals, for details see Tost et al., (2019)) to meet the technical challenge of tracking locations both energy-efficiently and precisely (Stumpp, 2014; Falaki et al., 2010). Thereafter, we compiled a data set consisting of raw coordinates provided by the algorithm and interpolated geolocations provided by the software Geocoder (movisens GmbH, Germany, www.movisens.com), resulting in geolocation coordinates in minutely resolution for each study participant and at each given time point within our study (for details see Tost et al., (2019)). To ensure data quality, we included only geolocation data points with a mean accuracy of at least 100 meters, the maximum inaccuracy of GPS-tracking in cities (Falaki et al., 2010). In addition, we excluded data points if velocity between two consecutive points was >300km/h or <0 km/h. e.g., to account for signal jumps.

Table 2.2. Full text of the respective items, rating scales, target psychological constructs and symptoms

	Item	Assessment (Since the last beep, …)	Scale	Construct	Symptoms	Reference
1a.	valence	…I felt content - discontent. (…fühlte ich mich zufrieden-unzufrieden.)	Visual analog scale (0 - 100)	Multidimensional Mood Questionnaire (MDMQ)	Well-being (including perceived energy, tension and lack of drive)	(Wilhelm & Schoebi, 2007)
1b.		…I felt content - discontent. (…fühlte ich mich zufrieden-unzufrieden.)				
2a.	energetic arousal	…I felt tired - awake. (…fühlte ich mich müde-wach.)				
2b.		…I felt energetic - worn out. (…fühlte ich mich energiegeladen-energielos.)				
3a.	calmness	…I felt calm - alert. (…fühlte ich mich ruhig-unruhig.)				
3b.		…I felt relaxed - tense. (…fühlte ich mich entspannt-angespannt.)				
4.	loneliness	…I felt lonely. (…fühlte ich mich einsam.)	Likert Scale (1 - 7)	Positive and Negative Affect Schedule (PANAS)	Affective symptoms (including blunted affect)	Used in several EMA studies for psychosis and depression, e.g.: (Myin-Germeys et al., 2003, 2001, 2000)
5.	fearfulness	…I felt fearful. (…fühlte ich mich ängstlich.)				
6.	being alone	…I was alone. (…war ich allein.)	Yes/No (Ja/Nein)	Social context	Social withdrawal	(Collip et al., 2013; Myin-Germeys et al., 2001; Wilhelm & Schoebi, 2007)

<u>Data preprocessing</u>

Definition of time phases

To investigate the effect of COVID-19 restrictions on participants' mood during the first and the second wave of infection cases, we divided each relevant time period into two non-overlapping phases (i.e., phases) based on COSMO data (2020), indicating consequent increasing anxiety in the general population (see main Figure 2.1A). Specifically, we defined a preacute (wave 1: 02/01/2020 – 03/16/2020, wave 2: 14/09/2020 – 26/10/2020) and acute (wave 1: 03/17/2020 – 03/31/2020, wave 2: 27/10/2020 – 11/10/2020) phase, representing time periods before, and during the peak of rising infection cases, respectively.

As in many other countries, there was also a lockdown ordered by the government in Germany. The first COVID-19 related lockdown lasted from 03/22/2020 – 05/04/2020. However, this did not imposed a curfew, but only contained stay-at-home recommendations. However, many restrictions in public life, such as reduced social contacts or school, business and restaurant closures, took place.

In autumn, a lockdown with the same contact restrictions and restaurant closures was imposed again. Schools and shops, however, were allowed to remain open, which is why one speaks of a lockdown light in the period 10/02/2020 – 12/16/2020.

<u>Statistical analyses</u>

Multilevel model analyses (MLM): Active EMA data (e-diaries)

To investigate whether the COVID-19 pandemic had an effect on participants daily life, we conducted multilevel model analyses using the software SAS (SAS Inc 2013). In these models, we nested e-diary assessments of the six previously described items (level 1) within participants (level 2). We fitted linear mixed models and generalized linear mixed models according to the distribution of the outcome variables.

We entered within- and between-subject covariates (i.e., sex, group, time of day, time of day squared) previously shown to influence mental health symptomatology together with our predictors of interest. Each item was entered as outcome variable of interest, respectively, resulting in a total of six MLM for mental health symptomatology (see Tost et al., (2019). Additionally, two MLM were computed to analyze roaming patterns. The α-level was set to 0.05. Bonferroni-Holm-correction was applied to control for the false-positive rate. For testing the fixed effects in the MLM with our small sample size we used a Kenward Roger approximation to estimate the number of degrees of freedom with more accuracy.

First, we defined a categorical group variable (SZ, MDD, HC) to be able to model/estimate potential differences between the three groups (n = 65).

Equation 1

$$\mathbf{Y(item)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{group_j} + \beta_{02} * \mathrm{sex_j} + \beta_{10} * \mathrm{time\ of\ day_{ij}} + \beta_{20} * \mathrm{time\ of\ day_{ij}^2} + \mathrm{u_{0j}} + \mathrm{r_{ij}}$$

Then, to statistically test which psychological constructs were altered during the acute phases of the COVID-19 pandemic compared to the preacute phases, we introduced a phase variable (preacute, acute) into the model exemplified below. We computed a cross-level interaction, i.e. group*phase to test for differential phase effects.

Equation 2

$$\mathbf{Y(item)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{group_j} + \beta_{02} * \mathrm{sex_j} + \beta_{10} * \mathrm{time\ of\ day_{ij}} + \beta_{20} * \mathrm{time\ of\ day_{ij}^2} + \beta_{30} * \mathrm{phase_{ij}} + \boldsymbol{\beta_{31}} * \mathbf{group_j} * \mathbf{phase_{ij}} + \mathrm{u_{0j}} + \mathrm{r_{ij}}$$

In equation 1 and equation 2, Y_{ij} represents the level of the respective e-diary item (i.e. valence, energetic arousal, calmness, loneliness, fearfulness, being alone) in person j at the timepoint i.

On level 1, within-subject effects were calculated using e-diary entries at any assessment time (subscript i) of each participant (subscript j). On level 2, between-subject effects were estimated. Beta coefficients represent the intercept (β_{00}), the effects of our main predictor i.e., group (β_{01}, SZ, MDD, HC), sex (β_{02}, male, female) and phase (β_{30}, preacute and acute phases) and the effects of the level 1 covariates (β_{10}, time of day, β_{20}, time of day squared). The u_{0j} denote the random intercepts and residuals at level 1 are represented by r_{ij}.

Multilevel model analyses (MLM): Passive EMA data (geolocation tracking)

To assess the participants' spatial roaming behavior during the preacute and acute phases we temporally filtered the data to obtain data points for 01/02/2020 – 11/30/2020. We created a regular tessellation consisting of equilateral hexagons (in the following referred to as "cells") using the software QGIS (https://www.qgis.org/de/site/index.html. version 3.4). For each participant and each phase, we counted the number of different cells that intersect with at least one tracked geolocation per participant using PostgreSQL (https://www.postgresql.org/. version 10.14) with the PostGIS extension (https://postgis.net/. version 2.4.3.). Further data preprocessing steps to achieve a multilevel data set and all descriptive statistics, were conducted using the software SAS (SAS Inc 2013).

To statistically test for differences in participants' activity and spatial roaming behavior, we conducted two multilevel analyses with group, phase, and their interaction as predictors of interest as well as number of steps and visited cells as outcomes of interest (see Equation 3 and 4).

Equation 3

$$\mathbf{Y(steps)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{group_j} + \beta_{02} * \mathrm{sex_j} + \beta_{10} * \mathrm{cells_{ij}} + \beta_{20} * \mathrm{phase_{ij}} + \boldsymbol{\beta_{21}} * \mathbf{group_j} * \mathbf{phase_{ij}} + \mathrm{u_{0j}} + \mathrm{r_{ij}}$$

Equation 4

$$\mathbf{Y(cells)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{group_j} + \beta_{02} * \mathrm{sex_j} + \beta_{10} * \mathrm{steps_{ij}} + \beta_{20} * \mathrm{phase_{ij}} + \boldsymbol{\beta_{21}} * \mathbf{group_j} * \mathbf{phase_{ij}} + \mathrm{u_{0j}} + \mathrm{r_{ij}}$$

In equation 3 and equation 4, Y_{ij} represents the level of the number of steps per day and visited cells in person j at the timepoint i, respectively.

Personality traits and factor analysis

To further investigate the differences between healthy controls, we explored potential moderating effect of transdiagnostic factor indicating/representing general mental health risk. We therefor performed a principal component analysis (Streiner, 2020) implemented in SPSS (IBM), version 27 (Statistics, 2020). We focused on the first principal component or factor that explained most of variance in the data. Based on the resulting factor loadings, this factor summarized several pathological personality traits and can be thus likely interpreted as increased risk to develop a mental health illness. All measures and subscales included in the analysis were collected using REDCap electronic data capture tools (Harris et al., 2019). Details are outlined in Table 2.3.

Second, we used subjective mental health risk factor loadings (MHR) to compute a cross-level interaction for HC and phases, i.e. phase*MHR in the multilevel models detailed above. To better visualize the effect, we used the factor loadings of 25 percentile (low MHR), median and 75 percentile (high MHR) for subsequent post-hoc analyses.

<u>Results</u>

During the entire measurement period (02/01/2020 – 11/30/2020), the 65 participants completed a total of 14325 prompts with an average overall compliance rate of $M = 77.1\%$ ($SD = 16.2\%$). The average compliance rate during the first ($n=23$) and second ($n=31$) wave was $M = 72.9\%$ ($SD = 17.4\%$; 1802 prompts) and $M = 80.3\%$ ($SD = 13.9\%$; 2771 prompts). This is a non-significant difference in compliance rates (see Table 2.1).

In general (i.e., independent of time phases), patient groups differed significantly from healthy controls in each of the mood dimensions (i.e., valence, energetic arousal, calmness) and feelings of anxiety and loneliness (group: $p \leq 0.029$; Table 2.4 and Table 2.5), which is consistent with expected effects of patient group-specific psychopathology. Regarding mobility, SZ patients engaged in significantly more steps than MDD patients did ($p = 0.038$). There was no significant difference in the amount of visited cells (spatial roaming) between groups (all p-values > 0.07).

For the first wave, we found statistically significant interactions between group (SZ, MDD, HC) and phase (preacute and acute) for valence, energetic arousal, calmness, fearfulness, being alone and number of steps (group*phase interaction: all p-values ≤ 0.035), indicating different trajectories of mood and mobility over time between groups (Table 2.6). Post-hoc group comparisons of the phase effect revealed that SZ patients showed an increase in all well-being-related items (SZ: well-being: all p-values ≤ 0.006), while MDD patients only improved in calmness (MDD: $p \leq 0.008$). On the contrary, on average, healthy controls experienced a reduction in valence and calmness (p-values < 0.001) as well as an increase in fear ($p < 0.001$). All groups took significantly fewer steps from preacute to acute phase (all p-values ≤ 0.003), and MDD and HC spent more time being alone ($p \leq 0.026$). All further details are reported in Table 2.7.

During the second wave, again, interactions between group (SZ, MDD, HC) and phase (preacute and acute) were statistically significant for valence, energetic arousal, and fearfulness (p-values ≤ 0.024; Table 2.8). This points towards similar effects in wave 1 and 2. However, compared to the first wave, there was no change in mobility (steps: $p = 0.121$, cells: $p = 0.396$) or being alone ($p = 0.182$) in any of the groups. Instead, feeling lonely showed a significant interaction effect ($p \leq 0.046$). Furthermore, SZ patients showed slight improvements in their valence and energetic arousal (p-values ≤ 0.017), with a slight increase in fearfulness ($p < 0.001$). On the other hand, MDD patients felt less fearful and lonely (p-values ≤ 0.008). However, HC showed no change between preacute and acute phases in any of the analyzed items (Table 2.9).

Compared to ratings before the first wave, HC showed tendetially reduced well-being ratings (valence: $p = 0.052$, energetic arousal: $p = 0.056$, calmness: $p = 0.042$), but had no differences in being alone, feeling lonely and fearful or less mobile (all p-values > 0.05; Table 2.10 and Table 2.11).

Including mental health risk into the analysis, as a two-way interaction revealed significant results for all outcome variables (phase*MHR interaction: all p-values ≤ 0.011), except for energetic arousal and mobility. All main and interaction effects are provided in Table 2.12 and Table 2.13.

In HC, a significant decrease in general well-being and increase in anxiety was present across different MHR loadings, being most pronounced in individuals with high MHR values (valence, calmness, fearful: p-values < 0.001). Low MHR was associated with a significantly increased feeling of loneliness only ($p = 0.034$). All further simple effect comparisons are provided in Table 2.13 and shown in main Figure 2.3B.

Table 2.3. Subscales included in principal component analysis

	Measures	Abbreviation	Factor 1: mental health risk (MHR)
1.	**Barrat Impulsiveness Scale (ver.11)** (Patton et al., 1995)	BIS-11	
	Attention		0.352
	Cognitive Complexity		0.095
	Cognitive Instability		**0.659**
	Motor		-0.288
	Perseverance		**0.495**
	Self-Control		0.031
2.	**Childhood Trauma Questionnaire** (Bernstein et al., 2003)	CTQ	
	Emotional abuse		**0.721**
	Emotional neglect		**0.416**
	Neglect		**0.551**
	Physical abuse		0.321
	Sexual abuse		0.288
3.	**Emotion Regulation Questionnaire** (Abler & Kessler, 2009)	ERQ	
	Reappraisal		-0.259
	Suppression		**0.420**
4.	**NEO Five factor inventory** (Kanning, 2009)	NEO-30	
	Agreeableness		**-0.679**
	Conscientiousness		**-0.611**
	Extraversion		**-0.719**
	Neuroticism		**0.880**
	Openness		**0.487**
5.	**Schizotypal Personality Questionnaire** (Raine & Benishay, 1995)	SPQ	
	Cognitive-Perceptual		**0.603**
	Interpersonal		**0.773**
	Disorganised		**0.634**
6.	**State-Trait Anxiety Inventory** (Bieling et al., 1998)	STAI-T	
	Trait		**0.820**

Values in bold represent factor loadings > 0.4 and <-0.4.

Table 2.4. Main effect: group (n=65)

n = 65		Main effect	
Scale	Item	group	
		F-value (df1; df2)	p-value
Well-being			
0-100	valence	12.68 (2; 61.2)	<0.001*
	energetic arousal	10.27 (2; 61.1)	<0.001*
	calmness	10.46 (2; 61.3)	<0.001*
Anxiety			
1-7	fearful	8.81 (2; 61.1)	<0.001*
Social isolation			
1-7	lonely	7.57(2; 61.2)	0.001*
0-1	alone (logit)	3.78 (2; 57.18)	0.029*
Mobility (n=64)			
-	steps (ln transformed)	3.43 (2; 56.85)	0.039*
	cells (ln transformed)	3.34 (2; 57.85)	0.042*

Table 2.5. Main effect group: Post-hoc group comparison (n=65)

n = 65		SZ vs. HC		MDD vs. HC		SZ vs. MDD	
Scale	Item	Estimated Mean Difference	p-value	Estimated Mean Difference	p-value	Estimated Mean Difference	p-value
Well-being							
0-100	valence	**-12.45**	**0.040***	**-23.28**	**<0.001***	10.82	0.090
	energetic arousal	-12.62	0.052	**-22.1**	**<0.001***	9.48	0.210
	calmness	-10.27	0.180	**-23.29**	**<0.001***	13.02	0.056
Anxiety							
1-7	fearful	**1.12**	**0.004***	**1.22**	**0.001***	-0.09	1.000
Social isolation							
1-7	lonely	**1.02**	**0.016***	**1.23**	**0.002***	-0.21	1.000
0-1	alone (logit)	**1.48**	**0.025***	0.83	0.220	0.65	0.230
Mobility (n=64)							
-	steps (ln transformed)	0.233	0.287	-0.327	0.218	**0.56**	**0.038***
	cells (ln transformed)	-0.59	0.09	-0.63	0.07	0.04	0.900

* Significant Bonferroni-Holm corrected values (p < 0.05) are marked with an asterisk

Table 2.6. Main and interaction effects of wave 1: group and phase (n=23)

n = 23		Main effects				Interaction	
Scale	Item	group		phase		group*phase	
		F-value (df1; df2)	p-value	F-value (df1; df2)	p-value	F-value (df1; df2)	p-value
Well-being							
0-100	**valence**	8.39 (2;18.76)	0.003*	0.01 (1; 1778)	0.943	**9.48 (2; 1777)**	**<0.001***
	energetic arousal	7.64 (2; 18.67)	0.004*	3.91 (1; 1788)	0.048*	**3.36 (2; 1784)**	**0.035***
	calmness	6.66 (2; 18.91)	0.007*	4.14 (1; 1778)	0.042*	**15.70 (2; 1777)**	**<0.001***
Anxiety							
1-7	**fearful**	4.78 (2; 18.97)	0.021*	1.83 (1; 1780)	0.176	**11.72 (2; 1779)**	**<0.001***
Social isolation							
1-7	**lonely**	**9.33 (2; 18.91)**	**0.002***	1.41 (1; 1782)	0.235	1.06 (2; 1781)	0.345
0-1	**alone (logit)**	4.33 (2; 16.27)	0.031*	15.22 (1; 1787)	<0.001*	**4.49 (2; 1787)**	**0.011***
Mobility (n = 22)							
-	**steps (ln transformed)**	0.84 (2; 16.22)	0.450	56.24 (1; 837.9)	<0.001*	**4.35 (2; 837.6)**	**0.013***
	cells (ln transformed)	2.57 (2; 16.29)	0.107	**18.17 (1; 845.5)**	**<0.001***	2.1 (2; 842.8)	0.123

*Significant values (p < 0.05) are marked with an asterisk

Table 2.7. Interaction group*phase: Post-hoc phase comparison of wave 1 (n=23)

n = 23		SZ (n=7)			MDD (n=6)			HC (n=10)		
		acute vs. preacute			acute vs. preacute			acute vs. preacute		
Scale	Item	Estimated Mean difference	F-value (df1; df2)	p-value	Estimated Mean difference	F-value (df1; df2)	p-value	Estimated Mean difference	F-value (df1; df2)	p-value
Well-being										
0-100	valence	**4.27**	**7.51 (1; 1785)**	**0.006***	-0.47	0,1 (1; 1771)	0.750	**-3.98**	**13.21 (1; 1771)**	**<0.001***
	energeticarousal	**7.64**	**8.75 (1; 1780)**	**0.003***	0.60	0,06 (1; 1773)	0.807	-0.33	0.03 (1; 1774)	0.856
	calmness	**4.95**	**10.56 (1; 1785)**	**0.001***	**3.82**	**7.05 (1; 1771)**	**0.008***	**-3.98**	**13.92 (1; 1771)**	**<0.001***
Anxiety										
1-7	fearful	**-0.23**	**6.73 (1; 1786)**	**0.010***	**-0.17**	**4.32 (1; 1774)**	**0.038***	**0.22**	**12.40 (1; 1774)**	**<0.001***
Social isolation										
1-7	lonely	-	-	-	-	-	-	-	-	-
0-1	alone (logit)	0.04	0.02 (1; 1787)	0.879	**0.54**	**4.94 (1; 1787)**	**0.026***	**0.98**	**22.43 (1; 1787)**	**<0.001***
Mobility (n=22)										
-	steps (ln transformed)	**-0.58**	**19.31 (1; 845.2)**	**<0.001***	**-0.80**	**28.33 (1; 833)**	**<0.001***	**-0.30**	**8.97 (1; 829.1)**	**0.003***
	cells (ln transformed)	-	-	-	-	-	-	-	-	-

*Significant values ($p < 0.05$) are marked with an asterisk
- no post-hoc comparison for non-significant interaction displayed

Table 2.8. Main and interaction effects of wave 2: group and phase (n=31)

n = 31		**Main effects**				**Interaction**	
Scale	**Item**	**group**		**phase**		**group*phase**	
		F-value (df1; df2)	**p-value**	**F-value (df1; df2)**	**p-value**	**F-value (df1; df2)**	**p-value**
Well-being							
0-100	**valence**	1.07 (2; 27.14)	0.358	0.19 (1; 2520)	0.664	**3.76 (2; 2520)**	**0.024***
	energetic arousal	1.34 (2; 27.09)	0.278	1.85 (1; 2526)	0.174	**4.26 (2; 2525)**	**0.014***
	calmness	1.63 (2; 27.17)	0.215	0.69 (1; 2519)	0.405	0.14 (2; 2519)	0.870
Anxiety							
1-7	**fearful**	2.36 (2; 27.11)	0.113	0.36 (1; 2520)	0.550	**9.78 (2; 2519)**	**<0.001***
Social isolation							
1-7	**lonely**	0.98 (2; 27.16)	0.388	10.75 (1; 2522)	0.001*	**3.08 (2; 2522)**	**0.046***
0-1	**alone (logit)**	0.75 (2; 24.57)	0.482	1.99 (1; 2538)	0.158	1.71 (2; 2538)	0.182
Mobility (n = 31)							
-	**steps (ln transformed)**	**3.89 (2; 26.59)**	**0.032***	0.11 (1; 1318)	0.7441	2.11 (2; 1319)	0.121
	cells (ln transformed)	1.68 (2; 26.67)	0.2063	1.95 (1; 1314)	0.1623	0.93 (2; 1315)	0.396

*Significant values ($p < 0.05$) are marked with an asterisk

Table 2.9. Interaction group*phase: Post-hoc phase comparison of wave 2 (n=31)

n = 31		SZ (n=8)			MDD (n=16)			HC (n=7)		
		acute vs. preacute			acute vs. preacute			acute vs. preacute		
Scale	Item	Estimated Mean difference	F-value (df1; df2)	p-value	Estimated Mean difference	F-value (df1; df2)	p-value	Estimated Mean difference	F-value (df1; df2)	p-value
Well-being										
0-100	valence	**3.35**	**5.7 (1; 2522)**	**0.017***	-0.71	0.51 (1; 2522)	0.476	-1.66	1.33 (1; 2517)	0.250
	energetic arousal	**5.10**	**6.47 (1; 2529)**	**0.011***	-2.03	2 (1; 2529)	0.157	1.29	0.39 (1; 2520)	0.533
	calmness	-	-	-	-	-	-	-	-	-
Anxiety										
1-7	fearful	**0.21**	**12.24 (1; 2521)**	**0.001***	**-0.12**	**7.13 (1; 2521)**	**0.008***	-0.04	0.39 (1; 2518)	0.535
Social isolation										
1-7	lonely	**-0.15**	**4.67 (1; 2524)**	**0.031***	**-0.21**	**18.82 (1; 2524)**	**<0.001***	0.001	0 (1; 2519)	0.995
0-1	alone (logit)	-	-	-	-	-	-	-	-	-
Mobility (n=30)										
-	steps (ln transformed)	-	-	-	-	-	-	-	-	-
	cells (ln transformed)	-	-	-	-	-	-	-	-	-

*Significant values (p < 0.05) are marked with an asterisk
- no post-hoc comparison for non-significant interaction displayed

Table 2.10. Main effect of wave in HCs (n = 17)

n = 17 (HC only)		Main effect wave	
Scale	**Item**	**F-value (df1; df2)**	**p-value**
Well-being			
0-100	**valence**	4.52 (1; 14.02)	0.052
	energetic arousal	4.35 (1; 13.94)	0.056
	calmness	**5.03 (1; 14.04)**	**0.042***
Anxiety			
1-7	**fearful**	0 (1;13.97)	0.990
Social isolation			
1-7	**lonely**	1.04 (1; 14.14)	0.325
0-1	**alone (logit)**	2.66 (1; 12.2)	0.129
Mobility (n = 16)			
-	**steps (ln transformed)**	0.03 (1; 12.81)	0.870
	cells (ln transformed)	0.04 (1; 13.04)	0.842

Table 2.11. Post-hoc wave comparison in HCs (n=17)

n = 17 (HC only)		Main effect wave	
Scale	**Item**	**F-value (df1; df2)**	**p-value**
Well-being			
0-100	**valence**	-16.86	0.052
	energetic arousal	-17.24	0.056
	calmness	**-18.15**	**0.042***
Anxiety			
1-7	**fearful**	0	0.990
Social isolation			
1-7	**lonely**	0.27	0.325
0-1	**alone (logit)**	0.29	0.129
Mobility (n = 16)			
-	**steps (ln transformed)**	-0.05	0.870
	cells (ln transformed)	-0.09	0.842

*Significant values ($p < 0.05$) are marked with an asterisk

Table 2.12. Main and interaction effects of phase and mental health risk in HC during the first wave (n=9)

n = 9		Main effects				Interaction	
Scale	**Item**	**phase**		**MHR**		**phase*MHR**	
		F-value (df1; df2)	**p-value**	**F-value (df1; df2)**	**p-value**	**F-value (df1; df2)**	**p-value**
Well-being							
0-100	**valence**	29.13 (1; 798.1)	<0.001	7.39 (1; 6.046)	0.034	**18.08 (1; 798.3)**	**<0.001***
	energetic arousal	0.11 (1; 798.2)	0.736	**6.44 (1; 6.086)**	**0.044***	0.11 (1; 798.5)	0.744
	calmness	33.41 (1; 798.1)	<0.001	4.65 (1; 6.028)	0.074	**20.5 (1; 798.2)**	**<0.001***
Anxiety							
1-7	**fearful**	108.04 (1; 799.2)	<0.001	2.85 (1; 6.102)	0.142	**63.74 (1; 799.5)**	**<0.001***
Social isolation							
1-7	**lonely**	12.81 (1; 799.3)	<0.001	4.41 (1; 6.187)	0.079	**6.5 (1; 799.8)**	**0.011***
0-1	**alone (logit)**	0.5 (1; 803)	0.482	0.48 (1; 5.458)	0.519	**9.66 (1; 803)**	**0.002***
Mobility (n = 9)							
-	**steps (ln transformed)**	1.32 (1; 6.295)	0.293	1.67 (1; 375)	0.197	0.17 (1; 375)	0.679
	cells (ln transformed)	1.45 (1; 6.376)	0.271	5.31 (1; 375.6)	0.022	0.35 (1; 375.5)	0.555

*Significant values (p < 0.05) are marked with an asterisk

Table 2.13. Simple effect comparison divided by 25 percentile (low MHR), median and 75 percentile (high MHR) of subjective MHR factor loadings

n = 21		Low MHR Score		Median MHR		High MHR Score	
		acute vs. preacute		acute vs. preacute		acute vs. preacute	
Scale	Item	Estimated Mean difference	p-value	Estimated Mean difference	p-value	Esstimated Mean difference	p-value
Well-being							
0-100	valence	**-6.6**	**<0.001***	**-11.14**	**<0.001***	**-17.04**	**<0.001***
	energetic arousal	-	-	-	-	-	-
	calmness	**-7.07**	**<0.001***	**-11.90**	**<0.001***	**-18.16**	**<0.001***
Anxiety							
1-7	fearful	**0.45**	**<0.001***	**0.74**	**<0.001***	**1.12**	**<0.001***
Social isolation							
1-7	lonely	**0.21**	**<0.001***	**0.34**	**<0.001***	**0.50**	**0.001***
0-1	alone (logit)	0.03	0.415	-0.12	0.070	**-0.30**	**0.003***
Mobility (n=20)							
-	steps (ln transformed)	-	-	-	-	-	-
	cells (ln transformed)	-	-	-	-	-	-

*Significant values (p < 0.05) are marked with an asterisk
- no post-hoc comparison for non-significant interaction displayed

2.3 Study 2. Real-life behavioral and neural circuit markers of physical activity as a compensatory mechanism for social isolation

2.3.1 Abstract

Social isolation and loneliness pose major societal challenges accelerated by the COVID-19 pandemic, especially for mental health. In this cohort study using accelerometry, electronic diaries, and neuroimaging in a community-based sample of 317 young adults, we show that people felt affectively worse when lacking social contact, but less so when engaging in physical activity. This putative compensatory mechanism was present even at small physical activity doses and pronounced in individuals with higher brain functional connectivity within the default mode network signaling risk for depression. Social-affective benefits of movement were higher in people showing exacerbated loneliness and replicated throughout the pandemic. These findings extend the state of knowledge on the dynamic interplay of social contact and physical activity in daily life identifying an accessible protective strategy to mitigate the negative effects of social isolation, particularly among at-risk individuals, which comes with the potential to improve public health in the post-pandemic world.

2.3.2 Introduction

Social isolation and loneliness increase human mortality similarly to known health risk factors such as obesity, alcohol consumption, or smoking 15 cigarettes per day (Holt-Lunstad et al., 2015). Lack of social contact also impairs momentary affective well-being (Gan et al., 2021), impacts the structural and functional integrity of emotion regulatory brain networks (Lam et al., 2021; Spreng et al., 2020), and is a potent risk factor for mood disorders (Mann et al., 2022). Social distancing directives during the COVID-19 pandemic have exacerbated this public health problem and highlighted the importance of finding remedial strategies (Chu et al., 2020). One promising strategy to mitigate the negative affective consequences of lack of social contact is physical activity, a known protective factor for affective well-being and mental health (Bull et al., 2020) with neural mechanistic links to emotion-regulatory brain regions (Reichert, Braun, et al., 2020). However, the everyday relevance and biological basis are unknown. Here, we hypothesized that physical activity can compensate for the negative affective effects of lacking social contact in daily life and that individuals at increased neural (Spreng et al., 2020) and psychological (Escalante et al., 2021) risk for depression benefit most from this compensatory mechanism.

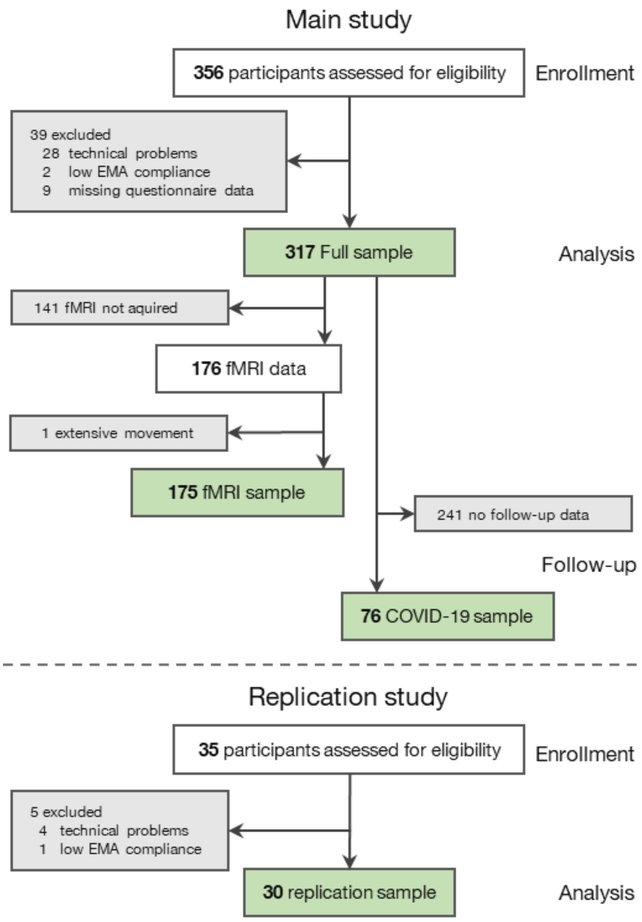

Figure 2.4. Participant flow chart: Participant numbers by the stages of the studies

2.3.3 Materials and Methods

The cohort study was conducted in accordance with ethical guidelines for medical research compliant with the Declaration of Helsinki. All participants provided written informed consent for a study protocol approved by the institutional review board of Heidelberg University. The Medical Faculty Mannheim (medical ethics committee II) at the Ruprecht-Karls-University in Heidelberg approved both studies (main study: 2014-555N-MA; replication study: 2019-733N). Participants received a monetary compensation for their effort. The flowchart depicts how the study size was arrived at in both the main and the replication study, see Figure 2.4.

Study population and measures

We studied a community-based cohort of 317 healthy young adults aged 18 to 28 years years (57.09 % females), recruited from September 2014 to November 2018, for 7 days in everyday life (main study, Tables 2.14 and 2.15). We further studied a replication sample of 30 healthy adults aged 18 to 63 years, recruited from December 2019 to July 2022, for 6 months in everyday life during the COVID-19 pandemic in Germany (Table 2.21). Biological sex of participants was determined using a questionnaire.

Participants wore accelerometers on their hip (main study) or wrist (replication study) to measure their physical activity, and repeatedly reported their real-life social contacts and affective valence using smartphone-based e-diaries (Figure 2.5A). Established multilevel reliability measures (Spearman-Brown; see (Eisinga et al., 2013)) yielded sound coefficients of $\rho = 0.80$ (within-subject level) and $\rho = 0.94$ (between-subject level) in our sample and for the two affective valence variables assessed (i.e., unwell to well and content to discontent). Moreover, within and between person correlations of the two items applied yielded positive correlations ($r_{within} = 0.66$; $r_{between} = 0.88$), which indicates convergent validity for the affective valence assessment instrument applied. Participants additionally completed a battery of psychological questionnaires (Bickart et al., 2011; Döring & Bortz, 1993), and we continuously tracked their geographic locations and situational contexts as previously described (Gan et al., 2021; see Figure 2.5B and supplementary information 1). 175 participants from the main sample additionally underwent a resting-state fMRI scan after the ambulatory study week to quantify default mode network (DMN) connectivity (supplementary results 2), a neural risk marker for social isolation and depression (Spreng et al., 2020; Whitfield-Gabrieli & Ford, 2012). In 76 participants from the main study, we additionally assessed individuals' perceptions of loneliness during the ongoing first wave of the COVID-19 pandemic (supplementary results 4).

Power analysis

Since statistical power analyses of multilevel models strongly depend on a host of assumptions (e.g., on random slopes, covariance structure) that cannot be drawn in the absence of the final data set (Arend & Schäfer, 2019) we estimated whether our final sample size of N = 317 is suitable to detect the expected effects referring to the most recent simulation studies (Bolger et al., 2012). Following this simulation studies a sample size of N = 200 is necessary to detect small minimum detectable effect size (MDES = 0.08) in a level-1 direct effect analysis given a level 1 sample size of at least 30 at a power of 80%, which provides evidence for the sufficient power of our analysis.

Data analysis

All statistical analyses were performed with the SAS software v. 9.4. Brain imaging data was analyzed using the CONN-toolbox v.19c in MATLAB v. 9.8 (R2020a). Main study: Within participants (main model), we analyzed the main and interaction effects of momentary social contact (predictor; alone vs. in company) and momentary physical activity (moderator; mean of milli-g in the 60 minutes preceding an e-diary prompt) on momentary affective valence (outcome) using multilevel models with time of day, time of day squared, current location (level 1), sex, age, and BMI (level 2) as covariates. Between participants, we predicted trait loneliness (outcome) with the main and interaction terms of social network size (Bickart et al., 2011; predictor) and habitual physical activity level (moderator; hours/week). In addition, we predicted the frequency of perceived loneliness during the first COVID-19 lockdown (outcome) by extracting random slopes from multilevel interaction of social contact and physical activity on affective valence (predictor; from main model) and fitting an ordinal logistic regression model assuming proportional odds. At the neural level, we computed DMN connectivity estimates from participants' resting-state fMRI data (Figure 2.6) and introduced them as an additional moderator into our main model, resulting in a three-way multilevel interaction analysis. In the second sample, we used the main model to replicate findings during the ongoing COVID-19 pandemic. See supplementary information 2 for more details.

2.3.4 Results

Individuals' physical activity significantly moderated the known relationship (Gan et al., 2021) between momentary social isolation and decreased affective valence in everyday life (β, 0.01; 95% CI, 0 – 0.02; P = .020, Tables 2.16a and 2.16b). Specifically, higher physical activity significantly decreased the reduction in affective well-being associated with the lack of social contact (Figure 2.5C, main study). According to our data, about 349 milli-g physical activity across one hour (e.g., walking approximately 3 miles per hour) are necessary to fully compensate for the lack of affective well-being in everyday life (see supplementary results 1). We successfully replicated this effect in our second sample that we studied during the COVID-19 pandemic (β, 0.03; 95% CI, 0.02 – 0.04; P < .001; Figure 2.5C, replication study, Tables 2.22a and 2.22b). At the neurobiological level, individuals with higher resting-state functional connectivity within the default mode network, a risk phenotype for loneliness (Spreng et al., 2020) and depression (Whitfield-Gabrieli & Ford, 2012), compensated best for this momentary "social-affective deficit" through physical activity (β, 0.14; 95% CI, 0.01 – 0.26; P = .029; Figure 2.6B, Tables 2.17a, 2.17b and 2.17c). Moreover, we observed similar benefits of physical activity at the between-subjects level and related it to established psychological risk factors for mental health. Firstly, participants with small social networks and high habitual physical activity levels exhibited lower trait loneliness compared to those with low levels of habitual physical activity (β, 0.05; 95% CI 0.001 –

0.092, $P = .046$; Figure 2.5D, Table 2.18). Second, individuals with a pronounced compensatory mechanism were less likely to frequently feel lonely during the first COVID-19 lockdown (odds ratio [OR] = 0.92; 95% CI, 0.85 – 0.99; $P = .021$; Table 2.19). Further exploratory analyses showed that offsetting the social-affective deficit with physical activity is effective even under pandemic-like constraints (curfews, closed gyms), for example, when only light physical activity (β, 0.04; 95% CI, 0 – 0.8; $P = .040$; Tables 2.20a and 2.20b) and physical activity at home (β, 0.08; 95% CI, 0.01 – 0.15; $P = .032$; Tables 2.20a and 2.20c) is considered.

Table 2.14. Main study: Demographic and psychological characteristics, Ambulatory Assessment and neuroimaging parameters

Measure	full sample (n = 317)			fMRI sample (n = 175)			COVID-19 sample (n = 76)		
	Mean	SD[b]	n[a]	Mean	SD[b]	n[a]	Mean	SD[b]	n[a]
Demographic variables									
Age [years]	23.08	2.83	317	23.19	2.75	175	22.6	2.70	76
Sex (female/male)	181/136	-	317	80/95	-	175	42/34	-	76
Education [years]	12.24	1.17	304	12.35	1.01	168	12.41	1.00	73
Nationality (German/other)	297/20	-	317	163/12	-	175	71/5	-	76
Body mass index [kg/m^2]	23.20	4.54	317	23.24	3.50	175	23.12	5.41	76
Smoking(non-smoker/ smoker)	239/74	-	313	134/39	-	173	61/15	-	76
Household size (individuals)	2.65	1.33	316	2.69	1.31	175	2.53	1.21	76
Household income [€/month][c]	2305	1035	269	2225	2260	151	2012.5	1042.5	65
Psychological variables									
Socioeconomic status (SES)	14.31	3.30	317	14.31	3.30	175	14.16	3.47	76
Physical activity (h/Week)	5.08	3.63	280	5.03	3.35	159	4.73	3.42	67
Social network size (individuals)	18.98	8.01	192	18.95	8.22	174	19.27	8.17	72
Trait neuroticism (NEO-FFI-30-N)[d]	1.31	0.77	316	1.20	0.72	174	1.19	0.73	76
Loneliness Scale (UCLA)	1.59	0.50	315	1.57	0.77	174	1.57	0.52	76
Trait anxiety (STAI-T)[e]	36.07	9.45	316	35.17	8.43	174	35.54	8.93	76
Schizotypical traits (SPQ)[f]	4.04	3.56	304	3.6	3.26	166	4.34	3.79	73
Ambulatory Assessment									
Movement Acceleration Intensity [milli-g/min][g]	68.82	22.09	317	69.77	21.77	175	66.41	19.69	76
E-diary prompts per day	12.31	2.65	317	12.39	2.60	175	12.28	2.64	76
Compliance [%]	80.90	24.37	317	81.19	24.13	175	81.76	44.14	76
Affective valence	71.31	11.48	317	71.67	11.10	175	72.54	12.32	76
ICC: affective valence[h]	0.35	-	317	0.35	-	175	0.42	-	76
fMRI data quality									
Number of valid scans	-	-	-	208.2	3.10	175	-	-	-
Mean frame-wise displacement (mm)	-	-	-	0.15	0.06	175	-	-	-

[a] n = number of individuals for which the information for a given sample and variable is available
[b] SD = standard deviation
[c] We assessed monthly household income after taxes in 13 ordinal categories, i.e., 1) less than 500 €, 2) 500 – 749 €, 3) 750 – 999 €, 4) 1000 – 1249 €, 5) 1250 – 1499 €, 6) 1500 – 1749 €, 7) 1750 – 1999 €, 8) 2000 – 2249 €, 9) 2250 – 2499 €, 10) 2500 – 2999€, 11) 3000 – 3999€, 12) 4000 – 4999€, and 13) more than 5000€. For the descriptive comparison of the two samples in this table we assigned category means to individuals, e.g., a value of 624.5 € to a participant reporting a category
[d] Trait neuroticism: 6 self-rated items (5-point-scale; Körner et al., 2008)
[e] Schizotypical traits: 22 self-rated items (yes/no – 1 point for yes; Raine & Benishay, 1995)
[f] Trait anxiety: 20 self-rated items (response options 1 to 4; Spielberger et al., 2003)
[g] Values were averaged across participants and the study week, respectively.
[h] We used intra class correlation coefficients (ICC) to calculate variance estimates of our outcome variables: In the study, 35.0% of the variance in affective valence can be attributed to within-subject variation.

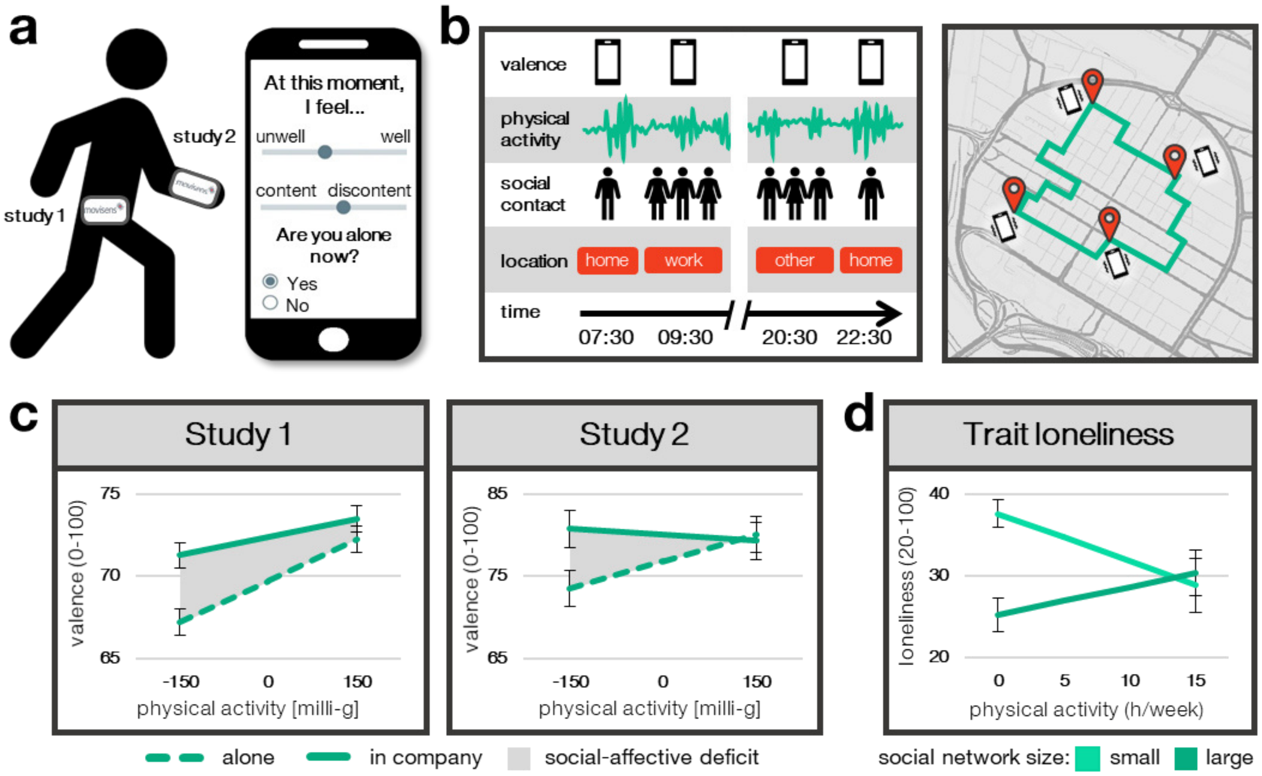

Figure 2.5. Ambulatory Assessment procedure and study findings on the behavioral level

A: Accelerometry was used to measure physical activity, while affective valence and social contact were assessed through Ambulatory Assessment (AA). Smartphone image by ElisaRiva (http://www.pixabay.com).

B: Exemplified sampling scheme: Geolocations were continuously tracked and assigned using an advanced day reconstruction method (e.g., at home, work). E-diaries were triggered either location-based or at random times. Map image by © OpenStreetMap contributors (https://www.openstreetmap.org/).

C: Study 1 (n = 317; Table 2.14): Physical activity engagement (x-axis) offsetting the social-affective deficit (y-axis) associated with the absence of real-life social contact as illustrated by the gray-colored area between the solid (in company) and dashed (alone) green lines. The regression lines, derived from the multilevel interaction analyses (outcome: affective valence, predictor: real-life social contact, moderator: physical activity centered within-subjects) demonstrate that the more participants had been physically active prior to an e-diary assessment, the less affective loss they experienced when being alone. Physical activity values to the very left of the x-axis refer to sedentary behavior such as sitting, while values to the very right depict moderate activities such as walking.

Study 2 (n = 30; Table 2.21): Replication of the compensatory effect of physical activity during the COVID-19 pandemic. P-values for beta coefficients are two-sided and derived from the t-statistics of the multilevel model. Error bars indicate the standard errors of the respective estimated mean valence scores.

D: Trait loneliness: Participants with small social networks (light green) who engaged in high habitual levels of physical activity reported lower trait loneliness compared to those engaging in low average levels of physical activity (Table 2.18). P-values are two-sided and derived from the t-statistics of the multiple linear regression. Error bars indicate the standard errors of the respective estimated mean loneliness scores.

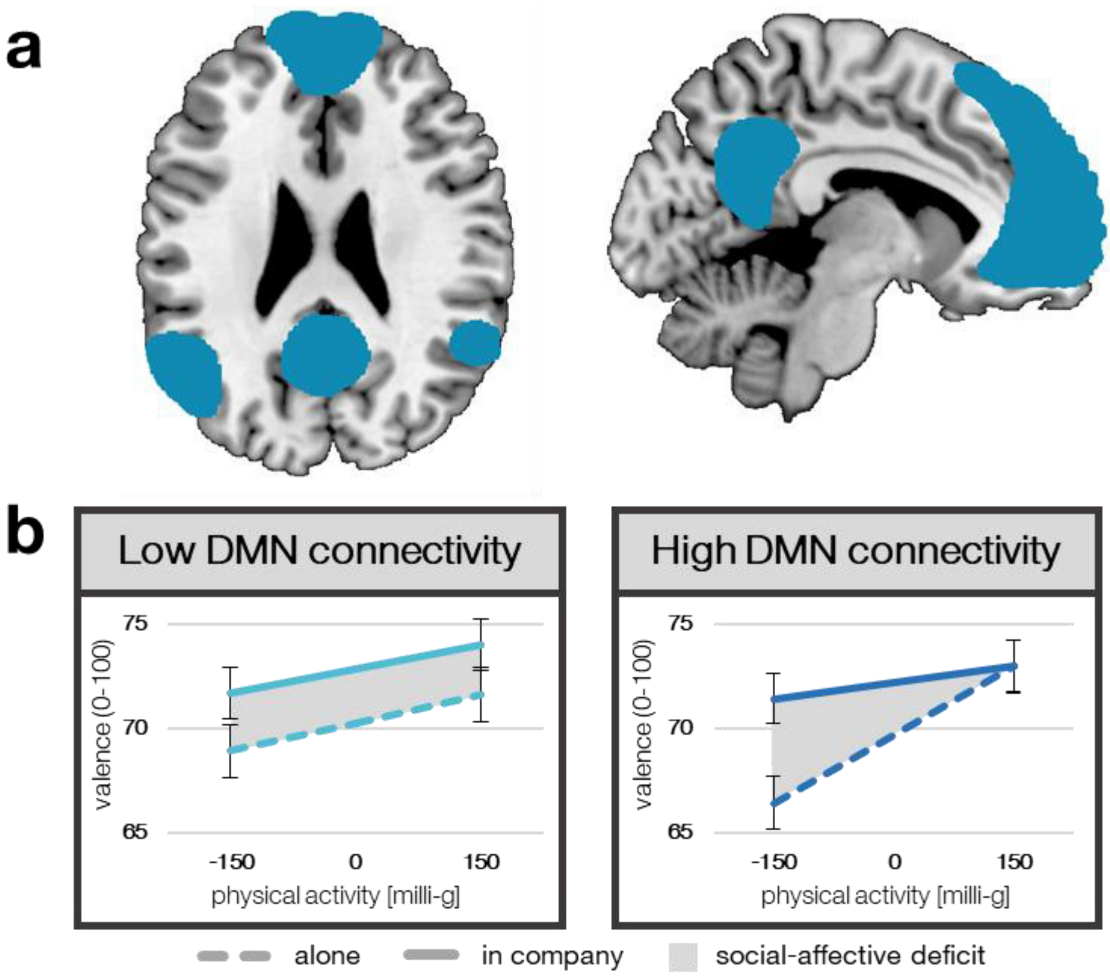

Figure 2.6. Default mode network (DMN) and study findings on the neural level

A: Following neuronal signatures seen in 'lonely brains', we analyzed the within-network connectivity of the DMN based on the 7 networks Schaefer-Yeo parcellation atlas (Schaefer et al., 2017).

B: Participants with higher within-DMN connectivity, a neuronal signature repeatedly found in lonely individuals and being associated with affective disorders, showed a pronounced compensation of the momentary "social-affective deficit" through physical activity (Tables 2.17a, 2.17b, 2.17c). P-values for beta coefficients are two-sided and derived from the t-statistics of the multilevel model. Error bars indicate the standard errors of the respective estimated mean valence scores.

2.3.5 Discussion

Our intensive e-diary and accelerometer-based longitudinal data suggest that physical activity can effectively and reproducibly compensate for the loss of affective well-being associated with lack of social contact in real-life. While social contact and physical activity are well-known protective resources for mental health (Mann et al., 2022, Bull et al., 2020, Holt-Lunstad et al., 2015), previous studies have predominantly examined these factors using questionnaires or individually in the real world health (Gan et al., 2021; Reichert et al., 2020). Our naturalistic study extends the state of knowledge by showing a dynamic interplay of both factors impacting human affective well-being in everyday life. Our data further show that about 1 hour of walking at a speed of 3 miles per hour can compensate for the “social affective deficit” in everyday life and that this beneficial effect even persists when physical activity is performed at lower doses and only at home. This indicates a considerable potential of physical activity to counteract negative affective consequences of social isolation in everyday life. Importantly, the effect was larger in people at higher neural risk for affective disorders. These include people from the general population with risk-related changes in the DMN brain connectivity (Spreng et al., 2020; Whitfield-Gabrieli & Ford, 2012), smaller social networks (Bickart et al., 2011) and frequently perceived loneliness under the regulatory constraints of the COVID-19 pandemic. Thus, our data not only suggest an effective and accessible strategy to mitigate the negative effects of social isolation and loneliness in everyday life, but also contribute to the identification of likely responders and enrich existing evidence-based recommendations for the preventive management of affective dysfunction in the post-pandemic world (Chu et al., 2020; Escalante et al., 2021).

<u>Limitations</u>

We captured affective valence via an established scale specifically developed and validated for investigating mood in everyday life (Cloos et al., 2023; Wilhelm & Schoebi, 2007). Therefore, our study provides insights into mood changes provoked by physical activity and social interaction, but given the ongoing discussions on mood assessments in the field, future studies should examine the effects of physical activity in the context of lacking social contact on specific emotions (e.g., anxiety, anger). Moreover, although our real-life observational data have high ecological validity, they do not allow for causal inferences. In particular, our findings do show correlations and temporal directionality of effects, but we cannot rule out potential influences of hidden third variables. Future studies should address the causality question by incorporating experimental manipulations such as just-in-time adaptive interventions into their real-life investigations.

Our multimodal epidemiological cohort study shows that physical activity is reproducibly linked to better well-being in people lacking social contact in daily life, especially in persons at neural and psychological risk for affective disorders. These data suggest an effective and accessible strategy to mitigate the negative effects of social isolation and loneliness that can improve public health and enrich existing evidence-based recommendations for the preventive management of social isolation in the post-pandemic world.

2.3.6 Supplementary Material

Supplementary information 1. General study information (main study)

Ethics

The cohort study was conducted in accordance with ethical guidelines for medical research compliant with the Declaration of Helsinki. All eligible participants were in oral and written form informed about the study procedures before written informed consent was obtained. All participants were free to withdraw from the study at any time. The Medical Faculty Mannheim (medical ethics committee II) at the Ruprecht-Karls-University in Heidelberg approved the study.

Study procedures and participants

Based on a two-stage proportionally layered procedure (stratified by age, sex, and nationality), participants were randomly selected from population registries at the Psychiatric-Epidemiological Center at the Central Institute of Mental Health (CIMH; Mannheim, Germany) between September 2014 and October 2018. To the best of our knowledge, there was no self-selection bias. Participants with chronic endocrine, cardiovascular, immunological, neurologic or psychiatric disorders (as determined by the Mini-DIPS or the SCID-IV interview) and reported standard magnetic resonance imaging (MRI) contraindications (e.g., metal implants and pregnancy) were excluded. This resulted in 356 healthy adults between 18 and 28 years initially participating in the study. All participants wore an accelerometer and a study smartphone and completed additional baseline questionnaires (Table 2.15). Following established procedures, we excluded participants if the following criteria applied: (i) severe technical problems with the accelerometer such as a prematurely terminated measurement (N = 28), (ii) e-diary compliance below 30% (N = 2), or (iii) missing questionnaire data (N = 9). The final sample consisted of 317 healthy participants (57.09 % females) with a mean age of 23.08 years (SD = 2.83; Table 2.14).

Participants were informed about the study, provided written consent, and received monetary compensation for participation at the end of the study. Participants received an extensive technical briefing at the PEZ, including testing, and thereafter carried a study smartphone and an accelerometer for seven consecutive days in their everyday life. After one week, participants returned the devices and reported on their most important locations visited. To enhance participants' recall, we applied an established procedure similar to the Day Reconstruction Method (Kahneman et al., 2004). Briefly,

we used a time-stamped digital map (movisens Geocoder) that showed all geolocations visited and routes covered (tracked via smartphones). Participants were asked to label all situational contexts retrospectively (such as being at home, at work, out with friends etc.). These location labels were later assigned to three categories: 'home', 'work' and 'other', representing the situational context. In addition, after the week of Ambulatory Assessment (AA), a subsample of N = 176 participants underwent functional magnetic resonance imaging (fMRI) scans. For fMRI analysis, data of one participant was removed due to >20% of motion related outlier scans (see fMRI methods below), resulting in a final fMRI sample of 175 participants (Table 2.14).
During the first lockdown of the COVID-19 pandemic, participants were recontacted and asked to fill out questionnaires about their everyday life experiences under pandemic restrictions. In total, n = 149 subjects filled out the custom-developed questionnaire, of which data from n = 76 subjects who had previously participated in both accelerometry and e-diary assessments could be subjected to the analysis (Table 2.14).

Questionnaires assessed prior to Ambulatory Assessment procedure

Prior to the AA procedures, participants completed a questionnaire battery including sociodemographic information, height and weight, and several psychological assessments as detailed in the Table 2.15.

Supplementary methods 1. Data assessment (main study)

Physical activity assessment

Participants wore a triaxial accelerometers (Move II or Move III; movisens GmbH, Germany) for seven consecutive days during waking hours on the right hip. The accelerometer captures movements of as much as ± 8 g with a resolution of 12 bits and a sampling frequency of 64 Hz and appropriately assesses human physical activity (Anastasopoulou et al., 2014). To compute Movement Acceleration Intensity (the predictor of the main multilevel model, see below), i.e., the vector magnitude of the acceleration in milli-g [(g)/1000] assessed at the three sensor axes, we used the software movisens DataAnalyzer (version 1.6.12129). In short, gravitational components were eliminated by a high-pass filter (0.25 Hz), and artifacts (e.g., vibrations when cycling on a rough road surface or shocks of the sensor) were eliminated by a low-pass filter (11 Hz).These established procedures are described in detail elsewhere (Movisens Docs). To differentiate light physical activity, we computed the metabolic equivalent of task (MET), a measure of energy expenditure and defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ)* kg-1*h-1, with 1 MET representing the resting metabolic rate obtained during quiet sitting(Ainsworth et al., 2000). Based on METs, activities can be categorized, e.g., into light-intensity physical activity (1.6-2.9 METs; see Barbara E. Ainsworth et al., 2011). We calculated the METs using the software DataAnalyzer (movisens GmbH, Germany). Prior to the MET calculations, gravitational components were eliminated by a high-pass filter (0.25 Hz), and artifacts (e.g., vibrations when cycling on a rough road surface or shocks of the sensor) were eliminated by a low-pass filter (11 Hz). The METs were calculated in two steps: First, an activity class was estimated based on acceleration and barometric signals. Based on the detected class, the corresponding model for MET calculations was chosen, and based on movement acceleration, altitude change extracted from barometric data, age, sex, weight, and height, MET values were calculated, established procedures described elsewhere (Movisens Docs).

E-diary (electronic diary) procedures and assessments

E-diaries and the sampling strategy were implemented via the Ambulatory Assessment software movisensXS, version 0.6.3658 (movisensXS; Movisens GmbH). After thorough instruction, participants carried a smartphone (Motorola Moto G, Motorola Mobility) for seven consecutive days and were prompted via an acoustic, visual, and vibration signal to fill in the e-diary multiple times per day. The prompt could be postponed for 5, 10, or 15 minutes. The prompts were triggered based on a mixed time- and location sampling scheme that is superior to traditional time-based sampling schemes (e.g., missed rare events) and increases the within-person variance of interest (Trull & Ebner-Priemer, 2013). On each day during the study week, e-diary prompts were triggered between 7.30 AM and 10.30 PM with a minimum time-interval of 40 minutes and a maximum of 100 minutes between two e-diary prompts. This resulted in a total of 9 to 23 e-diary prompts per day. The location-based trigger algorithm monitored the distance between the participants' current and previous locations continuously. When a distance larger than 500 meters was covered, a prompt was triggered. In addition, participants were triggered at two fixed times every day (8 AM and 10.20 PM).

To assess affective valence, we used an established two-item short scale with appropriate reliability and sensitivity to measure within-subject fluctuations of mood (Wilhelm & Schoebi, 2007). The two items were presented as bipolar scales with a score range from 0 to 100 ('content' to 'discontent'; in German, 'zufrieden' to 'unzufrieden' and 'unwell' to 'well'; in German, 'unwohl' to 'wohl') in reversed polarity at the edges of two computerized visual analogue scales. The two item scores were later rectified, averaged, and used as outcome variable in our multilevel analyses. Real-life social contact at the time of the e-diary prompt was assessed via an established binary scale that asks participants whether or not they are in the company of others (Collip et al., 2013; Myin-Germeys et al., 2003). The e-diary assessments are illustrated in Figure 2.5B (see main manuscript).

Table 2.15. Main study: Basic assessments

Variable	Measurement
Socio-economic status	SES (Lampert et al., 2012) Multidimensional index based on self-reported occupational status, educational attainment, and household income
Body-mass-index (BMI)	Participants self-reported height and weight, which was used to calculate the body-mass-index (BMI).
Physical activity	How many hours a week are you physically active in your free time (e.g., sports, cycling, etc.) so that you sweat or noticeably increase your breathing? Open response
Loneliness	UCLA Loneliness Scale (Russell et al., 1980) 20 self-rated items (4-point-scale)
Social network	Social network index (Cohen, 1997) The Social Network Index assesses participation in 12 types of social relationships, including relationships with • Spouses • Parents • Parents-in-law • Children • Other close family members • Close neighbors • Close friends • Workmates • Schoolmates • Fellow volunteers (e.g., charity, community work) • Members of groups without religious affiliations (e.g., social, recreational, professional) • Members of religious groups. For each type of relationship on which respondents indicate that they speak to someone in that relationship at least every 2 weeks, one point assigned, resulting in a maximum score of 12 points. In addition, the total number of people a person talks to at least once every 2 weeks was assessed as the number of network members.
Trait neuroticism	NEO Five-Factor Inventory–30 6 self-rated items (5-point-scale).
Schizotypical traits	SPQ 22 self-rated items (yes/no – 1 point for yes)
Trait anxiety	State-Trait Anxiety Inventory (STAI-T; Bieling et al., 1998) 20 self-rated items (response options 1 to 4)

Supplementary results 1. Physical activity engagement reduces the momentary affective loss associated with the absence of social contact in everyday life

Statistical analysis

To investigate whether physical activity engagement reduces the affective loss associated with the absence of social contact, we conducted established multilevel modeling procedure applying full maximum likelihood estimation, which includes all available data using the SAS software (SAS 9.4., SAS Institute). The α-level was set to 0.05. We followed established procedures and averaged milli-g across 60-minute segments prior to each e-diary assessment, an interval length chosen due to previous findings regarding associations with affective valence ratings (60-min intervals of physical activity intensity have been evidenced to be highly correlated with both momentary affective valence ratings and daily physical activity intensity levels, and, they have been shown to predict cross-system reactivity (Reichert, Braun, et al., 2020; Merikangas et al., 2019; Reichert et al., 2017). We centered the physical activity predictor on the subject's mean. We then nested repeated e-diary ratings of affective valence (level 1) within participants (level 2; Bolger & Laurenceau, 2013). The models included physical activity [milli-g] as a continuous and social contact [alone/in company] as a dichotomous predictor of interest, as well as their interaction term to investigate the effectiveness of physical activity in offsetting affective loss due to social isolation in everyday life. Additionally, we included within- and between-subject covariates to control for other possible confounds on affective valence. These variables included age, sex and body-mass-index (BMI) on level 2, as well as time of day and time of day squared, and current location (i.e., at home, at work, or others) on level 1 (Equation 1 and Tables 2.16a and 2.16b). We standardized the time of day and time of day squared predictors by subtracting the daily study start time (7.30 AM). P-values for the beta coefficient are two-sided and derived from the t-statistics of the multilevel model.

Equation 1 (main model):

$$\mathbf{Y(affective\ valence)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{age}_j + \beta_{02} * \mathrm{sex}_j + \beta_{03} * \mathrm{BMI}_j + \beta_{10} * \mathrm{time\ of\ day}_{ij} + \beta_{20} * \mathrm{time\ of\ day}_{ij}^2 + \beta_{30} * \mathrm{location}_{ij} + \beta_{40} * \mathrm{physical\ activity}_{ij} + \beta_{50} * \mathrm{social\ contact}_{ij} + \boldsymbol{\beta_{60}} * \mathbf{physical\ activity_{ij}} * \mathbf{social\ contact_{ij}} + u_{0j} + r_{ij}$$

In our model, Y_{ij} represents the level of affective valence in person j at time i. The within-person effects are captured by the participants' (subscript j) e-diary entries at any time (subscript i). Beta coefficients represent the intercept, the effects of our main predictor's physical activity, social contact, and their interaction, as well as the effects of level-1-predictors of no interest (time of day, time of day squared, and location). Between-subject effects (age, sex, BMI) were estimated on level 2. Level-1 residuals are indicated by r_{ij}. The random intercept, represents individual variation around the sample's mean, is denoted by u_{0j}.

We introduced practical effect sizes, also known as benchmarking, to quantify the compensatory capacity of physical activity for a lack of social contact shown in the present study in its practical relevance in everyday life. This method adheres to the recommended standard procedure for interpreting the effects observed in daily life (Rhodes et al., 2023). In particular, we first compared effects in our data with the existing literature. According to a prior important study by (Killingsworth & Gilbert, 2010), influences of social activities on well-being exhibit effects that are in size among the strongest seen in humans everyday life and range, e.g., from taking care for children (an within-subject increase of happiness of about 2 points on a 0 – 100 scale) to engaging in conversation (a within-subject increase of happiness of about 9 points on a 0 – 100 scale). Social contact/presence as a composite measure of social activities (i.e., being in company vs. alone in daily life) in this study yields a considerable practical effect which is in its size just placing in-between the influences described (an increase of affective valence of 2.7 points on a 0 – 100 scale; see Table 2.16b). This effect size was already evidenced in a prior study which unraveled trait mental health and neural correlates (Gan et al., 2021). Second, we quantified the compensatory capacity of physical activity for a lack of social contact shown in the present study in its practical relevance in everyday life as follows: To fully compensate for the lack of affective well-being in everyday life, about 349 milli-g total physical activity within one hour (i.e., 69 milli-g average PA in the typical subject of our data + 280 milli-g additional PA to achieve 74 affective valence on a 0 – 100 scale in both the 'alone' and 'in company' conditions; see Table 2.16a and Table 2.16b) are necessary according to our data. To achieve this, one would have to engage in 1 hour of walking at a speed of 3 miles per hour (given that walking at 3.1 mph equal 367 milli-g following established accelerometry validation studies with the devices used in this study, i.e. movisens move II and III accelerometers (Giurgiu et al., 2020; Anastasopoulou et al., 2014). Given these data, and since we conducted a naturalistic study in real life in which the participants were not aware of our goal of quantifying the effects of social contact on affective valence, our findings indicate a considerable potential of physical activity to counteract negative affective consequences of social isolation in everyday life.

Table 2.16a. MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction on real-life momentary affective valence (outcome): F-test

n = 317 (14641 e-diary prompts)	Fixed effects	
Predictor	**F-value (df1; df2)**	**p-value**
age	0.60 (1; 310)	0.440
sex	0.56 (1; 307.2)	0.455
BMI	1.37 (1; 343)	0.242
time of day	0 (1; 14378)	0.948
time of day^2	0.47 (1; 14367)	0.492
location	39.14 (2; 14531)	<0.001*
physical actvity	36.09 (1; 14318)	<0.001*
social contact	91.49 (1; 14478)	<0.001*
physical activity * social contact	**5.45 (1; 14353)**	**0.020***

Table 2.16b. MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction on real-life momentary affective valence (outcome): two-sided t-tests of the estimated parameters

Predictor	Estimate	Standard Error	DF	t-Value	95 % CI	p-Value
(Intercept)	81.90	6.170	317.6	13.20	69.27 – 93.53	<0.001*
time of day	0.01	0.142	14378	0.06	-0.27 – 0.29	0.948
time of day^2	0.01	0.008	14367	0.69	-0.01 – 0.02	0.492
location						
work	-3.77	0.454	14495	-8.30	-4.65 – -2.88	<0.001*
other	-0.51	0.328	14512	-1.55	-1.15 – 0.13	0.120
home (reference)	0	.	.	.	.	.
age	-0.18	0.229	310	-0.77	-0.63 – 0.27	0.440
sex						
male	-0.98	1.311	307.2	-0.75	-3.56 – 1.60	0.455
female (reference)	.	.	.	.	.	.
BMI	-0.17	0.150	343	-1.17	-0.47 – 0.12	0.242
physical activity	0.01	0.003	14335	2.72	0 – 0.01	0.006*
social contact						
alone	-2.67	0.279	14478	-9.57	-3.22 – -2.12	<0.001*
in company (reference)	0	.	.	.	.	.
physical activity * social contact						
alone	**0.01**	**0.004**	**14353**	**2.34**	**0 – 0.02**	**0.020***
in company (reference)	**0**	**.**	**.**	**.**	**.**	**.**

To ensure the robustness of this approach, we additionally calculated individual within-DMN connectivity values after denoising of fMRI data with the CompCor approach and the additional inclusion of individual participant gray matter masks derived from standard SPM-based segmentation of individual T1-weighted MPRAGE images. Our sensitivity analyses showed that individual within DMN connectivity values derived from the originally used approach (see above) and the ones including individual participant gray matter masks yield highly similar results (correlation of individual within DMN connectivity values: $r = 0.998$).

Functional connectivity was calculated by computing pairwise Pearson correlations between the time series of two DMN regions of interest, as defined by Spreng and coworkers (Spreng et al., 2020) and derived from the Schaefer-Yeo parcellation atlas (Schaefer et al., 2017). Subsequently, these correlations were Fisher-Z transformed and averaged, resulting in a single DMN functional connectivity value for each individual. For within-system connectivity (Chan et al., 2014) we computed average pairwise functional connectivity between all nodes of the default mode network (specifically, regions 38 – 50 and 90 – 100 of the atlas) as defined by the 100 regions 7 networks parcellation (Schaefer et al., 2017). Although our approach was strictly hypothesis-driven and focused on the DMN, we further probed the specific role of the DMN for the finding by alternatively computing the connectivity of the global network, as represented by the average connectivity across all 7 brain networks defined by the Schaefer-Yeo atlas (Schaefer et al., 2017). Notably, there were no significant associations found between global connectivity and physical activity (P =.641), suggesting a rather specific role of the DMN in this context.

Statistical analysis

To investigate the underlying neurobiological mechanisms, we introduced participants' individual functional connectivity of the default mode network (DMN: continuous variable; Spreng et al., 2020) as a moderator of the compensatory effect of physical activity for a lack of real-life social contact. Accordingly, we modeled a three-way-interaction with DMN moderating the interactions of physical activity and social contact on affective valence and the respective post-hoc analyses (see Equation 2 and Tables 2.17a, 2.17b, 2.17c).

Equation 4:

$$\mathbf{Y(affective\ valence)_{ij}} = \beta_{00} + \beta_{01} * \mathrm{age_j} + \beta_{02} * \mathrm{sex_j} + \beta_{03} * \mathrm{BMI_j} + \beta_{03} * \mathrm{DMN_j} + \beta_{10} * \mathrm{time\ of\ day_{ij}} + \beta_{20} * \mathrm{time\ of\ day_{ij}^2} + \beta_{30} * \mathrm{location_{ij}} + \beta_{40} * \mathrm{physical\ activity_{ij}} + \beta_{50} * \mathrm{social\ contact_{ij}} + \beta_{60} * \mathrm{physical\ activity_{ij}} * \mathrm{social\ contact_{ij}} + \beta_{70} * \mathrm{DMN_j} * \mathrm{physical\ activity_{ij}} + \beta_{80} * \mathrm{DMN_j} * \mathrm{social\ contact_{ij}} + \boldsymbol{\beta_{90}} * \mathbf{DMN_j} * \mathbf{physical\ activity_{ij}} * \mathbf{social\ contact_{ij}} + \mathrm{u_{0j}} + r_{ij}$$

Table 2.17a. MLM analysis of the main model and its moderation by default mode network (DMN) connectivity: F-tests

n = 317 (*14641* e-diary prompts)	Fixed effects	
Predictor	**F-value (df1; df2)**	**p-value**
age	0.04 (1; 170.7)	0.852
sex	0.01 (1; 168.2)	0.946
BMI	0.03 (1; 169)	0.873
DMN	0.23 (1; 169.3)	0.632
time of day	1.50 (1; 8230)	0.220
time of day^2	0.07 (1; 8197)	0.786
location	34.05 (2; 8273)	<0.001*
physical activity	0.01 (1; 8170)	0.910
social contact	4.65 (1; 8263)	0.031*
physical activity * social contact	2.31 (1; 8192)	0.129
DMN * physical activity	2.34 (1; 8170)	0.126
DMN * social contact	0 (1; 8263)	0.951
DMN * physical activity * social contact	**4.75 (1; 8190)**	**0.029***

Table 2.17b. MLM analysis of the main model and its moderation by default mode network (DMN) connectivity: two-sided t-tests for the estimated parameters

Predictor	Estimate	Standard Error	DF	t-Value	95 % CI	p-Value
(Intercept)	74.40	9.547	172.8	7.79	55.55 – 93.24	<0.001*
time of day	0.22	0.181	8203	1.23	-0.13 – 0.58	0.220
time of day^2	0	0.011	8197	-0.27	-0.02 – 0.02	0.786
location						
work	-4.51	0.594	8265	-7.59	-5.68 – -3.35	<0.001*
other	-0.51	0.423	8272	-1.21	-1.34 – 0.32	0.227
home (reference)	0	.	.	.	.	.
age	-0.06	0.311	170.7	-0.19	-0.67 – 0.56	0.852
sex						
male	0.14	1.781	168.2	0.08	-3.37 – 3.66	0.936
female (reference)	0	.	.	.	.	.
BMI	0.04	0.248	169	0.16	-0.45 – 0.53	0.873
DMN	-5.70	11.707	178	-0.49	-28.80 – 17.41	0.627
physical activity	0.01	0.017	8180	1.15	-0.01 – 0.03	0.240
social contact						
alone	-2.62	1.220	8263	-2.16	-5.01 – -0.24	0.031*
in company (reference)	0	.	.	.	.	.
physical activity * social contact						
alone	-0.02	0.017	8192	-1.52	-0.06 – 0.01	0.128
in company (reference)	0	.	.	.	.	.
DMN * physical activity	-0.02	0.038	8178	-0.56	-0.10 – 0.05	0.578
DMN * social contact						
alone	0.29	4.683	8263	0.06	-8.89 – 9.47	0.951
in company (reference)	0	.	.	.	.	.
DMN * physical activity * social contact						
alone	**0.14**	**0.064**	**8190**	**2.18**	**0.01 – 0.26**	**0.029***
in company (reference)	**0**	**.**	**.**	**.**	**.**	**.**

Table 2.17c. Effect of physical activity for different combinations of social contact and DMN connectivity; post-hoc comparisons of estimated means while being alone versus in company.

n = 317 (*14641* e-diary prompts)	**Post-hoc: comparison alone vs. in company under different physical activity**			
	DMN connectivity: low (0.19; 25th percentile)		**DMN connectivity: high** (0.31; 75th percentile)	
Predictor	**Estimated Mean difference**	**p-value**	**Estimated Mean difference**	**p-value**
Below person- average (-150)	**-2.79**	**0.005***	**-5.05**	**<0.001***
Person-average (0)	**-2.57**	**<0.001***	**-2.54**	**<0.001***
Above person-average (150)	**-2.34**	**0.017***	-0.02	0.980

Statistical test for mean difference was a two-sided t-test against 0, without adjusting for multiple testing.
Calculations are based on the full multilevel model to probe the three-way interaction.

Supplementary results 3. Participants with small social networks and high habitual physical activity levels show lower trait loneliness

<u>Statistical analysis</u>

To investigate whether the within-person findings translate to the trait-level (between-person), we conducted multiple linear regression, and introduced habitual physical activity and social network size (the total number of social network members), as well as their interaction as predictors of trait-loneliness assessed via UCLA loneliness questionnaire (Russell et al., 1980; eTable 2.18).

Table 2.18. Multiple regression analysis (two-sided) to test the habitual physical activity – social network interaction effect on trait loneliness

n = 184	**Estimate**	**Standard Error**	**t-value**	**p-value**
Intercept	43.86	3.075	14.76	<0.001*
physical activity (hours/week)	-1.05	0.506	-2.07	0.040*
social network (number of people)	-0.62	0.152	-4.07	<0.001*
physical activity * social network	**0.05**	**0.023**	**2.01**	**0.046***

Supplementary results 4. Individuals with a pronounced compensatory mechanism were less likely to frequently feel lonely during the first COVID-19 lockdown

Additionally, we examined participants' feeling of loneliness during the last 4 weeks of the COVID-19-related lockdown ("In the last 4 weeks, how often have you felt lonely?") and their potential relation to the compensatory mechanism. For this analysis, we merged the five questionnaire categories of the questionnaire into three categories for content, interpretive, and statistical reasons, especially to do justice to categories to which too few participants responded (e.g., "very often" by n = 7 and "often" by n = 2).

This combination allowed us to ensure that each resulting category had a sufficient number of participant responses ("very often" and "often": n = 9, "sometimes": n = 19, "almost never" and "never": n = 48). To ensure the robustness of the result, we conducted an additional analysis in which we merged the originally 5 categories into two categories by combining individuals endorsing “very often”, “often” and “sometimes” (n = 28) and comparing them to the individuals endorsing “almost never” or “never” (n = 48). Again, we received a significant result (odds ratio [OR] = 0.92; 95% CI, 0.85–0.99; *P* = .046), which lends further support to the finding that individuals with a pronounced compensatory mechanism were less likely to frequently feel lonely during the first COVID-19 lockdown. Second, we recomputed the main multilevel model (see above, Equation 1), however, we additionally included the interaction term social contact*physical activity into the random part of the model. The resulting multilevel model revealed a significant effect for the social contact*physical activity interaction (*P* = 0.045) as well as a significant random variation of the social contact*physical activity interaction (*P* = 0.039). Third, we extracted the individual slope values of the multilevel interaction from the random part of the main model, which reflect the strength of moderation of physical activity on the association of social contact and affective valence. Fourth, we fitted an ordinal logistic regression model assuming proportional odds, in order to explore the association of the individual slope values (predictor) and participants' feeling of loneliness during the COVID-19-related lockdown (outcome). Additionally, we performed a Score Test for the proportional odds assumption.

The ordered logistic regression analysis revealed a significant association of the extracted individual slope values with the feeling of loneliness, such that beta = -0.09 is the decline in log odds (=logit) for scoring lower vs. higher in the outcome with one-unit decrease in the slope variable. Translated to practice, individuals with a pronounced compensatory mechanism were less likely to frequently feel lonely during the first COVID-19 lockdown (odds ratio [OR] = 0.92; 95% CI, 0.85–0.99; *P* = .021; Table 2.19).

Table 2.19. Proportional odds logistic regression (one-sided) of individual slope values of the multilevel interaction from the random part of the main model: maximum likelihood estimates

n = 76	Estimate	Standard Error	Wald Chi-Square	p-value
Intercept (1.0)	-2.11	0.370	32.74	<0.001*
Intercept (2.0)	-0.57	0.247	0.25	0.022*
Individual slope values	**-0.09**	**0.038**	**5.32**	**0.021***

Supplementary results 5. Physical activity engagement reduces the momentary affective loss associated with the absence of social contact even under pandemic-like constraints (i.e., considering only light physical activity or light physical activity at home)

Next, we addressed the question whether humans can achieve the affective benefit of physical activity during pandemic-like restrictions (e.g., closed gyms, exit restrictions). Since light intensity physical activities (LPA; e.g., strolling, stair-climbing) are accessible during lockdown-measures, we restricted our analysis to established LPA thresholds (< 3 metabolic equivalent of task; MET). We again received a significant MLM interaction result (P = .040, Table 2.20a left and Table 2.20b), providing evidence that even LPA-loads can compensate for a lack of real social contact.

Given that lockdown-measures may require humans to stay at home, we further restricted our analyses to stay-at-home situations. While this cut 74.5% of all e-diary assessments thus limiting statistical power of the analysis, we still reached a significant MLM interaction result (P = .032; Table 2.20a right Table 2.20c), indicating applicability of compensation-effect to the home-context.

Table 2.20a. Main MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction on real-life momentary affective valence (outcome) restricted to light physical activity (LPA) and at-home situational context: F-tests

Fixed effects	**Light physical activity**		**Light physical activity at home**	
	n = 313 (*14403* e-diary prompts)		**n = 267** (*3732* e-diary prompts)	
Predictor	**F-value (df1; df2)**	**p-value**	**F-value (df1; df2)**	**p-value**
age	0.64 (1; 306.3)	0.425	0.13 (1; 257.1)	0.715
sex	0.52 (1; 303.4)	0.472	0 (1; 253.3)	0.967
BMI	1.39 (1; 338.9)	0.240	0.53 (1; 282.5)	0.467
time of the day	0 (1; 14140)	0.952	2.11 (1; 3560)	0.147
time of the day^2	0.48 (1; 14128)	0.488	3.24 (1; 3552)	0.072
location	45.3 (1; 14275)	<0.001*	-	-
light physical activity (LPA [min])	19.3 (1; 14081)	<0.001*	6.21 (1; 3546)	0.013*
social contact	91.58 (1; 14241)	<0.001*	14.42 (1; 3682)	<0.001*
LPA * social contact	**4.22 (1; 14123)**	**0.040***	**4.6 (1; 3530)**	**0.032***

Table 2.20b. Main MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction on real-life momentary affective valence (outcome) restricted to light physical activity: two-sided t-tests for the estimated parameters

Predictor	Estimate	Standard Error	DF	t-Value	95 % CI	p-Value
(Intercept)	79.95	7.690	278.2	10.40	64.81 – 95.08	< 0.001*
time of day	-0.44	0.304	3560	-1.45	-1.04 – 0.16	0.147
time of day^2	0.03	0.017	3552	1.80	0 – 0.06	0.072
location (home only)	0	.	.	.	.	.
age	-0.10	0.282	257.1	-0.37	-0.66 – 0.45	0.715
sex						
male	-0.07	1.593	253.3	-0.04	-3.20 – 3.07	0.967
female (reference)	0	.	.	.	.	.
BMI	-0.13	0.128	282.5	-0.73	-0.47 – 0.22	0.467
light physical activity (LPA [min])	0	0.028	3543	0.26	-0.05 – 0.06	0.798
social contact						
alone	-2.17	0.572	3682	-3.80	-3.29 – -1.05	<0.001*
in company (reference)	0	.	.	.	.	.
LPA * social contact						
alone	**0.08**	**0.036**	**3530**	**2.15**	**0.01 – 0.15**	**0.032***
in company (reference)	**0**	**.**	**.**	**.**	**.**	**.**

Table 2.20c. Main MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction on real-life momentary affective valence (outcome) restricted to light physical activity at home: two-sided t-tests for the estimated parameters

Predictor	Estimate	Standard Error	DF	t-Value	95 % CI	p-Value
(Intercept)	81.97	6.218	314.5	13.18	69.74 – 94.20	<0.001*
time of day	0.01	0.144	14140	0.06	-0.27 – 0.29	0.952
time of day^2	0.01	0.008	14128	0.69	-0.01 – 0.02	0.488
location						
work	-3.87	0.458	14259	-8.44	-4.77 – -2.97	<0.001*
other	-0.18	0.329	14273	-0.55	-0.83 – 0.46	0.580
home (reference)	0	.	.	.	.	.
age	-0.19	0.232	306.3	-0.80	-0.64 – 0.27	0.425
sex						
male	-0.95	1.318	303.4	-0.72	-3.54 – 1.64	0.472
female (reference)	0	.	.	.	.	.
BMI	-0.17	0.150	338.9	-1.18	-0.47 – 0.12	0.240
light physical activity (LPA [min])	0.02	0.012	14098	1.80	0 – 0.05	0.072
social contact						
alone	-2.70	0.282	14241	-9.57	-3.25 – -2.15	<0.001*
in company (reference)	0	.	.	.	.	.
LPA * social contact						
alone	**0.04**	**0.019**	**14123**	**2.05**	**0 – 0.08**	**0.040***
in company (reference)	**0**	**.**	**.**	**.**	**.**	**.**

Supplementary information 2. General study information (replication study during the COVID-19 pandemic)

Ethics

For a detailed description of the ethics involved, please refer to the previously described section supplementary information 1. General study information (main study): Ethics.

Study procedures and participants

Participants were recruited as part of a longitudinal naturalistic study with a total assessment period of 24 weeks. The sample consisted of healthy individuals (n = 30; Table 2.21), recruited from the local community by advertisement between December 2019 and July 2022. For study participation, participants had to be aged between 18 and 63 years. Participants were excluded from the study if they had a lifetime history of significant general medical, psychiatric, or neurological illness, prior psychotropic pharmacological treatment, head trauma, or the presence of a first-degree relative with a history of psychiatric illness. Participants were informed about the study, provided written consent, and received monetary compensation for participation at the end of the study. Participants received an extensive technical briefing, including testing, thereafter answered e-diary prompts on a smartphone, and wore an accelerometer on their non-dominant wrist across 24 weeks.

Supplementary methods 2. Data assessment (replication study)

Physical activity assessment

Participants wore a triaxial accelerometers (Move 4; movisens GmbH, Germany) on their non-dominant wrist. All device related details for data assessment and processing are described in supplementary methods 1. Data assessment (main study): Physical activity assessment.

E-diary (electronic diary) procedures and assessments

E-diaries and the sampling strategy were implemented using a custom experience sampling software developed by the movisens GmbH (movisensXS v. 1.5-INDICATE). The smartphone application was installed on participants' smartphones. As the application only ran on smartphones with Android system, participants with iPhones or Windows-phones were provided with study smartphone (Nokia 6.2 or Nokia 7.2, Nokia Corporation; n = 8).

Participants were thoroughly instructed on the use of the smartphone-application together with a demonstration of exemplified e-diary ratings. During the whole study period of 24 weeks, participants were subjected to two sampling schemes, i.e. basic and intense sampling. Basic sampling included fixed-time prompts per day. In addition, participants received 3 intense phases with six daily prompts for ten days each. The starting day of the intense phase was randomized. Assessments were obtained up to 6 times between 9.00 AM and 9.00 PM (2 fixed and 4 random prompts) could be postponed up to 30 minutes. In these analyses, however, only the data from the intense sampling were used, as they best capture the current mood and movement of the subjects in everyday life (Ebner-Priemer et al., 2013).

To assess affective valence, we used exactly the same assessment instrument as in the first study: an established two-item short scale with appropriate reliability and sensitivity to measure within-subject fluctuations of mood. For details see section supplementary methods 1. Data assessment (main study): Electronic diaries (e-diaries) procedures and assessments.

Supplementary results 6. Replication study: Physical activity engagement can reduces the momentary affective loss associated with the absence of social contact during the COVID-19 pandemic

Statistical analysis

We followed exactly the same statistical procedures as in the main study to investigate if physical activity can reduce the affective downsides of social isolation during the COVID-19 pandemic. We conducted the same multilevel analysis as described for the first study sample (for details see supplementary information 1: Statistical analysis, Equation 1). Results are listed in Tables 2.22a and 2.22b.

Table 2.21. Replication study: Demographics, psychological characteristics and Ambulatory Assessment parameters

Measure	full sample n = 30		
	Mean	SD[b]	n[a]
Demographic variables			
Age [years]	40.63	11.86	30
Sex (female/male)	15/15	-	30
Education [years]	11.67	1.44	30
Nationality (German/other)	28/2	-	30
Body mass index [kg/m^2]	24.91	3.88	30
Smoking (non-smoker/ smoker)	4/26	-	30
Household size (individuals)	2.40	1.5	30
Household income (€/month)[c]	2385	972.5	30
Psychological variables			
Physical activity (h/Week)	6.00	9.29	26
Neuroticism (NEO-FFI-30-N)	0.45	0.46	29
Trait anxiety (STAI-T)	29.72	5.47	29
Schizotypical traits (SPQ)	2.41	2.60	29
Ambulatory Assessment			
Movement Acceleration Intensity [milli-g/min][d]	123.79	35.35	30
E-diary prompts per day	5.75	3.14	30
Compliance [%]	87.15	9.85	30
Affective valence (0-100)	79.3	12.38	30
ICC: affective valence[e]	0.53	-	30

[a] n = number of individuals for which the information for a given sample and variable is available
[b] SD = standard deviation
[c] We assessed monthly household income after taxes in 13 ordinal categories, i.e., 1) less than 500 €, 2) 500 – 1000 €, 3) 1000 – 1500 €, 4) 1500 – 2000 €, 5) 2000 – 2500 €, 6) 2500 – 3000 €, 7) 3000 – 3500 €, 8) 3500 – 4000 €, 9) more than 4000€. For the descriptive comparison of the two samples in this table we assigned category means to individuals, e.g., a value of 675 € to a participant reporting a category
[d] Values were averaged across participants and the study week, respectively.
[e] We used intra class correlation coefficients (ICC) to calculate variance estimates of our outcome variables: In the study 53.0% of the variance in affective valence can be attributed to within-subject variation.

Table 2.22a. MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction effects on real-life momentary affective valence (outcome): F-Tests (replication across the COVID-19 pandemic)

Predictor	F-value (df1; df2)	p-value
time of day	0.68 (1; 3120)	0.411
time of day^2	0.56 (1; 3120)	0.455
location	5.07(2; 3130)	0.006*
age	0.70 (1; 26.08)	0.411
sex	3.40 (1; 26.07)	0.077
BMI	4.77 (1; 26.07)	0.038*
physical activity	12.50 (1; 3121)	<0.001*
social contact	49.01 (1; 3130)	<0.001*
physical activity * social contact	**31.03** (1; **3123)**	**<0.001***

Table 2.22b. MLM analysis of the within-person social contact (predictor) – physical activity (moderator) interaction effects on real-life momentary affective valence (outcome): two-sided t-tests (replication across the COVID-19 pandemic) of the estimated parameters

Predictor	Estimate	Standard Error	DF	t-Value	95 % CI	p-Value
(Intercept)	45.05	16.994	27.89	2.65	10.23-79.87	0.013*
time of day	0.35	0.428	3120	0.82	-0.49 – 1.19	0.411
time of day^2	-0.01	0.014	3120	-0.75	-0.04 – 0.02	0.455
location						
work	-2.29	0.724	3131	-3.16	-3.71 – -0.87	0.002*
other	-0.73	0.489	3129	-1.50	-1.69 – 0.23	0.134
home (reference)	0	.	.	.	.	.
age	0.15	0.187	26.08	0.83	-0.23 – 0.54	0.411
sex						
male	-8.06	4.368	26.07	-1.84	-17.03 – 0.92	0.077
female (reference)	0	.	.	.	.	.
BMI	1.24	0.567	26.07	2.18	0.07 – 2.40	0.038
physical activity	-0.01	0.003	3123	-1.50	-0.01 – 0	0.134
social contact						
alone	-3.2	0.457	3130	-7.00	-4.10 – -2.3	<0.001*
in company (reference)	0	.	.	.	.	.
physical activity * social contact						
alone	**0.03**	**0.005**	**3123**	**5.57**	**0.02 – 0.04**	**<0.001***
in company (reference)	**0**	**.**	**.**	**.**	**.**	**.**

3 DISCUSSION

The primary aim of this work is to provide a comprehensive overview of modern approaches of ecologically valid real-life assessment of affective, psychological, and contextual factors in the everyday life of psychiatric and healthy populations in times of social isolation.

As shown in study 1, despite initial concerns, the pandemic did not lead to a decline in daily-life well-being for psychiatric patients, likely due to access to mental health services and adaptive coping strategies. In contrast, healthy individuals, especially those at risk for mental disorders, were more susceptible to pandemic-related stressors. In general, this study highlights the need for preventive measures and targeted support for individuals at risk for mental disorders during crisis situations. It suggests that at-risk healthy individuals may be more affected by stressful events like the COVID-19 pandemic compared to individuals with severe mental illnesses. Moreover, the study shows that even during stressful events, daily smartphone-based assessments of well-being are feasible not only in healthy individuals, but also in psychiatric patients.

The results of study 2 indicate that physical activity engagement effectively moderates the relationship between momentary social isolation and decreased affective well-being in daily life. More specifically, higher physical activity diminishes the reduction in well-being associated with the lack of social contact. This effect was replicated during the COVID-19 pandemic, demonstrating its effectiveness under pandemic-like constraints. At the neurobiological level, individuals with higher functional connectivity within the default mode network, a risk phenotype for loneliness and depression, benefited most from physical activity in compensating for the social-affective deficit.

3.1 Solitude in daily life

It is widely agreed that current assessment methods fall short in capturing the daily functioning behaviors of patients with SMI (Durand et al., 2021; Ben-Zeev et al., 2012). This is partly due to challenges in self-assessment (Harvey & Pinkham, 2015), which extend to social cognition and social outcomes across psychiatric conditions (Strassnig et al. 2018; Durand et al. 2015). In recent years, Ambulatory Assessment studies have yielded valuable insights into the daily occurrences of solitude for both healthy individuals and psychiatric patients, enhancing our comprehension of social functioning and isolation across various contexts.

Among healthy individuals, research has shown a positive effect of social presence on daily well-being (Gan et al., 2021). This effect is further supported by the findings in study 2, where participants reported worsened emotional states when being alone. In contrast, individuals with schizophrenia spectrum disorder tend to spend more time alone, and often experience social stress, less pleasure and a stronger desire to be on their own in social settings (Granholm et al., 2020; Mote & Fulford, 2020). This tendency aligns with reduced engagement in daily social and leisure activities and a preference for solitary participation (Lipskaya-Velikovsky et al., 2016; Schneider et al., 2017). Additionally, specific momentary symptoms like paranoid ideation were linked to an increased desire to distance oneself from social interactions (Orth et al., 2022), while individuals with persecutory ideation were generally less social and reported more severe auditory and visual hallucinations (Buck et al., 2019). These observations underscore the contribution of disorder-related symptoms that motivate social withdrawal.

Furthermore, patients with schizophrenia experience more negative moods when leaving home and feel better upon returning (Parrish et al., 2020). Similar results were observed in study 1 in patients with schizophrenia and major depression. Of note, approximately 90% of adults with psychotic disorders are unemployed, and 60% are single, which translates to significant differences in how they spend their time, often engaging in solitary (Kasanova et al., 2018). Specific situations like being alone at home may pose significant challenges for patients, since it is linked to passive, unproductive activities, such as watching TV or doing nothing, which have been associated with momentary sadness (Strassnig, Miller, et al. 2021).

Despite the voluntary isolation, it is however surprising that the anticipation of being alone is linked to elevated risk of suicidal ideation (Parrish et al., 2022). This association seems to be more rooted in the inability to experience pleasure and the belief that social interactions are not worth the effort rather than the perceived competence during interactions or the number of social contacts per se (Depp et al., 2016). For individuals with serious mental illness, the limited reward from social interactions may stem from their poor quality or due to anticipation of negative outcomes in social situations (Parrish et al., 2020). Compared to healthy controls, people with schizophrenia engage in similar numbers of conversations. However, these interactions are often not initiated by the patients themselves and are of a lower quality, involving roommates or care providers instead of family or friends (Abel et al., 2021; Granholm et al., 2020).

Contextual factors like lifestyle, employment, housing situation, and disease-specific symptoms collectively influence real-life social behavior in severe mental illness (Kasanova et al., 2018). It is therefore important to use common mobile technologies to identify current factors and symptoms contributing to isolation in daily life, assess the quality of social contacts, and intervene when necessary.

3.1.1 Importance of social support and networks

Social support emerges as a resilience factor and plays a pivotal role in enhancing the well-being of both healthy individuals and people with SMI. In patients with SMI, social support benefits symptom management and mitigates responses to stressors, leading to better mental health outcomes and medication adherence (Yao et al., 2022; Holt-Lunstad, 2021; Ozbay et al., 2007; Kawachi & Berkman, 2001). In schizophrenia, social support buffers against stress, enhances treatment adherence, and aids recovery (Hsieh et al., 2023; Shettima et al., 2022; Shivarudraiah & Muralidhar, 2021). Having a greater number of friends can boost self-esteem, mitigate the impact of socioenvironmental stressors, and reduce depressive symptoms through increased social integration and a heightened sense of belonging (Degnan et al., 2018). Furthermore, elevated risk of major depressive disorder and more severe symptoms were found to correlate with loneliness, underscoring the vital role of social connectedness as a protective factor against depression and anxiety (Wickramaratne et al., 2022).
As indicated in study 2, young adults with small social networks reported higher levels of loneliness. Both depression and schizophrenia patients also often exhibit limited social networks (Wickramaratne et al., 2022; Degnan et al., 2018). Schizophrenic individuals with small friendship networks have repeatedly been found to experience more psychotic symptoms (especially delusions and thought disorder) as well as negative symptoms, compared to those with larger networks (Degnan et al., 2018; de Sousa et al., 2015; Horan et al., 2006). Additionally, the size and strength of these networks, along with the level of social support, correlate negatively with factors like internalized stigma, recovery attitudes, and hospitalization frequency (Shettima et al., 2022; Albert et al., 1998). The quality of relationships within an individual's social network significantly influences recovery from mental illness and affects the utilization of mental health services (Salehi et al., 2019; Wyngaerden et al., 2019). Utilizing social support systems in conjunction with routine nursing care has been shown to effectively enhance mental well-being, self-worth, and overall quality of life for individuals with men-

tal illness (Yang et al., 2022). The strong associations between insufficient social connectedness and the risk of depression highlight the need for improved clinical identification of high-risk patients, including those with low received or perceived social support and heightened perceived loneliness (Wickramaratne et al., 2022).

Furthermore, it is essential to consider the nature and origin of social support. Family support, in particular, plays a substantial role for mental health, especially in times of crisis. During the pandemic, the “COVID-19 social study” in the UK (Fancourt et al., 2020) demonstrated a powerful protective effect of close friends, social support, and social interactions against loneliness (Bu et al., 2020) and depressive symptoms (Sommerlad et al., 2021). Likewise, a study conducted during the initial pandemic outbreak in the Netherlands found that undergraduate students reported decreased levels of loneliness despite social-distancing measures, possibly due to spending more time at home with their families (Fried et al., 2022). Furthermore, healthcare workers emphasized the importance of social support from family and friends to cope with psychological distress during the pandemic (Alnazly et al., 2021). For patients, family support is even more valuable in the recovery process, with research indicating that active family involvement and nurturing familial relationships contribute to enhanced treatment adherence and decreased rates of relapse (Duckworth & Halpern, 2014; Glick et al., 2011; Nasser & Overholser, 2005). Additionally, sharing personal experiences in peer support programs have exhibited promising outcomes in enhancing the well-being of psychiatric patients (Chinman et al., 2014). Research has shown that online social networking, through forums and chats, has a positive impact on reducing isolation in schizophrenia (Highton-Williamson et al., 2015). Online peer-to-peer support not only presents opportunities to combat stigma but also fosters consumer engagement, providing access to online interventions that promote both mental and physical health (Rayland & Andrews, 2023; Naslund, Aschbrenner, et al., 2016).

3.1.2 Psychological impact of the COVID-19 pandemic

Both studies investigated the impact of the COVID-19 pandemic on individuals' well-being, social contact, and mental health outcomes. Study 1 suggests that patients with SMI, who may have already been familiar with solitude, experienced little additional impact on their daily well-being. In contrary, some healthy individuals, especially vulnerable ones, found social distancing highly stressful, leading to worsened well-being, anxiety, mobility problems, and social isolation. Study 2 shows that at-risk participants felt lonelier but benefited more from physical activity, even during the pandemic. However, both studies emphasize the importance of social connections, especially during times of crises.

Specifically, the COVID-19 pandemic has led to significant changes to daily life, including social distancing measures that contribute to increased social isolation, highlighting its negative consequences. In efforts to slow the spread of the virus, the pandemic has imposed restrictions on social gatherings, closure of non-essential businesses, and increased remote work, leading to reduced social interactions. Social isolation is a significant risk factor for poor physical and mental health outcomes, and the COVID-19 pandemic has exacerbated this problem. A study by Torales et al. (2020) found that the pandemic and the ensuing social isolation had a significant impact on mental health, resulting in increased anxiety, depression, and stress. Moreover, social isolation has affected vulnerable populations disproportionately. College students, elderly, individuals from low socioeconomic backgrounds or with preexisting mental health conditions, were particularly at risk of social isolation during the pandemic (Brooks et al., 2020).

During the course of the pandemic, there was a significant increase in the prevalence of anxiety and depression rates (Bäuerle et al., 2020). At the same time, the access to psychiatric care services was limited, contributing to a rise in mental health problems. This is noteworthy because the patients in study 1 mostly already had access to mental health services, whereas healthy controls may have faced limitations, compelling them to cope with feelings such as anxiety and loneliness without professional support.

3.1.3 Advantages of solitude

In contrast to forced, involuntary isolation, Perceived Desired Social Distance (PDSD) is a clinically relevant state of enjoying being alone, which is valued in stress-reduction programs for its potential health benefits (Campagne, 2019). As shown in study 1, being socially isolated did not have a negative impact on the mental health of patients during the COVID-19 pandemic, in some cases even bringing a relief.

Patients may prefer spending time alone for various reasons. Social withdrawal, at times, can have a positive impact on their symptoms, as being around people, especially strangers, can trigger or intensify symptoms like paranoia or hallucinations (Collip et al., 2011; Myin-Germeys et al., 2009). Solitude can serve as an escape from overwhelming sensory experiences (Landon et al., 2016) or social pressures (Sells et al., 2004; Sass & Parnas, 2001). Research indicates that intentional solitude can lead to

lower loneliness levels and increased well-being (Nguyen et al., 2018; Chua & Koestner, 2008). It can serve as a restorative experience, fostering self-reflection, creativity, and spiritual insight (Seeman, 2017). Solitary activities are associated with better mental health outcomes, suggesting that those who find satisfaction in isolation may adapt well to their condition (Leary et al., 2003). Moreover, some individuals with schizophrenia seek solitude in public places or use music, headphones, or the internet to be alone while remaining in touch with others (Seeman, 2017; Miranda et al., 2012).
However, it's crucial to differentiate between chosen and imposed isolation when evaluating the implications of solitude. While some may voluntarily seek solitude for various benefits, others may be isolated due to practical reasons like financial constraints (Topor et al., 2016).

3.2 Ecological Momentary Interventions (EMI)

Studies 1 and 2 highlight the susceptibility of individuals at higher risk of mental illness to stressful situations (e.g. COVID-19 related measures) or social isolation, emphasizing the importance of early identification of critical mental states and the need for preventive action and targeted support.
Rapid technological advances have opened new opportunities for treatment delivery in the daily life of psychiatric patients (Myin-Germeys et al. 2016). After the successful application of AA in a diverse range of mental disorders, it is increasingly gaining recognition as a valuable tool for improving mental health care (van Os et al. 2017; van Os et al. 2013; Wichers et al. 2011). These digital tools, also called Ecological Momentary Interventions (EMIs), have the potential to extend existing approaches and develop entirely new interventions by bringing the therapy from the clinical setting into real life (Miralles et al., 2020). They can be deployed as a standalone treatment, but are most effective when used in blended care, combining face-to-face therapy with mobile apps (Myin-Germeys et al., 2016).
According to a study by Wittchen et al. (2011), over one-third of the EU population suffers from a mental disorder in every year, most of which do not receive any proper treatment. EMIs have emerged as promising approaches, by making interventions cheaper and more easily accessible to a wider patient population (Myin-Germeys et al. 2016). The latest advancement in digital psychological interventions is Just-In-Time-Adaptive Interventions (JITAIs; Nahum-Shani et al. 2018). By leveraging mobile technology and Ecological Momentary Assessment, JITAIs offer personalized, contextual, at-the-moment interventions that can address symptoms, enhance coping strategies,

and promote well-being when they are most relevant and impactful (Wang & Miller, 2020).

Several studies have shown the effectiveness of EMIs in common psychiatric disorders, including symptom reduction, increased treatment adherence, and improved overall functioning (Balaskas et al. 2021; Myin-Germeys et al. 2016; Granholm et al. 2012). For example, a study by Kramer et al. (2014) used a PsyMate device (Myin-Germeys, Birchwood, and Kwapil 2011) to provide feedback on contextual patterns of positive affect in depressed patients, leading to reduced depressive symptoms over time. Additionally, real-time monitoring has been linked to increased self-efficacy and reduced loneliness (Hanssen et al., 2020; Schlosser et al., 2018).

EMIs can also provide real-time support for individuals dealing with social withdrawal by delivering positive affirmations, coping strategies, and social interaction suggestions through mobile applications. The PRIME program aided young patients with schizophrenia-spectrum disorders using a virtual peer community and motivation coaches, resulting in significant improvements in social motivation, depression, and motivation/pleasure-related symptoms (Schlosser et al., 2018). The FOCUS smartphone app offers real-time support for individuals with schizophrenia using personalized interventions targeting social interaction, medication adherence, mood regulation, and sleep problems (Ben-Zeev et al., 2013, 2014). Additionally, a study utilizing personalized text messages and socialization interventions based on cognitive behavioral therapy (CBT) led to increased social interactions (Granholm et al., 2012).

Overall, EMIs have the potential to provide simple, cost-effective, and user-led treatment for psychiatric disorders (Bell et al., 2017). Future EMIs may leverage mobile sensing and advances in natural language processing and machine learning to reduce user burden and increase personalization and sophistication (Balaskas et al., 2021). Offering treatment when it is most needed requires a sound knowledge of the dynamics of mental health problems, as well as insights into the underlying psychological and physiological processes that can be measured in real time (Teepe et al., 2021; Wang & Miller, 2020).

3.2.1 Promoting physical activity

Study 2 explores the potential of physical activity as a resilience strategy to counteract the negative affective impact of social isolation and loneliness, being especially beneficial for individuals at-risk for psychiatric disorders and therefore suggesting a high importance of promoting physical activity. Physical activity has been found to strengthen resilience, reduce the risk of developing psychiatric symptoms following life stressors (Szuhany et al., 2023), lower depressive symptoms (Gianfredi et al., 2020; Mammen & Faulkner, 2013; Priyono & Pramana, 2020) and improve quality of life (Rosenbaum et al., 2014). Since physical activity interventions are broadly applied in people with mental illness, there is a big potential not only to identify low levels of physical activity but also to promote more daily activity and deliver therapies through AA techniques (Dao et al., 2021).

There is currently a growing interest in utilizing EMIs for health promotion and disease prevention, which have demonstrated effectiveness in encouraging tailored physical activity engagement in daily life (Heron & Smyth, 2010; Kaplan & Stone, 2013). Besides the direct beneficial effect on physical and mental health, engaging in physical activity, whether through team sports, fitness classes, or recreational pursuits, provides opportunities for social interactions and fosters supportive relationships. Social connectedness further strengthens the beneficial effect of physical activity on loneliness, highlighting the importance of improving neighborhood psychosocial interventions in managing social isolation (Gyasi et al., 2021).

3.3 Methodological and ethical challenges

Despite the obvious strength and novelty of AA, there arise additional ethical considerations and responsibilities, including data storage and transfer, data ownership, user anonymity, access to technology, and communication of clinically relevant results (Capon et al., 2016). The five key aspects are inclusivity, privacy and consent, intervening on worrisome responses (e.g., suicidal ideation), participant burden and reactivity. While some ethical concerns, like informed consent and privacy, are not unique, the real-time, remote data collection, and the depth of data detail introduce additional ethical complexities, demanding further consideration (Myin-Germeys and Kuppens 2021; Cornet and Holden 2018). In the following, I will focus on methodological challenges of specific relevance to Ambulatory Assessment in the broad area of mental health research in clinical populations.

3.3.1 Technological barriers

Many psychiatric patients may have limited access to smartphones and other digital devices, often due to financial constraints or a perceived complexity in using technology (Wong et al., 2020; Ash et al., 2017; Ramsey et al., 2016). Patients with mental illness are less likely to own mobile devices and smartphones, to have internet access, and to use mobile applications for health purposes compared to people without mental illness (Bauer et al., 2020). This issue is particularly problematic, as smartphones have become integral tools for daily activities, including internet access and maintenance of social connections. The absence of smartphones can additionally exacerbate social isolation, potentially leading to exclusion from broader social engagement.

Nevertheless, with rapid advancing technologies, smartphones become cheaper, so that most patients with mental health problems possess a mobile phone (Abu Rahal et al., 2018). Studies suggest that up to 80% of psychiatric outpatients are interested in using their smartphones to monitor their mental health and own the smartphones capable of running mental healthcare related mobile applications (Torous et al., 2014).

Not the mental illness per se, but a high symptom severity, is a barrier to using and accessing information and communication technologies (Abu Rahal et al., 2018). Therefore, there is a pressing need to improve patients' digital skills through educational programs (Rodriguez-Villa et al., 2021; Hatch et al., 2018) and to promote the relevance of digital technology use in mental health care (Iliescu et al., 2021; Torous et al., 2021). This can be achieved for example through patient education programs, sufficient training and resources that emphasize the therapeutic potential of smartphones (Ramsey et al., 2016).

3.3.2 Inclusivity

The core idea of Ambulatory Assessment lies in multiple daily self-evaluations over time (Vachon et al., 2019). The use of smartphone-based assessment may therefore not be suitable for all psychiatric population, especially those with severe symptoms or cognitive impairments (Ramsey et al., 2016; Raugh et al., 2019). Cognitive dysfunction is a notable concern in the implementation of technology-based assessments, and common mental health issues like depression or psychosis can potentially reduce motivation and confidence in utilizing such technology (Ramsey et al., 2016). This could lead to a systematic exclusion of patients with specific symptoms (e.g., avolition, social anxiety, or cognitive dysfunction) from research studies due to their condition and resulting non-compliance (Vachon et al., 2019). Consequently, it is plausible that relying solely on patient self-report may not capture all symptoms and degrees of severity.

To address this challenge, comprehensive training in prior device usage alongside with a user-friendly interface is essential. Additionally, adopting a combination of simple questions and passive measurements may offer a better overview of a patient's current state (e.g., heart rate during stressful situations). However, further research is currently needed in this regard.

3.3.3 Participant burden

Ambulatory Assessment research involves intensive longitudinal data collection, with participants providing usually multiple responses per day over extended periods, which can become demanding and reduce the compliance (Rintala et al., 2019). Additionally, repeatedly evaluating the emotional states of individuals experiencing persistent negative moods may result in heightened perceived burden (van Genugten et al., 2020). This burden can manifest when questionnaires are too long (Eisele et al., 2022) or if the frequent prompts disrupt participants' daily routines or coincide with other assessments (Bos et al., 2019).

However, recent studies have shown that questionnaire length plays a more significant role than sampling frequency, emphasizing the importance of keeping questionnaires concise. For longer assessments, the number of daily prompts could be fixed or reduced (Trull & Ebner-Priemer, 2020), questions tailored to relevant aspects, or participants reminded to complete the entry if not already done on their own (Bos et al., 2019). Besides, mobile sensing technologies could be used to passively assess several parameters, such as physical activity or social contacts, without an active involvement of the patient (Aung et al., 2017). Although EMA was initially feared to be too burdensome to those suffering from psychopathology, studies in general have shown that patients find short-term EMA feasible and acceptable in research settings (Palmier-Claus et al., 2011; Vachon et al., 2019).

3.3.4 Compliance and adherence

High participant adherence is essential in daily-life research, as it often involves cooperation for extended periods (Reichert et al., 2021). Participants in AA studies may not always comply with study protocols, or become annoyed by frequent prompts, leading to decreased adherence over time (Vachon et al., 2019). Poor compliance can lead to missing data which can then result in limited statistical power and poor validity (Bolger & Laurenceau, 2013).

Low compliance can be attributed to various factors, including the influence of immediate environmental and contextual factors, such as inconvenient timing (e.g., while

driving or in a meeting), potential avoidance of specific topics due to impaired perception or shame, challenges of describing internal experiences, and participant fatigue or irritation caused by the frequency or length of prompts (Vachon et al., 2019).
Generally, compliance among psychiatric patients is approximately 75%, often lower compared to healthy individuals, yet still adequate to gain insights into daily fluctuations and connections within clinical populations (Ottenstein & Werner, 2022; Rintala et al., 2019; Vachon et al., 2019). In research, one practical strategy is to offer financial compensation as an incentive for study participation (Ottenstein & Werner, 2022). However, given the potential financial needs of psychiatric patients, data validity should be treated with caution. A more effective strategy to maintain participants' motivation involves regular contact during the study (Gloster et al., 2017). Moreover, intrinsic motivation plays a crucial role, particularly when participants anticipate favorable outcomes related to their well-being or symptomatology. This intrinsic motivation can be further reinforced through real-time feedback, which has proven to be motivating as it demonstrates a genuine interest in and commitment to the patient's well-being (Trull & Ebner-Priemer, 2013). In later clinical practice, it is therefore essential to consider patients' preferences during questionnaire design and execution to achieve a high compliance (e.g., adjusted prompt times or targeting specific symptoms; Bos et al. 2022).
Despite the discussed challenges, research indicates that AA is feasible for diverse psychiatric disorders (Vachon et al. 2019; Myin-Germeys et al. 2018; Palmier-Claus et al. 2011). The benefits of using it in clinical populations outweigh the disadvantages, however, the limitations mentioned above should be taken into account. Feasibility will likely not depend on diagnosis but rather on the intrinsic motivation of patients, symptom severity, stage of care, and study design (Bos et al., 2019; Vachon et al., 2019). Understanding the quality and properties of the collected data is crucial for its proper interpretation, especially in digital phenotyping studies.

3.4 Future directions: Ambulatory Assessment in clinical practice

As Ambulatory Assessment technology advances and becomes more user-friendly and cost-effective, it is expected to become seamlessly integrated into routine clinical practice, offering the potential to enhance assessment and intervention in fundamental ways (Carpenter et al., 2016). An essential future direction in advancing precision psychiatry involves the application of knowledge from daily-life studies into clinical interventions. If these interventions prove effective, they could form the basis for personalized, real-time treatments in everyday life, automatically delivered via mobile devices at the precise moments and locations when needed, and thus expanding therapeutic assistance beyond conventional clinical settings (Reichert et al., 2021).

While self-monitoring, such as daily blood pressure and glucose level tracking, is common in various medical fields, it is also informative for diagnosis and treatment planning. Similarly, mental health treatment could also benefit from a more frequent approach of self-monitoring of daily symptoms, contextual experiences, and treatment-related factors compared to existing monitoring methods. The necessary requirements for this are met by Ambulatory Assessment. Initial empirical studies on the clinical utility of EMA indicate positive impacts on self-management, therapeutic relationship, and treatment outcomes of psychiatric patients, as reported by both patients and clinicians (Piot et al., 2022; Folkersma et al., 2021; Bos et al., 2019).

First, frequent self-monitoring through AA is suggested to improve patients' self-management. By reflecting on one's mood and symptoms and gaining insights into how various situations impact their emotional state may grant patients' greater control over their overall well-being (Alpay et al., 2011). As such, monitoring of own symptoms may already serve as an intervention (Hanssen et al., 2020; Beckjord & Shiffman, 2014). Furthermore, mobile applications or wearable devices can be used to trigger personalized prompts, reminders, or interventions in real-time which can be tailored based on the individual's context, preferences, and specific needs.

Second, data visualization offers insights into mechanisms of psychopathology (Stadel et al., 2023; Von Klipstein et al., 2023; Bringmann et al., 2021; Bringmann, 2021). Such feedback could range from simple illustrations of daily mood variations to more complex statistical models, such as personalized network models, or the detection of early warning signals (Bringmann, 2021; Wichers et al., 2020). Consequently, personalized feedback has the potential to facilitate a collaborative approach to diagnosis and treatment, promoting shared decision-making in the relationship between patient and therapist (van Os et al., 2017; Alpay et al., 2011). For example, Stadel et al. (2023) used personal social networks as an interactive feedback that focuses on a person's social relationships and their influence on mental health. Such approaches could have particular relevance for a clinical context, as it reveals relationships that may have a positive or negative impact on the patient's well-being, facilitating therapeutic decisions and collaboration between patient and clinician.

Several digital applications which implement evidence-based techniques are already available for daily use without additional clinical support. Clarity (https://cbtthoughtdiary.com/) and Mindshift (https://www.anxietycanada.com/resources/mindshift-cbt/) offer interactive CBT-based tools to help individuals to overcome stress, worry, social anxiety, phobias, panic, or negative thoughts. Moodtrack Social Diary not only gives the possibility to monitor daily mood, but also to share your results and get in touch with other users (http://www.moodtrack.com/). Another internet-based intervention (Mobilyze) combined an interactive website for behavioral skills training, email support from a coach, and smartphone-based mood tracking to provide participants with tailored feedback for dealing with deteriorations of depressive symptoms (Burns et al., 2011). These apps show promise, but their actual effectiveness needs rigorous scientific investigation, and to be suitable for clinical use, they must adhere to robust scientific frameworks and data protection requirements.

On the other hand, a new web-based application for personalized treatment by real-time assessment (PETRA) is currently being clinically examined as a supportive module in mental health care (Bos et al., 2022). The web application incorporates a decision aid feature to assist in the creation of personalized e-diaries tailored to the patient's specific symptoms, along with a feedback module to visualize the collected data, which can subsequently be reviewed and discussed with the therapist (Von Klipstein et al., 2023).

To sum up, research indicates that AA and EMI are well-accepted and feasible in the treatment of psychiatric disorders (Miralles et al. 2020; Bell et al. 2017; Myin-Germeys et al. 2016). Nonetheless, the transition will likely be gradual with several obstacles to overcome before AA data can become a primary source of information for clinicians (Carpenter et al., 2016).

4 CONCLUSION

Involuntary solitude is a widespread issue in today's society, significantly impacting physical and mental health. Providing preventive and effective therapy options targeting the adverse effects of social isolation, including loneliness, is crucial for both healthy individuals and psychiatric patients. To realize this objective, it is essential to identify those affected as well as determine the most suitable timing and treatment approaches. In this context, the utilization of Ambulatory Assessment has demonstrated its practicality and potential effectiveness in examining how mood, symptoms, and social context interact in the daily lives of patients. Mobile apps and wearable devices allowing real-time data collection, remote monitoring, personalized interventions, and social support open up opportunities towards precision psychiatry for more tailored treatment (Myin-Germeys 2023). These tools hold promise for enhancing mental health care, improving outcomes, and empowering patients in their journey towards improved social functioning and well-being.

However, further research is needed to deepen our understanding of real-life mental health dynamics and to determine how these digital technologies can be effectively integrated into clinical settings, with the potential to innovate psychiatric care if resources are used wisely (Myin-Germeys, 2023).

5 SUMMARY

Solitude can have tremendous negative effects on physical and mental health, including intense feelings of loneliness, depression, anxiety and elevated stress levels. For people suffering from mental illnesses, who already experience social exclusion, prolonged solitude can become a way of life, resulting in social deficits, withdrawal, permanent isolation, and stigmatization, in turn causing individuals to withdraw further from social interactions. The complexity of daily-life environmental factors poses a challenge in accurately assessing and understanding the unique social context and subjective feelings within controlled laboratory settings. Traditional methods like paper-pencil questionnaires and clinical interviews have limitations that affect the accuracy and granularity of the data. To address this issue, there is a pressing need for innovative assessment methods, especially in the field of mental health care.

A novel approach called Ambulatory Assessment offers researchers and clinicians a more accurate and ecologically valid understanding of the dynamic interplay of psychopathology and environmental factors by capturing real-world experiences, overcoming recall and response biases, and providing high-temporal resolution data. First, the integration of subjective e-diaries and continuous mobile sensing, which includes actigraphy and GPS tracking, provides with a comprehensive view of psychiatric patients' symptoms and social interactions in daily life, which may not be captured by traditional assessments. Second, AA can help identify triggers for symptoms such as social withdrawal, facilitating early detection of changes in mood and behavior and creating personalized treatment plans to meet individual's unique needs to reduce isolation. Third, AA can enhance patient engagement and treatment satisfaction by offering a tailored approach. It can be used to promote effective strategies, such as physical activity engagement or social support and networking that mitigate social isolation using feedback, reminders, and psychoeducational materials in Ecological Momentary Interventions. Overall, Ambulatory Assessment (AA) has shown great potential to identify specific triggers of social isolation and social withdrawal, to monitor intervention effectiveness in enhancing social functioning, and creating personalized treatment plans for psychiatric patients. It is a proven, well-accepted, and feasible tool for exploring various facets of daily life, even during significant crises like the COVID-19 pandemic, and across a broad spectrum of mental disorders, holding the potential to greatly transform mental health care.

6 ZUSAMMENFASSUNG

Alleinsein kann enorme negative Auswirkungen auf die körperliche und geistige Gesundheit haben. Dazu zählen Gefühle intensiver Einsamkeit, Depression, Angst, und erhöhter Stress. Für psychisch kranke Menschen, die bereits soziale Ausgrenzung erfahren, kann dauerhaftes Alleinsein zu sozialen Defiziten, langanhaltender Isolation und Stigmatisierung führen, was wiederum weiteren Rückzug von sozialen Kontakten nach sich zieht. Die Komplexität äußerer Einflussfaktoren im Alltag erschwert die Messung sozialer Kontexte unter kontrollierten Laborbedingungen. Darüber hinaus liefern traditionelle Methoden wie Fragebögen und klinische Interviews Daten mit begrenzter zeitlicher Auflösung und Genauigkeit. Um dieses Problem anzugehen, besteht ein dringender Bedarf an innovativen Erhebungsmethoden, insbesondere im Bereich der psychischen Gesundheit.

Ein neuartiger Ansatz namens „Ambulantes Assessment“ (AA) bietet Forschern und Klinikern ein besseres Verständnis des dynamischen Zusammenspiels von Psychopathologie und Umweltfaktoren. Mittels AA können reale Lebenssituationen mit verringerten Erinnerungsverzerrungen sowie erhöhter ökologischer Validität erfasst werden. Zum einen bietet die Integration persönlicher elektronischer Tagebücher sowie kontinuierlicher Aktigraphie und GPS-Tracking einen umfassenden Überblick über Symptome und soziale Interaktionen psychiatrischer Patienten im täglichen Leben, die durch herkömmliche Beurteilungen nicht erfasst werden können. Zum anderen kann AA dazu beitragen, Auslöser für Symptome, wie z.B. sozialen Rückzug, zu identifizieren und Stimmungs- und Verhaltensänderungen frühzeitig zu erkennen, um sozialer Isolation entgegenzuwirken. Des Weiteren kann AA die Behandlungszufriedenheit der Patienten steigern, sowie wirksame Strategien, wie körperliche Aktivität oder soziale Unterstützung, im Rahmen von Ecological Momentary Interventions fördern. Insgesamt bietet AA die Möglichkeit, spezifische Auslöser sozialen Rückzugs zu identifizieren, die Wirksamkeit von erlernten sozialen Funktionen zu überwachen und personalisierte Behandlungspläne zu erstellen. Es ist ein gut akzeptiertes und praktikables Instrument zur Untersuchung verschiedener Facetten des alltäglichen Lebens, sowohl in schweren Krisen wie der COVID-19-Pandemie als auch bei einem breiten Spektrum psychischer Störungen, und birgt das Potenzial, die psychische Gesundheitsversorgung erheblich zu verändern.

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8 PUBLICATION LIST

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Benedyk, A, Moldavski, A., Reichert, M., Reinhard, I., Lohr, S., Schwarz, K., Berhe, O, Höflich, A, Lautenbach, S, von der Goltz, C, Ebner-Priemer, U, Tost, H, & Meyer-Lindenberg, A. (2023). Initial response to the COVID-19 pandemic on real-life well-being, social contact and roaming behavior in patients with schizophrenia, major depression and healthy controls: A longitudinal ecological momentary assessment study. European Neuropsychopharmacology, 69, 79-83.

Benedyk, A*, Reichert, M*, Giurgiu, M, Timm, I, Reinhard, I, Nigg, C, Berhe, O, Moldavski, A, von der Goltz, C, Braun, U, Ebner-Priemer, U, Meyer-Lindenberg, A, Tost, H (2024): Real-life behavioral and neural circuit markers of physical activity as a compensatory mechanism for social isolation (in press at Nature Mental Health)

Other publications

Fritze, S, Brandt, G, **Benedyk, A**, et al. (2023). Psychomotor slowing in schizophrenia is associated with cortical thinning of primary motor cortex: A three cohort structural magnetic resonance imaging study. European Neuropsychopharmacology, 77, 53-66.

Praus P, Proctor T, Rohrmann T, **Benedyk A**, et al. (2023). Female sex and burden of depressive symptoms predict insufficient response to telemedical treatment in adult attention-deficit/hyperactivity disorder: results from a naturalistic patient cohort during the COVID-19 pandemic. Frontiers in Psychiatry, 14.

Rohrmann, T, Praus, P, Proctor, T, **Benedyk, A**, et al. (2022). Patients with affective disorders profit most from telemedical treatment: Evidence from a naturalistic patient cohort during the COVID-19 pandemic. Frontiers in Psychiatry, 13, 971896.

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In press

Benedyk, A*, Reichert, M* (2024). Research Briefing: Physical activity compensates affective downsides of daily life aloneness (Nature Mental Health)

Under review

Giurgiu M*, **Benedyk A***, Reichert M, Braun U, Berhe O, Ebner-Priemer U, Tost H, Meyer-Lindenberg A: Associations of accelerometer measured sedentary behavior and grey matter volume in healthy young adults

*authors contributed equally

9 CURRICULUM VITAE

PERSONALIEN

Vorname:	Anastasia
Nachname:	Benedyk
Geburtsdatum:	22.04.1994
Geburtsort:	Odessa, Ukraine
Nationalität:	German

AUSBILDUNG

06.2019 – heute	**Doktorandin** AG Systemische Neurowissenschaften in der Psychiatrie; Zentralinstitut für Seelische Gesundheit Supervisor: Prof. Dr. Dr. Heike Tost
10.2016 – 03.2019	**Master of Science** Cognitive and Integrative Systems Neuroscience Philipps-Universität Marburg Abschlussarbeit: *“Functional resting-state abnormalities in patients with bipolar disorder and schizophrenia”*
10.2013 – 09.2016	**Bachelor of Science** Medical Engineering Science Universität zu Lübeck Abschlussarbeit: *“Neural activity supression as a function to predict odor similarity in a forced-choice study and their representation in 2DG-uptake-pictures of rats”*
08.2007 – 06.2013	**Abitur** F. F. Runge Gymnasium

BERUFLICHE ERFAHRUNG

11.2015 – heute	**Dolmetscherin/Übersetzerin** (DE – UA – RU)
05.2022 – 06.2022	**Gastwissenschaftlerin** University of Groningen, Niederlande
05.2018 – 08.2018	**Gastwissenschaftlerin** UQCCR Brisbane, Australien
02.2017 – 12.2018	**Wissenschaftliche Hilfskraft** Clinic for Psychiatry Marburg, Supervisor: Dr. Bianca van Kemenade

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