A progressive deterioration in people’s will and emotional life was central to Kraepelin’s concept of his newly described illness, dementia praecox. When Bleuler coined the term schizophrenia, the ‘four As’ that defined the fundamental symptoms of schizophrenia (allogia, affect blunting, autism and ambivalence) strongly resemble what we now call negative symptoms. The advent of the antipsychotic era brought about a focus on a disorder centred on positive symptoms, shunting motivation and emotional life to the outskirts of the disorder’s definition. Although treatment frequently ameliorates psychosis, most people do not achieve a return to a satisfactory level of functioning owing to untreated negative and cognitive symptoms. Interest in these symptoms resurfaced in the 1970s under the ‘negative symptoms’ term, in part as a response to this clinical need. Fifty years later, these symptoms are still a major unmet therapeutic need in people diagnosed with schizophrenia.

The quest for defining and understanding negative symptoms resulted in the creation of new symptom scales, including the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS). These were important contributions but unsatisfactory for several reasons, including the assessment of cognitive deficits and disorganisation, as well as poor coverage of motivation-related negative symptoms in the PANSS. Both scales rely on behavioural proxies for internal experiences that are at the core of motivation or experiential impairments in individuals with schizophrenia spectrum disorders. The recent second-generation scales, such as the Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS), were developed to cover the five consensus domains of negative symptoms, as outlined by Kirkpatrick et al.1

Taken together, these three findings indicate the need to use specific scales to evaluate negative symptoms and consider the five separate domains of negative symptoms, as outlined by Kirkpatrick et al.1 A reduction in motivational and emotional life is no longer considered the end state of schizophrenia. In this issue, the meta-analysis of Salazar and colleagues found a high prevalence of negative symptoms in children and adolescents during the early stages of a psychotic disorder, with 79.6% of those at risk of psychosis and 60.8% of those with early-onset psychosis exhibiting negative symptoms. It is unclear whether those negative symptoms represent the outcome of faulty developmental trajectories, are secondary to other psychopathological aspects, or result from some form of bias. In any case, these results indicate the need for early recognition of negative symptoms in psychotic disorders.

There has been relatively little progress in the pharmacological treatment of negative symptoms. Non-pharmacological treatments are widely recommended, and Cella and colleagues’ reviewed their efficacy. Unfortunately, their review highlights the relative methodological weakness of the studies conducted to date and the modest positive effect they show for ameliorating negative symptoms.

Careful characterisation of negative symptoms will become increasingly important as more evidence emerges about differences among...
the five domains of negative symptoms with regard to risk factors and correlates. The second-generation scales should be more widely implemented in clinical and research settings. Indeed, poorly designed studies relying on inadequate scales might have yielded negative results in recent large trials. For the progress of pathophysiological studies and treatment development, the poor characterisation of negative symptom domains and the failure to distinguish primary and secondary negative symptoms have been major obstacles, as outlined in the editorial by Galderisi & Kaiser in this issue. Some alternatives to assessment scales for better characterisation and modelling of negative symptoms are in progress, but the research is in the early stages.1

The cognitive computational neuroscience approach holds the promise of dissecting the different components of negative symptoms from a transdiagnostic perspective using the framework of the Research Domain Criteria (RDoC) promoted by the US National Institute of Mental Health (NIMH). It has shown its value in the study of apathy in neurodegenerative conditions. There are promising results for motivation-related negative symptoms in schizophrenia, albeit much larger studies are needed for such complex phenomena in a heterogeneous disorder such as schizophrenia.

In any case, the refinement in assessment and neuroscience modelling will probably lead to a new era of clinical epidemiology, pathophysiological studies and treatment trials. We hope that the works in this themed issue will provide clues to find the much-needed new treatments in the future.

Author contributions
All authors participated in the conception, discussion and writing of this editorial.

Funding
E.F.-E. is supported by the 2022 MRC/NIHR CARP award (MR/W029987/1), and his research is supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the author(s) and not necessarily of the NIHR or the Department of Health and Social Care.

Declaration of interest
E.F.-E. has received consultancy honoraria from Boehringer-Ingelheim (2022), Astheneum (2022) and Rovi (2022), speaker fees by Alameda (2022) and Otsuka (2023) and training and research material from Merz (2023). A.M. received advisory board or consultant fees from the following drug companies: Gedeon Richter Bulgaria, Janssen Pharmaceuticals, Lundbeck, Otsuka Pharmaceutical, Pfizer, Pierre Fabre and Rovi Pharma outside the submitted work. J.L. has received honoraria from Sumitomo Pharmaceuticals, Lundbeck Singapore, Otsuka Pharmaceutical and Janssen Pharmaceutical. B.K. receives licensing royalties from ProPhase LLC for use of the Brief Negative Symptom Scale (BNSS) by for-profit groups; these fees are donated to the Brain and Behavior Research Foundation. He has also received honoraria and travel support from ProPhase LLC for training pharmaceutical company raters on the BNSS; consulting fees and/or travel support from Lundbeck, Acadia, ProPhase LLC, Otsuka and Minerva Neurosciences; fees from anonymised investors through Guideposts and Decision Resources Group; and an honorarium from Otsuka for preparation of educational materials. He is part owner of Quantic Innovations, which provides services related to digital phenotyping of people with psychiatric disorders, with clients including Karuna Therapeutics and Sunovion.

References